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Prevalence of Anti-Thyroid Peroxidase in Adults with Type 1 Diabetes Participating in Poznań Prospective Study*

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Type 1 diabetes (DM 1) is frequently associated with autoimmune thyroid diseases (AITD). Screening for AITD in adults is rarely performed. The aim of this study was to evaluate the prevalence of anti-thyroid peroxidase (anti-TPO) and thyroid function and their association with metabolic control in adults participating in Poznan Prospective Study (PoProStu).

Material and Methods. The analysis included 74 patients (26 women and 48 men) aged 38.5 (IQR: 34.5–42.5), who have had diabetes for 15.0 (14–16) years. All patients have been treated with intensive functional insulin therapy (IFIT) from the onset of the disease. Anti-TPO and thyroid-stimulating hormone (TSH) were determined. The concentration of anti-TPO ≥ 5.61 IU/mL was considered positive. Based on the levels of anti-TPO the patients were divided into two groups: anti-TPO positive and anti-TPO negative. Metabolic control was assessed by the level of glycated hemoglobin (HbA_{1c}).

Results. Anti-TPO was positive in 32 (43.2%) patients. Prevalence of autoantibodies was significantly higher in women (53% vs 21%; p = 0.009). There was no significant difference in HbA_{1c} levels [median (IQR): 7.6% (7.1–8.6) vs 7.6% (7.1–8.8); p = 0.82] and TSH levels [median (IQR): 2.05 μIU/mL (1.23–3.15) vs 1.62 μIU/mL (1.00–2.10); p = 0.06] between anti-TPO positive and negative patients. After excluding patients with a thyroid dysfunction, a significant difference in TSH levels between anti-TPO positive and negative group was found [median (IQR): 2.11 μIU/mL (1.29–3.31) vs 1.66 μIU/mL (1.29–3.31); p = 0.04].

Conclusions. High anti-TPO prevalence is found in adult patients with long-standing DM 1, and autoantibodies occur more often in women. Therefore, screening for asymptomatic thyroid dysfunction should be performed in this group, as already recommended by the joint statement of Polish Society of Endocrinology and Diabetes Poland (**Adv Clin Exp Med 2015, 24, 1, 79–84**).

Key words: type 1 diabetes, anti-thyroid peroxidase, metabolic control.

The prevalence of the autoimmune diseases is much higher in patients with type 1 diabetes (DM 1) than in the general population [1]. The most prevalent immunological diseases in patients with DM 1 are autoimmune thyroid diseases (AITD) and celiac disease. HLA genes as well as non-HLA genes, among others, the CTLA 4 gene, contribute to the shared susceptibility to both diseases [2–4].

The prevalence of positive peroxidase antibodies (anti-TPO) is estimated to be between 2% and 10% in the general population, whereas in the population of DM 1 patients it is much higher, reaching the level from 15% to 30% [5]. AITD with the presence of anti-TPO have been well described in pediatric patients. The literature confirms a high AITD prevalence in young adults with DM 1, with a predominance of females in this group [6].

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AITD incidence increases with longer DM 1 duration and higher anti-TPO prevalence [7]. Kordonouri et al. reported that after the mean time of 3.5 years after the first detection of anti-TPO in serum, 50% of children would develop thyroid dysfunction defined as elevated TSH levels (≥ 4.5 μIU/mL) and/or changes in sonography [8]. Kalicka-Kasperczyk et al. observed that newly diagnosed DM 1 is accompanied by a simultaneous diagnosis of thyroid dysfunction in 4.6% of Polish children [9].

The majority of the published studies so far are concerned with AITD prevalence in children or young adults. There are few reports on adults with long-standing DM 1. The need for screening for thyroid dysfunction was postulated 3 decades ago [10]. Currently, screening for AITD, according to Diabetes Poland [11], is recommended only in children, youth and pregnant women. International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines recommend controlling TSH level at the time of first diagnosis of DM 1 and every 2 years in patients without symptoms and goiter [12]. American Diabetes Association (ADA) recommends TSH control in all patients with DM 1, dyslipidemia or over the age of 50 if it has not been performed within the preceding year [13]. However, none of the above mentioned guidelines refer to regular TSH and anti-TPO control in adults from the diagnosis of DM 1. The only guidelines advising regular control of patients with positive anti-TPO level, and containing a regular description thereof are "Recommendations of the Polish Society of Endocrinology and Polish Diabetes Association". They concern management and treatment of thyroid dysfunction in patients with diabetes [14].

