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Investigating Thyroid Autoimmunity in Patients with Type I DiabetesMellitus

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ABSTRACT

Type I diabetes mellitus is the most common metabolic disorder in childhood and adolescence that as an autoimmune disorder is significantly associated with other autoimmune diseases. The aim of this study was to determine the prevalence of thyroid autoimmunity and thyroid autoimmune disease in patients with type I diabetes. In this cross-sectional study 119 patients with type I diabetes were enrolled. Profile of patients included age, sex, duration of diabetes, age at onset of diabetes, medications, history of different disease and body mass index were evaluated and recorded. Thyroid examination was carried out by endocrinologist. Body weight was measured without shoes using a digital scale and height also was measured in standing situation using a stadiometer. All blood samples were collected between 8 and 9 am and after 8 hours fast. Fasting plasma glucose (FPG), HbA1C, free thyroxin (fT_4), thyroid stimulating hormone (TSH), Anti-thyroid peroxidase (anti-TPO), Anti-thyroglobulin (anti-Tg) was measured. Quantitative variables were expressed as mean (and standard deviation) and qualitative variables as a percentage. All the analysis was done by software STATA version 12. In this study, a total of 119 patients with type I diabetes were attended that positive anti-TPO was found in 34 cases (28.6%) and positive anti-Tg was also found in 15 cases (12.6%). All the subjects who had positive anti-Tg at the same time had positive anti-TPO. Overt hypothyroidism was observed in 12 cases (10.1%) and subclinical hypothyroidism in 18 patients (15.1%). Eightynine subjects (74.8%) also had normal thyroid function. Thyroid autoimmune disorders in patients with type I diabetes has high prevalence. Hypothyroidism is more than other types of thyroid disorders. Due to the high incidence of thyroid dysfunction in diabetic patients with positive antibody titers, periodic evaluation of thyroid function in these patients appears to be essential for early diagnosis and treatment.

Key words: thyroid autoimmunity, type I diabetes mellitus

INTRODUCTION

Type I diabetes mellitus, is a fairly common chronic disease in children which is lead to insulin deficiency caused by immune-mediated destruction of pancreatic beta cells. Type I diabetes is the most common form of diabetes in children and constitute about two-thirds of newly diagnosed cases of diabetes in people younger than 19[1-3]. According to the World Health Organization it is predicted that the total number of people with diabetes is projected to rise from 171 million in 2000to 366million in 2030.Also, Iran is facing increasing prevalence of diabetes and the prevalence of diabetes in this population reaches 7% [4].

A genetic susceptibility is needed for incidence of type I diabetes that the same genetic predisposition increases the risk of developing other autoimmune diseases such as thyroid autoimmune disease, celiac disease, adrenal insufficiency, vitiligo, alopecia and pernicious anemia[5-11]. Autoimmune thyroid disease, is the most common autoimmune disorder in type I diabetes, which is often clinically silent but may also progress toward symptomatic disease[12-16]. Thyroid dysfunction can be appears in the form of overt or subclinical hypothyroidism or hyperthyroidism[17, 18]. Thyroid autoimmunity is appears by producing autoantibodies against thyroid gland, infiltration of T lymphocytes in the gland and thyroid dysfunction. Such antibodies are against specific proteins like

thyroglobulin which is an essential component of colloid and thyroid peroxidase, an enzyme that is involved in the production of thyroid hormone[19].

The prevalence of positive thyroid antibodies in patients with type I diabetes in different studies based on the methodology of the study and patient characteristics such as age, sex, race and genetic predisposition varied between 3 and 50% [10, 20-23],while this rate among general population is between 7-17% [24, 25]. Hypothyroidism can cause growth retardation, mental retardation, weight gain, menstrual disturbances, hyperlipidemia and cardiovascular disease in diabetic patients [18]. Hyperthyroidism can also worsen the metabolic control of diabetic patients and increase in required insulin dose and is associated with increasing the risk of developing diabetic ketoacidosis[26, 27].

A better understanding of the etiology and natural history of thyroid autoimmune disease in patients with type I diabetes can improve detection, treatment and prevention of its complications. A few studies are done in Iran about the prevalence of thyroid autoimmunity and thyroid disease in type I diabetes. The aim of this study was to determine the prevalence of thyroid autoimmunity and autoimmune thyroid disease in patients with type I diabetes.

