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Thyroid Function and Anti-Thyroid Antibodies in Iranian Patients with Type 1 Diabetes Mellitus: Influences of Age and Sex

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ABSTRACT

Type 1 diabetes mellitus is frequently associated with autoimmune thyroid disease (ATD).Genetic susceptibility for autoantibody formation in association with ATD and type 1 diabetes mellitus has been described with varying frequencies, but there is still debate about its prevailing situation in Iran.

We have therefore investigated the prevalence of anti-thyroid peroxidase (anti-TPO) and anti thyroglubolin (Anti TG) antibodies in type 1 diabetic patients, and compared the effect of age and sex on the thyroid autoimmunity in patients with type 1 diabetes mellitus in Iran.

Ninety one subjects with type 1 diabetes mellitus and one hundred and sixty three unrelated normal controls under the age of thirty years were recruited for the detection of anti-TPO and anti-TG. Radio Immuno Assay and chemiluminescence methods were used for anti-TPO and anti-TG detection respectively.

Among 91 type 1 diabetic patients, 36 (39.6%) were positive for anti-TPO and 27(30%) were positive for antiTG. Anti-TPO antibodies were detected only in 6.7% of control group. Comparing with those without thyroid autoimmunity, there was a female preponderance for the type 1 diabetic patients with thyroid autoimmunity (female: male, 28:14 *vs.* 28:20 respectively). Among the type 1 diabetic patients those with thyroid autoimmunity, tended to be older (p: 0.04) and to have higher TSH concentration (p: 0.03). Patients with high anti-TPO levels had longer duration of diabetes (P: 0.02).

The presence of anti-TPO in 39.6% of our type 1 diabetic patients comparing with 8.5% of normal subjects confirmed the strong association of ATD and type 1 diabetes mellitus.

Key words: Autoimmune thyroid disease; Anti-TPO, Anti-TG; Diabetes type 1; Diabetes mellitus; Iranian patients

INTRODUCTION

The association of type 1 diabetes mellitus with autoimmune thyroid disease (ATD) has been well documented in many populations.[1-8] The occurrence of thyroid auto antibodies against microsomes (AMA) and

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thyroglobulin (ATA), which are frequently observed in Hashimoto's thyroiditis and Graves' disease, has been reported in type 1 diabetes mellitus with varying frequency.[1,5-7,9] However, AMA tends to correlate better with thyroid dysfunction than does ATA.[10]

Although most type 1 diabetic patients are clinically euthyroid, screening for ATD by measuring AMA levels has been recommended since there is a risk of developing future thyroid dysfunction.[11-14] In a study in Germany thyroid dysfunction developed in up to 50% of diabetic patients with high titers of AMA after three years of follow up.[15] Recently, detection of antibodies against thyroid peroxidase (TPO), a major antigen for microsomal autoantibody, appears to obviate the need for AMA and ATA measurements because of the improvement in specificity and sensitivity of the method.[16]

Genetic susceptibility for autoantibody formation associated with ATD and type 1 diabetes mellitus has been described in the literature;[17-19] however, there is still debate about the situation in the Iranian population.

In the present study, we aimed to determine the frequency and titers of anti-TPO in patients with type 1 diabetes mellitus in Zanjan, a city in the north west of Tehran, and to compare the frequency of anti-TPO in diabetic and normal subjects.

MATERIALS AND METHODS

Sera were collected from 91 subjects with type 1 diabetes mellitus, and 163 unrelated normal controls after obtaining informed consent. All the individuals recruited in this study were living in Zanjan, a city in the north west of Iran.

The type 1 diabetic patients were recruited from the Diabetic Clinic of Zanjan University of Medical Sciences and also Vali-e- Asr Hospital, the referral center in Zanjan for admitting diabetic patients, in the period 2005-2006. The diagnosis of type 1 diabetes mellitus was based on the published criteria[20] with a typical clinical history of diabetic ketoacidosis and a requirement for insulin. Data about their age, sex, duration of the disease and the mean of their hemoglobulin A1c (HbA1c) in the last year were collected by filling a form.

The control subjects were recruited from subjects under the age of twenty five years who visited Zanjan blood transfusion organization for general health examination to donate their blood from 2005 to 2006.