The aim of this study was to evaluate the prevalence of anti-TPO and thyroid function, as advised in "Recommendations of the Polish Society of Endocrinology and Polish Diabetes Association", and their association with metabolic control in adults with DM 1 participating in Poznan Prospective Study (PoProStu).

Material and Methods

The cross-sectional analysis included 74 patients with DM 1 (26 women and 48 men) in the mean age 38.5 years participating in PoProStu. PoProStu was designed as a prospective study. Recruitment was carried out in the years 1994–1999. Prospective observation comprised 100 consecutive patients with newly diagnosed DM 1 aged below 35 years, hospitalized due to diabetic ketoacidosis at the Department of Internal Medicine and Diabetology in Poznan [15]. All patients have been treated with intensive functional insulin therapy (IFIT) from the onset of the disease. The data was derived from the follow-up conducted from October to December 2012 at the Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences. The study was approved by the local Ethics Committee. The aims of the study were explained to the participants who gave written consent. The study is registered at ClinicalTrials.gov (NCT 01411033). Clinical characteristics of the study group are presented in Table 1.

Anti-TPO and thyroid-stimulating hormone (TSH) were determined. Metabolic control was assessed by the level of glycaeted hemoglobin (HbA_{1c}), lipid profile, systolic and diastolic blood pressure.

Plasma glucose, total cholesterol, high density lipoproteins (HDL) cholesterol, low density lipoproteins (LDL) cholesterol, triglycerides, high

Table 1. Clinical characteristics of the study group

N	74
Sex (m/f)	48/26
Age (years)	38.5 (34.5–42.5)
DM 1 duration (years)	15.0 (14–16)
Insulin demand (units/kg/day)	0.6 (0.5–0.7)
Body mass (kg)	76.5 (68.0–86.4)
BMI (kg/m^2)	24.9 (22.5–27.7)
Waist circumference (cm)	87.6 (82.3–96.0)
WHR	0.9 (0.8–0.9)
SBP (mm Hg)	132.5 (120.7–142.0)
DBP (mm Hg)	83.0 (77.0–90.3)
HbA 1c (%)	7.6 (7.1–8.7)
hsCRP (mg/L)	1.2 (0.6–2.8)
Total cholesterol (mmol/L)	5.2 (4.5–5.8)
LDL Cholesterol (mmol/L)	3.1 (2.4–3.8)
Triglycerides (mmol/L)	1.0 (0.7–1.3)
HDL cholesterol (mmol/L)	1.6 (1.4–2.0)
TSH (μIU/mL)	1.9 (1.2–2.4)
Anti-TPO (IU/mL)	0.8 (0.1–146.0)
Creatinine (mg/dL)	0.87 (0.78–0.97)
eGFR (mL/min)	90.7 (84.5–108.2)
Retinopathy n (%)	28 (38%)
Nefropathy n (%)	28 (38%)
Neuropathy n (%)	17 (23%)

Data shown as median (IQR), number (%) of patients, BMI – body mass index, WHR – waist-hip ratio, SBP – systolic blood pressure, DBP – diastolic blood pressure, TSH – thyroid stimulating hormone, LDL – low-density lipoprotein, HDL – high-density lipoprotein, hsCRP – high sensivity C-reactive protein, anti-TPO – anti-thyroid peroxidase, eGFR – estimated glomerular filtration rate.

sensitivity C-reactive protein (hsCRP) and creatinine levels were measured using standard methods. Estimated glomerular filtration rate (eGFR) was calculated using Modification of Diet in Renal Disease (MDRD) formula.

