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RESEARCH LETTER

Patients with diabetes type 1 and thyroid autoimmunity have low prevalence of microangiopathic complications

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Introduction

The prevalence of thyroid dysfunction in T1DM is higher than in general population [1–3]. Unrecognized thyroid dysfunction may impair metabolic control of diabetes [2, 4, 5]. Substantial proportion of patients with T1DM develop microangiopathic complications [6]. The significance of the coexisting comorbidity of AITD and T1DM in assessment of the risk of development of diabetic microangiopathy is unknown.

The aim of the present study was to determine the association between anti-thyroid antibody positivity and the presence of microangiopathy in adults with T1DM without prior evidence of the thyroid disease.

Materials and methods

We evaluated consecutive patients with type 1 diabetes under the cure of the Department of Internal Medicine and Diabetology in Poznan, Poland. T1DM was diagnosed based on the presence of classical symptoms at the onset, blood glucose concentration >11.1 mmol/l and the presence of at least one from assessed autoantibodies [islet cells (ICA), glutamic acid decarboxylase (anti-GAD), insulinoma-associated tyrosine phosphatase (IA-2A)] [7, 8].

Exclusion criteria were diabetes duration less than 5 years, diabetic ketoacidosis or ketonuria at the time of laboratory measurements, use of drugs affecting glucose metabolism, history of thyroid disease, treatment of thyroxin or anti-thyroid drug, use of other medications affecting thyroid function (glucocorticosteroids, propranolol, prescription drugs containing iodine, salicylates, phentoin, phenobarbital, carbamasepine), renal failure (estimated glomerular filtration rate—eGFR below 60 ml/min/1.72 m^2), anemia (hemoglobin level below 6.8 mmol/l).

All patients underwent a complete physical examination with anthropometric and blood pressure measurements.

Thyroid assays

Serum thyroid-stimulating hormone (thyrotropin, TSH), free triiodothyronine (fT3), and free thyroxin (fT4) levels were assessed using electrochemiluminescence ECLIA Elecsys analyzers.

Normal range for TSH was 0.27–4.2 mU/l. The evaluation of TSH and free thyroid hormones was performed in patients in stable metabolic state of glycaemia between 70 and 180 mg/dl, absence of ketonuria.

Anti-thyroperoxidase autoantibodies (ATPO) and anti-thyroglobulin antibodies (ATg) were determined by the ARCHITECT ATPO and ATg assays. Results were expressed as international units per milliliter. Positive ATPO was defined as level of ATPO above 5.61 IU/ml and ATg above 4.0 IU/ml.

Anti-TSH receptor antibodies (TRAb) were determined by EUROIMMUN ELISA test. Positive TRAb was defined as level of TRAb above 2 IU/ml.

Thyroid ultrasonography was performed using Accuson Cv 70, Siemens with 2–10 MHz linear transducer.

Overt hypothyroidism was recognized if TSH was greater than 4.2 mU/l and fT4 levels lower than normal or TSH greater than 10 mU/l, subclinical hypothyroidism

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(SCH) if TSH was greater than 4.2–10 mU/l with free thyroid hormones in normal range. Subclinical hyperthyroidism was recognized if TSH was less than 0.27 mU/l and free thyroid hormones in normal range.

The diagnosis of AITD disease was based on the presence of anti-thyroid autoantibodies ATPO, ATg, TRAb, and ultrasonography (volume of thyroid, hypoechogenicity, lymph nodes).

Evaluation of microangiopathy

We diagnosed diabetic retinopathy using direct ophthalmoscopy through dilated pupils. Diabetic retinopathy was graded according to the classification of the American Academy of Ophthalmology as no retinopathy, mild non-proliferative, moderate non-proliferative, severe non-proliferative, and proliferative retinopathy [9].

We diagnosed diabetic kidney disease in the stage of albuminuria. We assessed urinary albumin excretion over 12 h. We recognized albuminuria in the case of urinary albumin excretion rate between 30 and 300 mg/24 h in two of three samples collected over 3 months. Before examination, the secondary causes of proteinuria (urinary tract infection, heart failure, acute febrile illness, hematuria, excessive physical activity) were excluded. We made the diagnosis of diabetic kidney disease in the case of persistent albuminuria and diabetes duration over 10 years or confirmed diabetic retinopathy [10].

