Thyroid function and thyroid autoimmunity in patients with type 1 diabetes mellitus

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ABSTRACT

Objective: An association between diabetes mellitus and autoimmune thyroid disease is well known. We have investigated the prevalence of thyroid dysfunction and autoimmunity in type 1 diabetic patients.

Methods: Seventy-nine type 1 diabetic patients were recruited in the study, and underwent complete investigations for thyroid function, which included free thyroxine, free tri-iodothyronine, and thyroid stimulating hormone, of those only 64 patients had performed thyroid autoantibodies (TAb); anti-thyroid peroxidase antibodies (TPOAb) or antimicrosomal antibodies and thyroglobulin antibodies (TgAb). They were compared with 127 healthy subjects matched for sex and age. This study was carried out at the National Center for Diabetes, Endocrinology and Genetics, Jordan University, Amman, Jordan between 2000 and 2001.

Results: In the diabetic group, 7 cases (8.9%) of thyroid dysfunction were detected, 4 of these were diagnosed as subclinical hypothyroidism, whereas the other 3 had overt hypothyroidism and were on thyroxine replacement therapy. In the control group, 6 (4.7%) subjects were diagnosed as subclinical hyperthyroidism. There was a significant difference in thyroid function variables between diabetics and controls. Among type 1 diabetic patients, 7 (9.2%) had thyroid autoantibodies, 5 with positive TPOAb only and 2 with positive TAb; TPOAb or antimicrosomal antibodies and TgAb; compared with 8 (6.3%) in the control group, 4 with positive TPOAb only and 4 with positive TAb; TPOAb or antimicrosomal antibodies and TgAb P=0.68.

Conclusion: Biochemical thyroid dysfunction and thyroid autoimmunity were evident in type 1 diabetics who were apparently euthyroid, with no significant difference between diabetics and controls.

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The association between type 1 diabetes mellitus (T1DM) and autoimmune thyroid disease has long been recognized.[1] In several studies of children and adults with T1DM, a high prevalence of thyroid autoantibodies (TAb) (8-44%) has been found as an indicator of thyroid autoimmune disease.[1-7] Most of those antibody-positive diabetic patients were clinically and biochemically euthyroid. It is uncertain how many of them will later develop thyroid dysfunction. The thyroid antibodies detected in previous studies have primarily been against thyroglobulin and microsomal antigens. It is now possible to measure the more sensitive and antigen-specific anti-thyroid peroxidase antibodies (TPOAb).[8,9] However, TAb does not always appear in

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the serum of patients with autoimmune thyroid diseases.[10] In the present study, we determined the prevalence of thyroid dysfunction and TAb abnormalities in T1DM patients compared with age and sex matched healthy controls. The aim of the present study was to assess the prevalence of thyroid dysfunction and autoimmunity in T1DM Jordanian patients attending the National Center for Diabetes, Endocrinology and Genetics in Amman, Jordan.

Methods.

All patients with T1DM receiving care at the National Center for Diabetes, Endocrinology and Genetics, Jordan University, Amman, Jordan between 2000 and 2001, were eligible for the study. A total of 79 patients were recruited in the study; 41 females (60%) and 38 males (40%) with a mean age of 19.6 ± 9 years (range 3-43) and a mean duration of diabetes of 5.96 ± 6.64 years (range 1-32). Three patients were known cases of hypothyroidism and were on L-thyroxine treatment. The age and sex matched control group, residing in the same geographical area, included 127 healthy subjects. The mean age of the control group was 20.9 ± 5.5 years (range 7-30). At the time of the study, none of the participants had acute or recent illness nor were receiving any drugs affecting thyroid function. All participants underwent complete physical examination. Venous blood samples were withdrawn and assayed for determination of thyroid function: free thyroxine (FT4), free tri-iodothyronine (FT3), thyroid stimulating hormone (TSH), anti-TPOAb or antimicrosomal antibodies (AMAb), thyroglobulin antibodies (TgAb) and glycosylated hemoglobin (HbA1c). Tests were either directly analyzed from venous blood samples or serum was frozen at -20ºC until analysis. All participants gave informed consent and the study was approved by the ethical committee of the Center.