MATERIALS AND METHODS

The present cross-sectional study was done on patients with Type I diabetes referred to endocrine clinic between October 2015 and February 2016 in Zahedan, Southeastern Iran. Patients with type I diabetes were enrolled continuously. Profile of patients included age, sex, duration of diabetes, age at onset of diabetes, medications, history of different disease and body mass index were evaluated and recorded. Subjects who have a recent history of acute disease, chronic liver and kidney disease, or taking drugs that affect thyroid function were excluded. Thus, 119 patients with type I diabetes were enrolled. Thyroid examination was carried out by endocrinologist. Body weight was measured without shoes using a digital scale and height also was measured in standing situation using a stadiometer. Body mass index was determined by this formula: weight in kilograms divided by the square of height in meters.

All blood samples were collected between 8 and 9 am and after 8 hours fast. Blood glucose was measured with glucose oxidase technique (Iran Pars test). Thyroid function was evaluated by measuring free T4 and TSH using immunochemiluminescent assays by an automated analyzer (Diagnostic Products LIAISON, 2011, Italy). Antithyroid peroxidase and antithyroglobulin was measured by immunochemoluminescent assays employing commercial kits (Diagnostic Products LIAISON). Anti-TPO Ab and anti-TgAb concentrations more than 16 and 100 IU/ml IU/ml, respectively, were considered positive. Normal thyroid function was defined as normal thyroid stimulating hormone [TSH: 0.4-4.2 mIU/L], normal free thyroxine [FT4: 0.8-1.8 ng/dL]. Overt hypothyroidism was defined as elevated TSH and low fT4, subclinical hypothyroidism as elevated TSH and normal fT4, overt hyperthyroidism as low TSH and elevated fT4 and subclinical hyperthyroidism as low TSH and normal fT4.

Quantitative variables were expressed as mean (and standard deviation) and qualitative variables as a percentage. T-test and Mann-Whitney U-test were used to compare quantitative variables and Chi-Square was used to compare qualitative variables. Multivariate logistic regression analysis with thyroid autoimmunity as the dependent variable and age, sex, duration of diabetes was performed as independent variables were done. All the analysis was done by software STATA version 12 (Stata Corporation, College Station, TX). The Zahedan University Ethics Committee for Human Studies approved the protocol (ethical code number: IR.ZAUMS.REC.91.1675). All participants or their parents provided informed consent.

RESULTS

In this study, 119 patients suffering from type I diabetes were enrolled. Among them 75 patients (63%) were female and 44 (37%) were male. The mean age of subjects was 13.8 ± 3.38 years (Table 1).

Table1. Demographic characteristics of study participants

Variable	Mean (SD) (n=119)	Range
Sex (female)	75 (63%)*	
Age (years)	13.8 (3.38)	2-19
Duration of DM (years)	4.36 (3.36)	0-12
Age at onset of DM (years)	6.49 (2.95)	2-17

** number (percent); SD: standard deviation*

As shown in Table 2, 28.6% of the subjects had positive Anti-TPO and 12.6% also had positive Anti-Tg. All subjects with positive Anti-Tg at the same time had positive Anti-TPO. Among all participants, 12 subjects (10.1%)

had overt hypothyroidism and 18 subjects (15.1%) had subclinical hypothyroidism. Eighty nine subjects (74.8%) also had normal thyroid function. No cases of overt or subclinical hyperthyroidism were observed.

Table 2: laboratory findings in study population

Variable	Mean (SD)	Range
fT_4 (ng/ml)	1.2 (0.32)	0.8-1.60
TSH (mIU/l)	3.2 (1.1)	0.7-3.9
Anti-TPO Ab (IU/m)	153.84 (405.74)	0.9-2000
Anti-TgAb (IU/m)	183.33 (689.04)	0.1-5000
Anti-TPO Ab positivity (%)	34 (28.6%)	
Anti-TgAb positivity (%	15 (12.6%)	
Anti-TPO and Anti-TgAb positivity (%)	15 (12.6%)	

TSH: thyroid stimulating hormone; FT_4: free thyroxin; Anti TPO: antithyroid peroxidase; Anti Tg: antithyroglobulin

After dividing the patients into two groups based on the positive or negative thyroid antibodies, a clear difference was not found between the two groups in terms of age, gender, age at onset of diabetes, duration of diabetes, HbA_1C, and TSH concentrations. But the incidence of subclinical and overt hypothyroidism was significantly different between the two groups (Table 3).