We evaluated peripheral neuropathy using pressure perception assessment (10 g monofilament), vibration perception (128 Hz tuning fork), and ankle reflex tests. Diabetic neuropathy was defined as the presence of two or more of the following four components: symptoms of neuropathy, absence of ankle tendon reflexes, abnormal scores for pressure, and/or of vibration perception [11].

Cardiovascular autonomic neuropathy assessment was performed based on clinical examination (resting tachycardia—heart rate more than 100 beats per minute, orthostatic hypotension—defined as the fall in systolic blood pressure of at least 20 mmHg and diastolic blood pressure of at least 10 mmHg in standing position) and evaluation of heart rate variability (HRV) (PROSCICARD III CPS MEDICAL) [12, 13].

Microangiopathy was defined as the presence of any of the microvascular complication such as retinopathy, neuropathy, and/or diabetic kidney disease or combination of them. The clinical characteristic of the study group is presented in Table 1.

Statistical analysis

In statistical analysis, Fisher exact test was used to compare frequencies in analyzed groups. Multivariate logistic regression was used to adjust for effect of variables that may modify the risk of diabetic complications.

Results

The prevalence of thyroid autoimmunity (positivity for ATPO or ATg or TRAb) in the study group was 31 %. In patients with AITD, 26 % were positive for only ATPO and 19 % for only ATg, 58 % for both antibodies, 3 % for TRAb. Subclinical hypothyroidism was diagnosed in 7 %, overt hypothyroidism in 2 % patients, and subclinical hyperthyroidism in 1 % of patients.

In the study group, 35 subjects had diagnosed at least one of microangiopathic complications. There was similar percentage of microvascular complications in T1DM subjects with newly diagnosed hypothyroidism in comparison to euthyroid ones (33.3 vs 36.3 %, $p = 1$). Among patients with AITD prevalence of any microangiopathy and prevalence retinopathy was lower than in patients without AITD [3 of 31 patients (9.7 %) vs 32 of 69 (46.4 %), $p = 0.0003$, 2 of 31 patients (6.5 %) vs 30 of 69 (43.5 %), $p = 0.00016$]. In multivariate logistic regression model, the presence of anti-thyroid antibodies was associated with lower odds of microangiopathy independently of sex, age, body mass index (BMI), cigarette smoking, systolic blood pressure, HbA1c value, serum TSH, and LDL-cholesterol concentrations (OR 18.3, 95 % CI 3.7–89.6, $p = 0.0003$).

Disscusion

In our study, nearly one-third of patients without previously diagnosed thyroid disease presented positivity for thyroid autoantibodies. This group of patients had higher level of TSH and 23 % of them manifested subclinical and over hypothyroidism. The present and previous studies suggest that only screening for thyroid autoimmunity in T1DM may identify large number of patients at risk of impaired thyroid function [4, 14].

In the literature, there are few studies which showed the association between SCH and microvascular complications in type 2 diabetes. In Asian patients with type 2 diabetes, the association between SCH and risk of retinopathy was found [15, 16].

In the patients with type 2 diabetes and prediabetes, subjects with SCH prevalence of microalbuminuria were higher in comparison to euthyroid ones [17].

Surprisingly, we demonstrated that patients with T1DM and positive thyroid antibodies develop less microangiopathy in comparison to group without AITD.

Traditionally, factors to protect against the diabetic microangiopathy are considered good metabolic control of

Table 1 The clinical characteristic of the study population. Comparison of groups with positive thyroid autoantibodies (autoimmune thyroid disease-AITD) with group without autoantibodies (median and IQR or mean ± SD or percentage of patients)