Biochemical measurements. Serum free thyroxine (normal range 9.1-23.8 pmol/l), serum FT3 [normal range 2.58-5.44 pmol/L] and serum TSH (normal range 0.40-5.0 mU/L) were determined by enzyme linked immunoassay (ELISA) (microparticle enzyme immunoassay, Abbott Lab United States of America). Serum anti-TPOAb (normal range <10 U/L) and serum TgAb (normal range <100 U/L) were determined by Immunoradiometric Assay, Diasorin, Italy), AMAb normal range <15 were determined by ELISA method (Diasorin). Glycoslylated hemoglobin (normal range 4.2-6.2%) was determined by high performance liquid chromatography. The following guidelines for detection of thyroid dysfunction[11] were considered: Subclinical hypothyroidism: TSH >5 mU/L with normal FT4. Subclinical hyperthyroidism: TSH <0.1 mU/L with normal FT4 and normal FT3. Overt hypothyroidism: TSH >10 mU/L with T4 < normal value. Overt hyperthyroidism: TSH <0.1 mU/L with FT4 and FT3 > normal values, or both. Antibodies were considered positive if they were more than the normal range mentioned above.

Statistical analysis. The data was analyzed using Epi Info Version 6. Results were expressed as mean, standard deviation and ranges. The prevalence of thyroid dysfunction among T1DM patients and controls was compared using chi-square test; the student t test was used to compare the 2 groups with respect to continuous variables. P values of <0.05 were considered significant.

Results.

Four patients (5.1%) with T1DM were identified to have subclinical hypothyroidism; one male, aged 25 and 3 females, aged 10, 15 and 24 years. With the following TSH values 7.6, 5.36, 5.4 and 20.35 mU/l, and normal FT4. Three type 1 diabetic patients (3.8%) were known cases of hypothyroidism; 2 females aged 43 and 32 and one male aged 40 years. Therefore, the total percentage of thyroid dysfunction in the diabetic group is 8.9%. Six individuals (4.7%) in the control group have subclinical hyperthyroidism; 4 females aged 15, 15, 23 and 29 years and 2 males aged 29 and 27 years with the following TSH values: 0.02, 0.02, 0.04 0.08, 0.08, 0.04 mU/L, All other diabetic patients and controls were clinically and biochemically euthyroid. There was no significant difference in the prevalence of thyroid dysfunction (p = 0.37) between diabetics and controls, but there was a significant difference in thyroid hormones and TSH values **(Table 1)**. Among the type 1 diabetics, 7 patients (9.2%) had TAb (4 positive TPOAb, and 3 positive for TPOAb or AMAb and TgAb, 4 females and 3 males. Clinical characteristics and the level of TAb are presented in **Table 2** None of those 3 known cases of thyroid dysfunction had records of TAb levels. Three out of 4 patients with elevated TSH have one or more positive TAb. There were no significant differences between diabetics with and without autoantibodies in age, duration of diabetes, HbA1c, TSH or thyroid hormones. In the control group **(Table 3)** only 8 (6.3%) had TAb, 4 with positive TPOAb and TgAb that is not significantly different from the diabetic patients (p = 0.68). Thyroid autoantibodies levels were negative in all control individuals who have subclinical thyroid dysfunction.

Discussion.

In this study, thyroid dysfunction was present in 7 T1DM patients (8.9%). Three patients were already known cases of hypothyroidism and were receiving L-thyroxine treatment. Four patients were diagnosed for the first time with subclinical hypothyroidism; one of them had a significantly high level of TSH (20.35 mU/l). This prevalence of thyroid dysfunction is in agreement with some studies on T1DM patients[3,5] but lower than others which demonstrated 13.4% and 20% prevalence rate[12,16] of clinical or subclinical thyroid dysfunction. Our study confirms that patients with T1DM have a higher prevalence of TAb (9.2%) than healthy controls (6.3%), but without significant difference p = 0.68. Similar findings 8-44% were reported in several other studies.[1-3,5-7] Possible explanations for this wide range of TAb prevalence in

Table 1 - Characteristics and biochemical measurements in diabetic patients and controls.