Quantitative levels of anti-TPO were measured by Chemiluminescent Microparticle Immunoassay (CMIA) on Architect i 2000SR (ABBOT Laboratories). Levels of anti-TPO below 5.61 IU/mL were considered normal for the population in question by the laboratory. Serum TSH concentration was measured by electrochemiluminescent immunoassays (ECLIA) in the Elecsys 2010 immunoassay system. HbA_{1c} was measured using high-performance liquid chromatography (HPLC) with Variant Haemoglobin A 1c Program (Bio-Rad Laboratories, Hercules, CA, USA).

Based on the levels of anti-TPO, the patients were divided into 2 groups: anti-TPO positive and anti-TPO negative. After excluding patients with a diagnosis of thyroid dysfunction, we divided them into subgroups by the TSH cut-off levels of 2 and 2.5 μIU/mL. The prevalence of anti-TPO was analysed above and below the cut-off level in each subgroup.

Statistical analysis was performed using STATISTICA 8. The results of continuous variables are shown as median values (IQR) and number and percentage of patients for categorical data. Mann-Whitney *U* test was used to compare subgroups. Chi square test was used to compare frequencies. P value < 0.05 was considered statistically significant.

Results

Anti-TPO levels outside the normal range were observed in 32 patients (43.2%). Antibodies were more prevalent in women (53% vs 21%; p = 0.009) (Table 2). In 9 subjects hypothyroidism had been previously diagnosed and at the time of the study they were treated with levothyroxine and, except in one patient, remained euthyroid. Negative anti-TPO level was found only in 1 person in this subgroup. One person had been

Table 2. Clinical characteristics and assessment of metabolic control in patients with positive TPO antibodies (anti-TPO+) and TPO antibodies concentration within normal range (anti-TPO-)

Parameter	Anti-TPO(+)	Anti-TPO(–)	p
Sex (m/f)	15/ 17	33/ 9	0.009
Age (years)	39.0 (36.0–41.0)	37.5 (34.0–43.0)	ns.
Diabetes duration (years)	15.0 (14.0–16.5)	15.0 (14.0–15.0)	ns.
Insulin demand (units/kg/day)	0.66 (0.51–0.77)	0.59 (0.44–0.64)	0.018
Body mass (kg)	73.0 (66.6–85.7)	78.8 (70.0–89.7)	ns.
BMI (kg/m^2)	25.7 (22.3–27.8)	24.2 (22.7–27.5)	ns.
Waist circumference (cm)	86.8 (80.0–95.2)	87.7 (83.0–100.3)	ns.
WHR	0.85 (0.80–0.90)	0.90 (0.84–0.93)	ns.
SBP (mm Hg)	132.5 (115.8–145.7)	132.4 (122.0–139.7)	ns.
DBP (mm Hg)	84.7 (78.0–90.9)	82.4 (77.0–87.3)	ns.
HbA 1c (%)	7.6 (7.1–8.6)	7.6 (7.1–8.8)	ns.
hsCRP (mg/L)	1.25 (0.67–2.68)	1.19 (0.51–2.92)	ns.
Total cholesterol (mmol/L)	5.30 (4.52–6.10)	5.20 (4.45–5.52)	ns.
LDL Cholesterol (mmol/L)	3.17 (2.76–3.94)	2.97 (2.25–3.47)	ns.
Triglycerides (mmol/L)	0.94 (0.76–1.13)	0.98 (0.72–1.33)	ns.
HDL cholesterol (mmol/L)	1.72 (1.37–2.10)	1.61 (1.45–1.94)	ns.
TSH (μIU/mL)	2.05 (1.23–3.15)	1.62 (1.00–2.10)	ns.
Anti-TPO (IU/mL)	172.22 (56.03–389.63)	0.10 (0.01–0.50)	< 0.001
Creatinine (mg/dL)	0.84 (0.74–0.94)	0.86 (0.82–1.02)	ns.
eGFR (mL/min)	90.7 (85.5–101.9)	92.0 (82.7–111.0)	ns.