All the subjects were clinically euthyroid. Autoantibodies to thyroid peroxidase (anti-TPO) were measured by radioimmunoassay (TPOAntibodies Radioimmunoassay Kit, Sorin Biomedica, Italy). The assay is based on the competition between anti-TPO in patients' sera and the solid-phase Fab to TPO (mouse monoclonal) for the fixed and limited number of labeled TPO binding sites. After incubation, the amount of anti-TPO present in the patients' sera is inversely related to that of labeled TPO bound to the solid phase. The results of anti-TPO were obtained using a calibration curve. The upper normal limit for anti-TPO, in agreement with the reference range suggested by the manufacturer was considered to be<16 IU/ml. The intra and inter assay coefficients of variation of the anti-TPO were calculated for 5 assays. The intra assay variation of anti-TPO were 5.1% at a mean value of 2.1 U/ml (n=5); 6.2% at 72.3 U/ml (n=5) and 6.5% at 760.8 U/ml (n=5). The interassay coefficients of variation were 6.1% at a mean value of 3.7 U/ml (n=5); 5.9% at 53.8 U/ml (n=5) and 11% at 369.9 U/ml (n=5). The presence of anti-TG antibodies was tested in samples from the type 1 diabetic patients with a chemiiluminescence method. The upper normal limit for anti-TG was considered to be 100 IU/ml according to the manufacturer's suggestion.

TSH concentrations in the diabetic patients were measured by Immuno Chemiluminescence assay.

The study was approved by the ethical committee of Zanjan University of medical sciences. An informed consent was obtained from all the participants. All tests were free of charge for the participants.

Comparison between means was performed by Student's t-test and Mann-Whitney test. Comparison between frequencies was carried out by chi-square and Wilcoxon's rank-sum test. Odd's ratio was calculated for abnormal thyroid function in patients with higher antithyroid antibody concentrations. Correlation between antibody concentrations and TSH levels and also duration of the disease were determined using correlation coefficient and regression analysis. A P value of 0.05 or less was interpreted as significant for the analysis.

RESULTS

Table 1 demonstrates the demographic characteristics and the frequency of thyroid autoimmunity among type 1 diabetic patients and their control group.

Table 1.General characteristics and biochemical markers of diabetic and control groups

Parameter	Diabetic group (N=91)	Control group (N=163)	P value
Age(years)	20.4 ± 0. 9	21 ± 0.4	NS
Male/Female	34/57	60/103	NS
Duration of the diabetes(month)	45.9 ± 5.3	--------	-------
HbA1c (%)	8.9 ± 1.2	---------	-----
Anti APO(MIu/l)	262 ± 54.5	46.8 ± 29.1	<0.0001
Anti Tg(MIu/l	242.5 ± 78.3	-------	-------
TSH(MIU/L)	2.6 ± 0.3	---------	-------

Anti TPO: Anti thyroid peroxidase; Anti Tg: Anti thyroglubolin; TSH: Thyroid stimulatig hormone;
Continues variables demonstrate as Mean± SE

Anti-thyroid peroxidase antibodies were detected in 36 (39.6%) out of 91 patients and 11(6.7%) out of 163 normal subjects (p= 0.001). As shown in Table 2, 13 out of 34 diabetic males (38.2%) and 23 out of 57 females (40.4%) had anti-TPO antibodies. Although no significant difference between two sexes was found for the frequency of anti thyroid peroxidase antibody (p= 0.8), a female predominance was noted in diabetic patients who were positive for anti thyroglobulin antibodies (p= 0.014).

A positive correlation was found between age and serum anti-TPO but not for anti-TG concentrations in the diabetic patients (r= 0.29, p= 0.006) (Figure 1). However there was a significantly higher frequency of anti-TPO positivity in older than in younger groups (Table 3).

There was a positive correlation between the duration of the diabetes and the titer of anti–TPO (r: 0.33, p: 0.004) (Figure 2) but no correlation was found with anti-TG in this study.

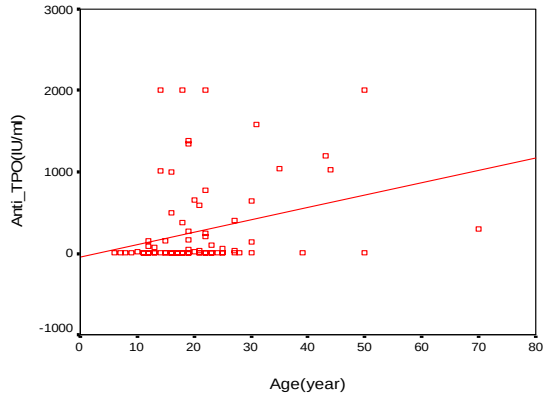

Figure 1. Scatter plot showing relation of age and serum Anti TPO titer (IU/ml) in patients with type 1 diabetes mellitus (*n* = 91) (r: 0.29, p: 0.006)