Parameter	Diabetic patients (N=79)	Controls (N=127)	P value
Age (years)	19.6 ± 9	20.9 ± 5.5	0.125
TSH (mU/I)	2.14 ± 2.33	1.61 ± 0.08	0.0216
FT4 (pm/I)	13.35 ± 3.61	14.9 ± 0.52	<0.0008
FT3 (pm/I)	3.87 ± 1.77	4.6 ± 0.10	0.00012
HbA1c (%)	7.2 ± 3	Not available	-
Duration of type 1 diabetes mellitus (years)	5.96 ± 6.64	Not available	-

TSH - thyroid stimulating hormone, FT4 - free thyroxine,
FT3 - free tri-iodothyronine
HbA1c - glycosylated hemoglobulin

Table 2 - Characterstics of patients with elevated thyroid antibodies.

Sex	Age (years)	Duration of DM (years)	TPOAb (U/L)	TgAb (U/L)	TSH (mu/l)
Female	13	2	640	Negative	0.73
Female	10	2	550	1280	20.35
Female	10	2	314	245	5.36
Female	43	3	*19	92	2.55
Male	25	2	100	Negative	1.76
Male	25	23	100	Negative	7.60
Male	30	3	297	126	1.71

DM - diabetes mellitus, TSH - thyroid stimulating hormone
*AMAb - anti-microsomal antibodies
TPOAb - anti-thyroid peroxidase antibodies
TgAb - thyroglobulin antibodies

Table 3 - Clinical characteristics of control group with elevated thyroid antibodies.

Sex	Age (years)	TPOAb (U/L)	TgAb (U/L)	TSH (mu/l)
Female	24	447	316	1.61
Female	27	13	496	1.34
Female	13	17	19	2.12
Female	14	1100	187	0.12
Female	28	64	45	1.51
Female	18	65	40	3.27
Female	12	16	55	2.44
Male	15	100	333	1.67

TPOAb - anti-thyroid peroxidase antibodies
TgAb - thyroglobulin antibodies
TSH - thyroid stimulating hormone

T1DM might be due to ethnic variations, difference in iodine intake, a more sensitive assay in the latter study[7] or alternatively immunological abnormalities present at diagnosis of T1DM before the start of insulin treatment. We found antibody-positive patients in all age groups, which are in contrast to Lorini et al[13] who found only TAb in children older than 10 years. In our antibody-positive patients, the duration of diabetes varied between 2 and 23 years. Another study found a higher prevalence in patients with duration of diabetes more than 10 years, but also found an overall higher prevalence of 30%.[14] Previous studies reported that TAb are more frequent among females than males,[1,3,14] while our study and other studies[3,7] did not find such difference. It has been questioned whether TgAb provides further diagnostic information compared with the single use of TPOAb or AMAb in the diagnosis of thyroid autoimmune dysfunction.[15,18] In our study TAb directed against thyroglobulin (Tg) were positive in 3 of 7 antibody-positive patients for TPOAb. This may indicate that anti-TPOAb is a more sensitive parameter than TgAb.

In conclusion, we showed that a considerable number of patients with T1DM have markers of autoimmune thyroid disease and few of them have thyroid dysfunction and many have TAb. There was statistically significant difference in the values of T4, T3 and TSH between the diabetic and control subjects. There was no statistically significant difference in the presence of thyroid dysfunction, and thyroid antibodies between diabetics and control subjects. The high prevalence of TAb stresses the importance of early screening for thyroid dysfunction in patients with T1DM.

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Abstract

Most individuals produce auto-antibodies and autoreactive T lymphocytes but only about 5% of any population develop an autoimmune disease. Organ specific autoimmune diseases, including insulin dependent diabetes mellitus (IDDM), tend to target functional elements such as enzymes. A 64 kD protein is a major islet antigen associated with IDDM and at least part of the antigen complex has been identified as glutamic acid decarboxylase (GAD), which exists as multiple isoforms and both forms are recognized by diabetes-associated antibodies. About 80% or more of newly diagnosed patients with IDDM have autoantibodies to intact 64 kD and its trypsin-released fragments. These antibodies could be important predictors of subsequent disease in non-diabetic individuals. Strategies for disease prevention will involve identification of high risk individuals and their treatment with immunomodulation, which alters the immune response to critical antigens such as GAD.