RESEARCH LETTER

Organ-specific antibodies in first-degree relatives of patients with type 1 diabetes

Katarzyna Siewko[1], Anna Popławska-Kita[1], Beata Telejko[1],
Saeid S. Abdelrazek[2], Maria Górska[1], Małgorzata Szelachowska[1]

1   Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Białystok, Poland
2   Nuclear Medicine Department, Medical University of Bialystok, Białystok, Poland

Correspondence to:
Katarzyna Siewko, MD, Klinika
Endokrynologii, Diabetologii i Chorób
Wewnętrznych, Uniwersytet
Medyczny w Białymstoku,
ul. M. Skłodowskiej-Curie 24a,
15-276 Białystok, Poland,
phone: +48-85-74-68-239,
fax: +48-85-74-47-611, e-mail:
katarzynasiewko@go2.pl

Introduction   It is well known that type 1 diabetes is frequently associated with other autoimmune diseases, such as Graves disease (GD), Hashimoto thyroiditis (HT), Addison disease (AD), celiac disease (CD), and autoimmune gastritis.[1] It has been shown previously that up to 8% of type 1 diabetes patients may have celiac disease; up to 20% of them may have GD; 1% to 15% can develop AD; and 8% to 60% may have HT.[2-4] A typical feature of autoimmune disorders is the appearance of circulating autoantibodies to endocrine cell proteins, which can be used as the most sensitive prognostic marker in the preclinical state of the disease.[2,5] The presence of circulating autoantibodies against β-cell antigens, such as glutamic acid decarboxylase (GADA), insulin (IAA), and tyrosine phosphatase (IA-2A), as well as of the Zinc transporter autoantigen antibodies (ZnT8), identifies the underlying islet autoimmune pathology and an increased risk of type 1 diabetes. In a previous study, we found that the presence of islet antibodies was markedly higher in the first-degree relatives of type 1 diabetes patients than in individuals with no family history of diabetes.[6] Therefore, in the present study, we hypothesized that the presence of other organ-specific antibodies may be also more frequent in these subjects. To test the hypothesis, we compared the prevalence of anti-21-hydroxylase antibodies (21-OH-Abs), antigastric parietal cell antibodies (GPC-Abs), antithyroglobulin antibodies (TG-Abs), antithyroid peroxidase antibodies (TPO-Abs), and antithyroid-stimulating hormone receptor antibodies (TSHR-Abs) in first-degree relatives of patients with type 1 diabetes and healthy persons with a negative family history of type 1 diabetes.

PATIENTS AND METHODS   A total of 153 first-degree relatives (parents, siblings, and offsprings) of patients with type 1 diabetes were tested with a 75-gram oral glucose tolerance test, and subjects with an abnormal result as well as those treated for any inflammatory or immune diseases were excluded. Finally, the study group consisted of 90 first-degree relatives of patients with type 1 diabetes and 60 healthy individuals with no family history of diabetes or autoimmune disorders. Written informed consent was obtained from all participants before enrollment, and the protocol was approved by the Ethics Committee of the Medical University of Bialystok.

GADA, IAA, IA-2A, 21-OH-Abs, GPC-Abs, TG-Abs, TPO-Abs, and TSHR-Abs were measured by radioimmunoassays (CIS Bio International, France; test sensitivity, 95%; specificity, 97%). The cut-off values for each antibody positivity were calculated as the 99th percentile of the antibody level in 350 nondiabetic persons and were as follows: 1.0 U/ml for GADA, 9.8 U/ml for IAA, 0.75 U/ml for IA-2A, 1.0 U/ml for 21-OH-Abs, 10.2 U/ml for GPC-Abs, 2.2 U/ml for TG-Abs, 50.0 IU/ml for TPO-Abs and 1.5 U/ml for TSHR-Abs.

Statistical analysis was performed using the STATISTICA 10.0 software (Statsoft, Tulsa, Oklahoma, United States). Before analysis, data were tested for normality of distribution using the Shapiro–Wilk test. Differences between the groups were compared by the Mann–Whitney test and relationships between variables were tested by Spearman correlations. A P value of less than 0.05 was considered statistically significant.

RESULTS   The relatives of diabetic patients had significantly higher levels of GADA and IAA (P <0.05 and P <0.01, respectively) as well as 21-OH-Abs, GPC-Abs, TPO-Abs, and TSHR-Abs (P <0.01) in comparison with controls (**TABLE**). At least 1 positive antibody against pancreatic islet antigens was found in 31 relatives (34.4%) and in none of the controls: IAA were detected in 21 persons (23.3%); GADA, in 15 (16.7%); and IA-2A,