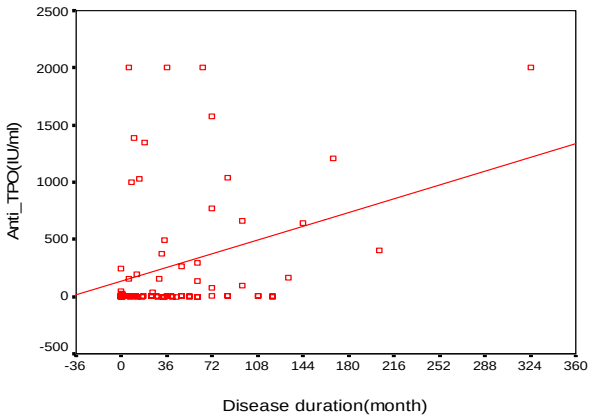

Figure 2. Scatter plot showing relation of serum Anti TPO titer (IU/ml) in patients with type 1 diabetes (*n* = 91) and the disease duration (r: 0.33, p: 0.004)

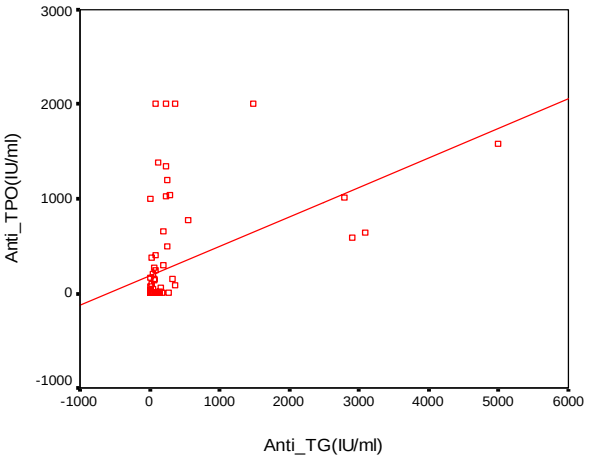

Figure 3. Scatter plot showing relation between serum Anti TPO and serum Anti TG titers (IU/ml) in patients with type 1 Diabetes mellitus (*n* = 91) (r: 0.44, p: 0.001)

Table 2. Frequency of Anti thyroid antibodies in male and female patients with type 1 diabetes mellitus (N: 91)

gender	Anti TPO		Anti Tg	
	Positive	Negative	Positive	Negative
Female (N: 57)	23(40.4%)	34(59.6%)	22(39.3%)	35(60.7%)
Male (N: 34)	13(38 %)	21(62%)	5(14.7%)	29(85.3%)
Total (N: 91)	36(39.6%)	55(60.4%)	27(30%)	64(70%)

Table 3. Frequency of positive results for Anti thyroid antibodies in different age groups of patients with type 1 diabetes mellitus (N: 91).

Age(y)	Anti TPO (%)	Anti Tg (%)	Total
<20	16(29%)	13(23.6%)	55
20-29	12(48%)	7(29.2%)	25
>=30	* 8 (72.7%)	**7(63.6%)	11
Total	36(39.5%)	27(29.6%)	91

*p:0.03, **P:0.07

Table 4. Frequency of abnormal TSH concentrations in patients with type 1 diabetes mellitus and positive anti thyroid antibodies.

Types of Antibody	TSH		Total
	Elevated	Suppressed	
Anti TPO	8(22.2%)	2(5.5%)	36
Anti Tg	7(25.9%)	2 (7%)	27

Table 5. Correlation between different variables in 91 patients with type 1 diabetes mellitus

Variable	HbA1c	TSH	Anti TPO	Anti Tg
Hb A1c	1	-0.04	-0.07	-0.07
TSH	-0.04	1	*0.23	*0.24
Anti TPO	-0.07	*0.23	1	**0.44
Anti Tg	-0.07	*0.24	**0.44	1

*P: 0.05, **P: 0.001

The occurrence of positivity of anti-TG in the presence of anti-TPO was 55.5% (20 out of 36 subjects positive for anti-TPO). This difference was statistically significant compared with 12.7% (7 out of 55) among cases negative for anti-TPO (p= 0.01). Twenty two patients with diabetes mellitus (22.4%) were positive for both of the anti thyroid antibodies. The correlation between the two types of antithyroid antibodies is demonstrated in figure 3 and table 5.