Mann-Whitney test, χ^2 test. Data shown as median (IQR), number of patients, BMI – body mass index, WHR – waist-hip ratio, SBP – systolic blood pressure, DBP – diastolic blood pressure, hsCRP – high sensivity C-reactive protein, LDL – low-density lipoprotein, HDL – high-density lipoprotein, TSH – thyroid stimulating hormone, anti-TPO – anti-thyroid peroxidase, eGFR – estimated glomerular filtration rate.

diagnosed with hyperthyroidism and treated with thiamazol. In this person, positive anti-TPO level was found. At the time of the study 1 person with positive anti-TPO antibodies was diagnosed with hyperthyroidism on the basis of TSH result.

Between the 2 groups with and without antibodies, the difference in antibodies level was significant [median (IQR): 172.22 IU/mL (56.03–389.63) vs 0.10 IU/mL (0.01–0.50); p < 0.001].82] (Table 2). There was no significant difference in HbA_{1c} [7.6% (7.1–8.6) vs 7.6% (7.1–8.8); p = 0.82] and TSH levels [2.05 μIU/mL (1.23–3.15) vs 1.62 μIU/mL (1.00–2.10); p = 0.06] (Table 2). Statistically significant difference in insulin demand was found [0.66 units/kg/day (0.51–0.77) vs 0.59 units/kg/day (0.44–0.64); p = 0.018] (Table 2). After excluding patients with thyroid dysfunction, significant difference in TSH levels between anti-TPO positive and negative group was found [2.11 μIU/mL (1.29–3.31) vs 1.66 μIU/mL (1.29–3.31); p = 0.04].

Analysing the subgroup divided by the TSH cut-off level of 2.5 μIU/mL we found a significantly higher prevalence of anti-TPO in patients with TSH ≥ 2.5 μIU/mL (85% vs 57%; p = 0.02; Fig. 1). In patients divided by the TSH cut-off level of 2 μIU/mL we did not observe statistically significant difference in the prevalence of anti-TPO between the groups with TSH above and below 2 μIU/mL (48% vs 74% respectively; p = 0.06).

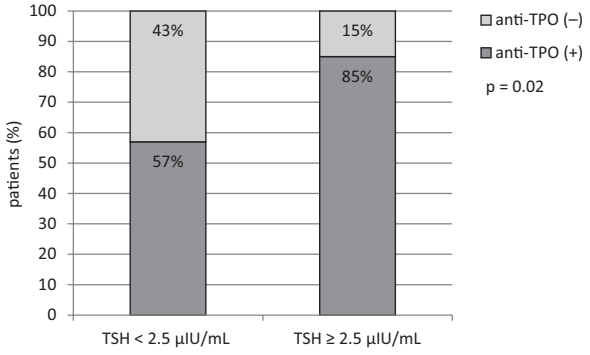

Fig. 1. Prevalence of anti-TPO according to TSH after excluding patients with thyroid dysfunction

Discussion

This cross-sectional study provides information that enables the assessment of thyroid dysfunction and the prevalence of anti-TPO, their association with TSH and metabolic control in adults with DM 1. The study, based on "Recommendations of the Polish Society of Endocrinology and Polish Diabetes Association", focuses on thyroid parameters used in clinical practice and, therefore, reflects real-life approach to thyroid screening in patients with DM 1.

According to the literature, the prevalence of anti-TPO is estimated to be between 15% and 30% in adults and 5% to 22% in children with DM 1, whereas its prevalence in the general population is found to be 10–13% and 1–4% respectively [1, 16]. However, in the quoted studies the mean diabetes duration was only 3.4 years. The positive correlation between the duration of diabetes and the presence of anti-TPO has been described by Kakleas K. and Umpierrez GE. [17, 18]. Higher prevalence of anti-TPO presented in our study might result from a longer mean diabetes duration. The mean disease duration of 15 years corresponds to 43% prevalence of anti-TPO. Similarly, in a study of patients with long-standing DM 1 (mean follow-up 18 years) by Umpierrez GE et al., the prevalence of anti-TPO was 33%. In other studies concerning patients with shorter disease duration the anti-TPO prevalence is much lower (19.3% and 21.8% respectively) [19, 20]. In a study conducted in Polish population, Madej A. reports the anti-TPO prevalence in 26.9% of patients with mean DM 1 duration of 12.7 years [21]. In our study we did not observe differences in disease duration between the 2 groups with and without antibodies. This might result from a prospective observation and homogeneity of the group in terms of DM 1 duration.