Table 3: clinical and laboratory characteristics of patients with and without positive antibodies

variable	Patients with positive thyroid antibody (n=34)	Patients withouth positive thyroid antibody (n=85)	P value
Age (years)	13.1 (2.83)*	13.7 (3.13)	NS
Sex (female)	30 (88.23%)	45 (52.94%)	0.02
Duration of DM (years)	4.16 (1.30)	4.06 (2.63)	NS
Age at onset of DM (years)	6.09 (1.59)	6.43 (2.05)	NS
HbA1c (%)	8.98 (1.61)	8.08 (1.56)	NS
fT4 (ng/ml)	1.1 (0.72)	1.5 (0.22)	NS
TSH (mIU/l)	3.09 (1.31)	2.91 (1.79)	NS
Anti-TPO Ab (IU/m)	195.30 (437.73)	12.50 (11.07)	<0.001
Anti-TgAb (IU/m)	489.35 (691.06)	29.10 (18.70)	<0.001
Subclinical hypothyroidism	14 (41.17%)	4 (4.70%)	0.005
Overthypothyroidism	10 (29.41%)	2 (2.35%)	0.02

* *Mean (SD)*

TSH: thyroid stimulating hormone; FT4: free thyroxin; Anti TPO: antithyroid peroxidase; Anti Tg: antithyroglobulin

As shown in table 4, in multiple logistic regression, various factors such as gender, age and diabetes duration had no effect on the incidence of thyroid autoimmunity.

Table 4: Effective factors in thyroid autoimmunity

variable		Patients with positive thyroid antibody	Patients without positive thyroid antibody	All patients	OR	95% CI	P value
Age (years)	**<10**	20	59	79	0.63	0.27-1.43	0.28
	≥10	14	26	40			
Gender	**Female**	30	49	79	0.41	0.17-1.03	0.06
	Male	4	36	40			
Duration of diabetes (years)	**<5**	21	57	78	0.79	0.34-1.81	0.67
	≥5	13	28	41			

CI: confidence interval, OR: odds ratio

DISCUSSION

In this study, a total of 119 patients with type I diabetes were attended that positive anti-TPO was found in 34 cases (28.6%) and positive anti-Tg was also found in 15 cases (12.6%). All the people who had positive anti-Tg at the same time had positive anti-TPO. Overt hypothyroidism was observed in 12 cases (10.1%) and subclinical hypothyroidism in 18 patients (15.1%). Eighty nine subjects (74.8%) also had normal thyroid function.

Several studies have shown that type I diabetes has a strong association with other autoimmune diseases, and among these diseases, thyroid autoimmune thyroid disorder, is the most common disease [13, 15, 16, 28, 29].The reason for this association is not clear and probably an environmental factor in a genetic predisposition is the cause of these diseases. Increasing response against specific antigens, the inability to develop tolerance to certain antigens or

antigen specific to individual tissues have been suggested as predisposing factors [26]. Several factors are associated with thyroid autoimmunity such as heredity, aging, female sex, puberty, estrogen, pregnancy and a diet rich in iodine [27, 30].The prevalence of positive thyroid antibodies in patients with type I diabetes is 28.6% on average that varies between 3-50% in different studies. In recent studies higher mean of antibody is reported that can be related to improving measurement techniques, furthermore, increasing the amount of iodine intake diet also leads to increased incidence of thyroid autoimmunity[10, 21-23].

The results of this study on the prevalence of thyroid antibodies were similar to previous studies[12, 31], but this prevalence is lower than in other studies [32, 33].Also, in this study, no cases of clinical or subclinical hyperthyroidism were observed. But overt hypothyroidism was found in 10% of cases and subclinical was found in 15% of cases that these differences can be attributed to differences in mean age and genetic background of individuals under study compared with previous studies. In accordance with previous studies, the prevalence of autoimmunity and thyroid autoimmune disease is more common in women than men[34, 35]. The limitation of our study is the lack of a control group. Also the lack of measurement of urinary iodine is another limitation of this study.

Autoimmune thyroid disease in patients with type I diabetes has high incidence. Hypothyroidism is higher than other thyroid disorders. Thyroid autoimmune disorders is high in females with type I diabetes and patients with positive Anti-TPO. Due to the high incidence of thyroid dysfunction in diabetic patients, periodic assessment of thyroid function in these patients appears to be essential for early diagnosis and treatment.

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Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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