	All patients	Group with AITD	Group without AITD	*p* value (*)
n	100	31	69	
Sex (women/men)	47/53	19/12	26/43	**0.032**
Age (years)	29 (±6)	30 (±5)	29 (±6)	0.18
Duration of diabetes (years)	13 (±6)	12 (±4)	13 (±6)	0.30
Smoking (*n*) (%)	21 (21 %)	6 (19.4 %)	15 (21.7 %)	1
BMI (kg/m^2)	24.8 (±4.2)	24.1 (±3.6)	25.2 (±4.4)	0.23
Waist circumference (cm)	84.8 (±12.7)	82.4 (±10.6)	85.9 (±13.5)	0.21
WHR	0.84 (±0.09)	0.82 (±0.08)	0.85 (±0.10)	0.084
SBP (mmHg)	127 (±13)	127 (±16)	127 (±12)	0.96
DBP (mmHg)	79 (±9)	79 (±10)	79.77 (±8)	0.68
HbA1c (%)	7.7 (±1.3)	7.4 (±1.2)	7.9 (±1.3)	0.069
FBG (mmol/l)	8.0 (±2.8)	8.1 (±2.9)	8.1 (±2.7)	0.99
PBG (mmol/l)	9.1 (±3.3)	8.6 (±2.6)	9.3 (±3.5)	0.27
Mean daily glycemia (mmol/l)	7.8 (±1.7)	7.5 (±1.7)	7.9 (±1.7)	0.25
TSH (uIU/mL)	2.50 (±2.42)	3.57 (±3.72)	2.02 (±1.28)	**0.0025**
FT3 (pmol/l)	11.45 (±1.43)	11.53 (±1.43)	11.42 (±1.43)	0.67
FT4 (pmol/l)	15.95 (±6.04)	14.67 (±2.44)	16.09 (±7.08)	0.17
eGFR (ml/s m^2)	85.4 (±8.6)	84.6 (±7.3)	85 (±9.1)	0.55
Albumin/creatinine ratio (mg/g)	35.3 (±141.7)	5.7 (±11.8)	49.1 (±169.9)	0.16
TC (mmol/L)	4.8 (±1.1)	4.6 (±1.0)	4.9 (±1.0)	0.22
HDL (mmol/L)	1.7 (±0.4)	1.8 (0.4)	1.7 (±0.4)	0.16
LDL (mmol/L)	2.9 (±0.9)	2.8 (±0.8)	2.9 (±1.0)	0.48
TAG (mmol/L)	1.1 (±0.6)	0.9 (±0.4)	1.2 (±0.7)	0.022
hs-CRP (mg/L)	2.0 (±2.7)	1.7 (±3.1)	2.2 (±2.5)	0.50
HRV index	10.57 (±4.61)	11.83 (±4.77)	10.00 (±4.45)	0.067
Hypertension (*n*) (%)	21 (21)	6 (19.4)	15 (22.4)	0.8
Microangiopathy (*n*) (%)	35 (35 %)	3 (9.7 %)	32 (46.4 %)	**0.00027**
Diabetic retinopathy (*n*) (%)	32 (32 %)	2 (6.5 %)	30 (43.5)	**0.00016**
Diabetic nephropathy (*n*) (%)	10 (10 %)	1 (3.2 %)	9 (13 %)	0.17
Diabetic neuropathy (*n*) (%)	6 (6 %)	0 (0 %)	6 (8.7 %)	0.17

Bold values are statistically significant ($p < 0.05$)

BMI body mass index, *WHR* waist-to-hip ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HbA1c* glycosylated hemoglobin, *FBG* fasting blood glucose, *PBG* postprandial blood glucose, *TSH* thyroid-stimulating hormone, *fT3* free triiodothyronine, *fT4* free thyroxin, *eGFR* glomerular filtration rate estimated using Modification of Diet in Renal Disease (MDRD) study equation, *TC* total cholesterol, *LDL* low-density lipoproteins, *HDL* high-density lipoproteins, *TAG* triglycerides, *hs-CRP* high-sensitivity C-reactive protein, *HRV index* heart rate variability index

* *p* value for comparison with group without autoantibodies

diabetes, early diagnosis and treatment of hypertension and dyslipidemia, maintaining a normal body weight, cessation of smoking [18, 19]. Our study provides new insight into the process affecting the progress of microvascular complications in diabetes. Probably, genetic profile of patients with polyglandular autoimmune syndrome causes that they are protected against the development of diabetic microangiopathy, despite higher risk of overt thyroid disease and other organ-specific disorders [4]. To our knowledge, this is the first study that demonstrated relationship between thyroid autoimmunity and lower rate of microvascular complications in T1DM.

Conclusions

Thyroid autoimmunity was associated with lower rate of microangiopathic complications in patients with T1DM. Prospective studies are needed to determine the causality of this finding.

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Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethics approval The study was approved by the Ethical Committee of Poznan University of Medical Sciences. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

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