In the group of diabetic patients, 9 out of 91 (9.9%) had elevated TSH concentrations and two patients (2.2%) had suppressed level of serum TSH. There was no significant difference between two sexes in terms of their TSH concentrations and the frequency of abnormal thyroid function (p= 0.5). Out of 9 patients with elevated TSH concentration, 8 (88.9 %) patients were positive for anti TPO and 7 patients (77.8%) were positive for anti TG (Table4). All subjects with suppressed TSH were positive for both anti thyroid antibodies. The chance for elevated TSH concentration in diabetic patients who were positive for anti TPO was 16 times more than those who were negative for this antibody (Odd's ratio: 16, CI 95%:5-56, p= 0.0001).

This chance for diabetics with positive anti TG was estimated to be 10.7(Odd's ratio: 10.7, CI 95%:2-55.6, p= 0.0001).

DISCUSSION

Type 1 diabetes mellitus has been recognized as an autoimmune disease[21-23] and is strongly associated with other organ-specific diseases such as ATD, pernicious anemia, and idiopathic adrenal insufficiency;[4,24-26] while ATD has been reported to be the most common coexisting autoimmune disease with type 1 diabetes mellitus.[18] There is also an increased prevalence of thyroid antibodies in type 1 diabetic patients with ATD.[25,27-29]

The reasons for the increased frequency remain obscure. It was thought to result from a generally increased propensity to react against certain antigens, or from a genetically impaired ability to acquire tolerance to some autoantigens, or perhaps from certain common antigens present in the tissues of subjects prone to autoimmune disease.[30] Among the thyroid autoantibodies, assays for anti-TPO autoantibody, in addition to AMA and ATA, have recently become available for the determination of thyroid autoimmunity.[16,31]

The prevalence of AMA in type 1 diabetic patients varied from 11.9% to 22%.[2,10] Chuang *et al*[9] reported that 22% and 27.7% respectively of type 1 diabetic patients were positive for AMA, while others reported an absence of thyroid autoimmunity in Chinese children with type 1 diabetes mellitus.[6]

Moreover, 10 to 24% of type 1 diabetic patients who were clinically euthyroid have been reported to be positive for anti-TPO.[16,32-34] From the sera of 91 type 1 diabetic patients in the present study, 36 (39.6%) were positive for anti-TPO. The data were in accordance with previous reports, indicating no ethnic difference in the association of ATD and type 1 diabetes mellitus.

High titers of anti-TPO were highly suggestive of ATD, and correlated well with thyroid dysfunction.[14,15] The positive anti-TPO titers in our type 1 diabetic patients showed wide distribution. Among the patients with positive anti-TPO, the anti-TPO titers were mostly below 500AU/ml (84.9%).

It is well known that organ-specific endocrine autoimmunity develops more frequently in women, including type 1 diabetes mellitus with thyroid autoimmunity.[12] The production of anti-TPO is inheritable in an autosomal fashion in women but not in men.[35]

In our study, female preponderance was also found in the type 1 diabetic patients with thyroid autoimmunity. The association was also valid for the subgroup of longstanding type 1 diabetic patients, but not for the shorter-duration group. We also found a tendency for anti-TPO to occur with increasing age, in agreement with the report by Verge *et al*[23] Taken together, a subgroup of type 1 diabetic patients associated with thyroid autoimmunity might present in the female patients of older age or with long-standing disease. The gene or other genetic predisposing factors responsible for this interesting phenomenon need to be investigated further.

As for human leukocyte antigen (HLA) genes, it has been previously identified that HLA DR3 and DR4 are associated with the susceptibility to type 1 diabetes mellitus regardless of thyroid autoimmunity in a Taiwanese population.[36] In that study, there was no difference in the HLA DR typing between the type 1 diabetic patients with or without positivity of anti-TPO.

Varying frequencies of anti-TG have been reported ranging from 5.9% to 14.2%,[32,34] comparing with a frequency of 30% in our study. Higher frequency of anti thyroid antibodies in Iranian diabetic patients comparing to other countries can be due to ethnic differences.

In accordance with previous reports describing a higher frequency of anti-TG in females compared with males, this study also showed this preponderance. There was no difference in the occurrence of positive anti-TG among patients with different duration of disease and different age at diagnosis.

In conclusion, the presence of anti-TPO in 39.6% of our patients with type 1 diabetes prompts the necessity for further thyroid function evaluation. The correlation between anti-TPO and TSH concentrations in the Iranian type 1 diabetic patients indicates a probable necessity for thyroid function evaluation in patients with higher concentrations of thyroid auto antibodies.

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