TABLE Clinical and biochemical characteristics of the study groups

	Study group (n = 90)	Control group (n = 60)	P value[a]
age, y	33.0 (18–65)	37.9 (18–65)	0.9
BMI, kg/m²	21.4 (16–29.0)	22.8 (18–28.2)	0.7
GADA, U/ml	0.8 (0.6–218.7)	0.7 (0.6–0.9)	<0.05
IAA, U/ml	6.8 (4.4–13.2)	4.5 (3.1–5.6)	<0.01
IA-2A, U/ml	0.6 (0.6–0.9)	0.6 (0.6–0.7)	0.7
21-OH-Abs, U/ml	0.6 (0.1–3.6)	0.2 (0.1–1.1)	<0.01
GPC-Abs, U/ml	2.6 (1.5–240.9)	2.0 (1.0–12.1)	<0.01
TPO-Abs, U/ml	6.1 (1.1–677.0)	3.7 (1.3–20.4)	<0.01
TG-Abs, U/ml	0.03 (0.01–0.2)	0.03 (0.01–0.2)	0.9
TSHR-Abs, U/ml	1.1 (0.5–7.4)	0.7 (0.1–1.1)	<0.01

Data are presented as median (minimum–maximum).

Abbreviations: BMI, body mass index; GADA, glutamic acid decarboxylase antibodies; GPC-Abs, antigastric parietal cell antibodies; IAA, insulin antibodies; IA-2A, tyrosine phosphatase antibodies; TG-Abs, antithyroglobulin antibodies; TPO-Abs, antithyroid peroxidase antibodies; TSHR-Abs, antithyroid-stimulating hormone receptor antibodies; 21-OH-Abs, antibodies to anti-21-hydroxylase

in 2 subjects (2.2%). Both IAA and GADA were found in 5 patients, and the presence of all 3 antibodies was noted in 1 patient. At least 1 other autoantibody was detected in 36 relatives (40%) and in 3 patients (5%) from the control group (GPC-Abs). Antithyroid antibodies were found in 26 relatives, including TPO-Abs in 26 patients (28.9%), TSHR-Abs in 10 patients (11.1%), and both antibodies in 10 patients (11.1%). None of the participants had positive TG-Abs, whereas GPC-Abs were found in 16 relatives (17.8%), and 21-OH-Abs—in 3 patients (3.3%).

In the group of relatives with positive antibodies against β-cell antigens, 29 patients (93.5%) had elevated concentrations of at least 1 other antibody: 23 of them had 1 additional antibody; 5 patients, 2 antibodies (TSHR-Abs and GPC-Abs in 2 of them, as well as TPO-Abs and TSHR-Abs in 5 of them); and 1, 3 antibodies (TSH-Abs, TPO-Abs, and GPC-Abs). From a subgroup of 5 relatives with 2 antibodies against β cell, 3 had 3 additional antibodies (TSHR-Abs, TPO-Abs, and GPC-Abs) and 2, 2 other antibodies (1 subject, TPO-Abs and GPC-Abs, and the second one, TPO-Abs and TSHR-Abs). The only relative with positive GADA, IAA, and IA-2A had also positive TPO-Abs, TSHR-Abs, and GPC-Abs. TPO-Abs were present in 20 relatives (64.4%) with positive β-cell antibodies; 21-OH-Abs, in 4 persons (12.9%) with positive GADA or IAA; GPC-Abs, in 13 relatives (41.9%); and TSHR-Abs, also in 13 relatives (41.9%) with positive anti-islet antibodies.

The levels of GPC-Abs, TPO-Abs, and TSHR-Abs were significantly higher in relatives with positive antibodies against β cells compared with relatives with no anti-islet antibodies (8.0 vs 2.5 U/ml, P <0.001; 102 vs 4.7 U/ml, P <0.001; 1.3 vs 1.0 U/ml, P <0.001, respectively). The concentrations of all antibodies did not differ between the subgroup of relatives without antibodies against β cell and controls.

In the whole group of relatives and in the subgroup with anti-islet antibodies, there was a positive correlation between IAA and TPO-Abs levels (r = 0.549, P <0.05 and r = 0.567, P <0.05, respectively).

DISCUSSION Our study showed that 34.4% of first-degree relatives of diabetic patients had at least 1 positive antibody against pancreatic islet antigens. Moreover, 40% of all relatives and 93.5% of those with positive anti-islet antibodies had other autoantibodies, mainly TPO-Abs, TSHR-Abs, and GPC-Abs. The presence of GPC-Abs was also noted in 3 persons from the control group. Furthermore, our study revealed that the relatives of diabetic patients had significantly higher levels of 21-OH-Abs, GPC-Abs, TPO-Abs, and TSHR-Abs compared with controls and that GPC-Abs, TPO-Abs, and TSHR-Abs concentrations were markedly higher in relatives with positive antibodies against β cells than in the subgroup without anti-islet antibodies.