Studies have shown the presence of low-grade inflammation process in patients with AITD [22]. Elevated CRP levels correspond to inflammation and are found to be higher in patients with AITD [23], which is in accordance with our results: elevated, although not yet statistically significant, CRP level was found in anti-TPO positive group. There is evidence that insulin resistant, thus requiring greater insulin dose, type 1 diabetic men have an increased hs-CRP level, which reflects low grade-inflammation process [24]. We confirmed this observation in our study: insulin demand was found to be higher in anti-TPO positive group with the presence of low-grade inflammation process. Alternative explanation for our results might be the fact that patients with AITD and DM 1 are more apt to have poorer metabolic control reflected in hypo- and hyperglycaemias due to labile thyroid function [27, 29]. Poor metabolic control might contribute to greater insulin demand in such patients.

It has been reported that the risk of developing AITD is increased in patients with elevated thyroid autoantibodies [25]. According to the "Recommendations of the Polish Society of Endocrinology and Polish Diabetes Association" in patients with anti-TPO titer above the reference value and TSH ≥ 2 μIU/mL a full functional assessment, including free thyroxine (fT 4) concentration and TSH measurement once a year should be performed [14]. It

has been reported that in 95% of the general population TSH level was found to be below 2.5 μIU/ /mL [26]. The presented research shows that high anti-TPO prevalence is associated with TSH values ≥ 2.5 μIU/mL and screening for thyroid autoantibodies in patients with DM 1 might reveal subclinical cases of autoimmune thyroiditis. In this phase, the presence of autoantibodies might not yet influence the patients' metabolism, and diabetes control. Probable progression to clinically evident symptoms suggests further observation of patients with present autoantibodies.

Limitations of the study include not employing ultrasonography diagnostics and other laboratory measurements used in investigation of AITD such as autoantibodies against thyroglobulin (anti-TG), free triiodothyronine (fT 3) and fT 4 concentrations. USG examination enables the detection of characteristics for AITD changes, often preceding the occurrence of hormonal changes. However, this cross-sectional study was designed for screening and assessing thyroid function in patients remaining in observation within PoProStu. The aim of the research was not to go beyond screening tools advised in "Recommendations of the Polish Society of Endocrinology and Polish Diabetes Association". Therefore, only anti-TPO and TSH levels were used to determine the patients' thyroid status. Those 2 laboratory tests have many advantages in everyday clinical practice: they are easily accessible, well-known by doctors and convenient for patients (can be ordered alongside with routine blood tests).

Hypothyroidism might influence metabolic control in patients with DM 1 [27]. In subclinical hypothyroidism, implementing treatment improves HbA_{1c} and fasting plasma glucose levels [28]. In our study there was no difference between HbA_{1c} levels in the group with and without autoantibodies. The results are in accordance with reports from the literature, which also do not reveal this association [17, 18, 21]. One of the reasons for the lack of the differences might be the presence of good metabolic control in the phase when only autoantibodies are detected and thyroid function deterioration is not yet observed. On the other hand, another reason might be the fact that HbA_{1c} value points only to mean glycaemia value from the previous 3 months, not distinguishing between the actual good metabolic control and significant glycaemic fluctuations. Mohn et al. showed [29] that patients with hypothyroidism have more symptomatic hypoglycaemic episodes during 12 months preceding the diagnosis of hypothyroidism which might be the reason for lowering HbA_{1c} level in patients with poor metabolic control, falsely indicating good metabolic control in this group.

In conclusion, a high percentage of patients with positive anti-TPO and high prevalence of hypothyroidism in patients with positive anti-TPO presented in this study confirms that screening for AITD in DM 1 adult patients, particularly in women and patients with long-standing DM 1 is necessary. This remains in accordance with "Recommendations of the Polish Society of Endocrinology and Polish Diabetes Association" and confirms that simple parameters such as anti-TPO and TSH levels seem to be sufficient to identify patients with AITD.

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