According to previous reports, autoimmune thyroid disease affects from 15% to 30% of patients with type 1 diabetes; autoimmune gastritis, about 5% to 20%; and Addison disease, 1%.[1,3,7] In children of parents with type 1 diabetes, the cumulative risk of developing TPO-Abs was estimated at 4.3% by 8 years, 7.3% by 11 years, and 20.3% by 14 years,[8] whereas the prevalence of positive antithyroid antibodies (TPO-Abs and Tg-Abs) among first-degree relatives of type 1 diabetes patients ranged from 7.8% to 25%[7,9] and was significantly higher than the percentage found in controls. Furthermore, there is evidence that the presence of GADA substantially increases the risk of developing other organ-specific antibodies, in particular antithyroid antibodies, both in type 1 diabetes patients[10-12] and in their children.[8] In our study, positive TPO-Abs were found in 28.9% of all relatives and in 54.8% of those with positive anti-islet antibodies. Moreover, the level of TPO-Abs correlated with the IAA concentration, suggesting that not only the presence of GADA but also IAA increases the risk of developing other autoimmune disorders, in particular HT. The present study also showed a markedly higher frequency of TSHR-Abs and GPC-Abs in the relatives of type 1 diabetes patients as compared with controls (11.1% vs 0% and 17.8% vs 5.0%, respectively). The appearance of GPC-Abs was previously analyzed by Jeager et al.[7] in a large population of first-degree relatives and healthy individuals, but the authors did not find significant differences between the groups studied (6% vs 3.2%). The least frequently noted autoantibodies were antiadrenal antibodies, detected in 3.3% of the relatives participating in our study and in 1.1% of a large cohort examined by Jeager et al.[7] The prevalence of 2 or more autoantibodies in first-degree relatives was estimated as 3.1% by Jeager et al.[7] and 11.1% in the present study, with a higher percentage of TPO-Abs and GPC-Abs observed in our population.

The main limitation of our study is a single measurement of circulating antibodies, with no clinical follow-up, so we cannot compare the risk of developing autoimmune disorders in individuals with and without 1 or more autoantibodies. However, our results demonstrated a significantly higher prevalence of antithyroid and antigastric parietal cell antibodies in the first-degree relatives of type 1 diabetes patients, in particular in the group with positive anti-islet antibodies. The finding suggests that these subjects may be at a higher risk of developing not only type 1 diabetes, but also autoimmune thyroiditis and autoimmune gastritis, whereas routine screening for 21-OH-Abs seems unjustified.

REFERENCES

1 Van den Driessche A, Eenkhoorn V, Van Gaal L, De Block C. Type 1 diabetes and autoimmune polyglandular syndrome: a clinical review. Neth J Med. 2009; 62: 376-384.

2 Bonifacio E, Mayr A, Knopff A, Ziegler AG. Endocrine autoimmunity in families with type 1 diabetes: frequent appearance of thyroid autoimmunity during late childhood and adolescence. Diabetologia. 2005; 52: 185-192.

3 De Block CE, De Leeuw IH, Vertommen JJ, et al. Beta-cell, thyroid, gastric, adrenal and coeliac autoimmunity and HLA-DQ types in type 1 diabetes. Clin Exp Immunol. 2001; 126: 236-241.

4 De Graaff L, Martin-Martorell P, Baan J, et al. Long-term follow-up of organ-specific antibodies and related organ dysfunction in type 1 diabetes. Neth J Med. 2011; 69: 66-71.

5 Warncke K, Frohlich-Reiterer E, et al. Polyendocrinopathy in children, adolescents, and young adults with type 1 diabetes. Diabetes Care. 2010; 33: 2010-2012.

6 Siewko K, Popławska-Kita A, Telejko B, et al. Prognostic markers for the development of type 1 diabetes in first-degree relatives of diabetic patients. Endokrynol Pol. 2014; 65: 176-180.

7 Jaeger C, Hatziagelaki E, Petzoldt R, Bretzel RG. Comparative analysis of organ-specific autoantibodies and celiac disease - associated antibodies in type 1 diabetic patients, their first-degree relatives, and healthy control subjects. Diabetes Care. 2001; 24: 27-32.

8 Bonifacio E, Bingley PJ, Shattock M, et al. Quantification of islet-cell antibodies and prediction of insulin-dependent diabetes. Lancet. 1990; 335: 147-149.

9 Kawasaki E, Yasui J, Tsurumaru M, et al. Sequential elevation of autoantibodies to thyreoglobulin and glutamic acid decarboxylase in type 1 diabetes. World J Diabetes. 2013; 15: 227-230.

10 Backer JM. Clinical review: Type 1 diabetes associated autoimmunity: natural history, genetic associations, and screening. J Clin Endocrinol Metab. 2006; 91: 1210-1217.

11 Baker JM, Yu J, Yu L, et al. Autoantibody "subspecificity" in type 1 diabetes: risk for organ- specific autoimmunity clusters in distinct group. Diabetes Care. 2005; 28: 850-855.

12 Horie I, Kawasaki E, Ando T, et al. Clinical and genetic characteristics of utoimmune polyglandulae syndrone type 3 variant in the Japanese population. J Clin Endocrinol Metab. 2012; 97: 1043-1050.