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Anti-GAD-Positive Patients with Type 1 Diabetes Mellitus Have Higher Prevalence of Autoimmune Thyroiditis than Anti-GAD-Negative Patients with Type 1 and Type 2 Diabetes Mellitus

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Summary

The aim of our study was to evaluate antibodies against thyroglobulin (anti-TG) and thyroid peroxidase (anti-TPO) – markers of autoimmune thyroiditis – in several groups of adult patients with type 1 and type 2 diabetes mellitus (DM). We were particularly interested whether the presence of thyroid antibodies is related to the positivity of glutamic acid decarboxylase antibodies (anti-GAD). We found elevated anti-GAD in 46 % (97/210) patients with type 1 DM. All patients with type 2 diabetes were anti-GAD-negative. At least one thyroid antibody (anti-TG and/or anti-TPO) was found in 30 % (62/210) patients with type 1 DM and 27 % (22/83) type 2 diabetes patients. The patients with type 1 DM were further grouped according to their anti-GAD status. The anti-GAD-positive patients had a higher prevalence of anti-TG antibodies than the anti-GAD-negative patients (25 % *vs.* 12 %, p=0.03) as well as anti-TPO antibodies (32 % vs. 12 %, p<0.001). At least one thyroid antibody was detected in 39 % (38/97) of anti-GAD-positive but only in 21 % (24/113) of anti-GAD-negative patients with type 1 DM (p=0.006). No significant difference in the frequency of thyroid antibodies was found between anti-GAD-negative patients with type 1 and type 2 DM (21 % *vs.* 27 %, p=0.4). The groups with or without thyroid antibodies in both type 1 and type 2 diabetic patients did not differ in actual age, the age at diabetes onset, duration of diabetes, body mass index or HbA1c level. Patients with elevated thyroid antibodies had significantly higher levels of TSH than those without thyroid antibodies (1.86 vs. 3.22 mIU/l, p=0.04 in type 1 DM; 2.06 *vs.* 4.89 mIU/l, p=0.003 in type 2 DM). We conclude that there is a higher frequency of thyroid-specific antibodies in anti-GAD-positive adult patients with type 1 DM than in anti-GAD-negative patients or in patients with type 2 DM. Patients with or without thyroid antibodies do not differ in age, DM onset and duration, BMI or HbA1c. Thyroid antibodies-positive patients have higher levels of thyroid stimulating hormone (TSH).

Key words

Diabetes mellitus • Thyroid antibody • Autoimmune thyroiditis • Glutamic acid decarboxylase antibody

Introduction

Type 1 diabetes mellitus is often connected with other autoimmune diseases. The most frequent concomitant disease is autoimmune thyroiditis. Several studies confirmed the higher prevalence of autoimmune thyroiditis in patients with type 1 diabetes compared with non-diabetic population (Jaeger *et al.* 2001, Hansen *et al.* 1999). The disease occurs in 4-6 % of children and 20-40 % of adults with type 1 diabetes mellitus, while the highest prevalence has been reported among middle-aged women (Matějková-Běhanová 2001, Perros *et al.* 1995). The differences in the prevalence rates reported in various studies are probably due to a different genetic background associated with differences in the selection of patients and/or also antibody determination. The prevalence of autoimmune thyroiditis in the general population ranges from 1 to 7 % (Tunbridge *et al.* 1977, Sawin *et al.* 1985, Bagchi *et al.* 1990).

At least two major clinical forms of chronic autoimmune thyroiditis can be distinguished – Hashimoto and atrophic. The Hashimoto type is characterized with small goiter, elevated anti-thyroperoxidase antibodies (anti-TPO), less commonly anti-thyroglobulin antibodies (anti-TG), and a typical ultrasound picture of thyroiditis. The function of the thyroid gland can be normal, later hypothyroidism can develop. The atrophic form is a less common type of chronic autoimmune thyroiditis characterized by early development of hypothyroidism and ultrasound signs of thyroid gland atrophy and production of fibrotic tissue. Serum levels of anti-TPO and anti-TG are also typically elevated (Vondra and Zamrazil 2002).

It has been suggested that the coexistence of hypothyroidism might cause disturbances in the metabolic control of patients with diabetes (ISPAD 2000). Even subclinical hypothyroidism (slightly elevated TSH without impairment of T4 and T3 levels) is associated with higher frequency of symptomatic hypoglycemia (Mohn *et al.* 2001). This finding can be explained, as the physiological effects of thyroid metabolism on carbohydrates metabolism are well known. Thyroid hormones stimulate glucose intestinal absorption, and glycogenolysis and hepatic insulin catabolism are also enhanced. These mechanisms have a hyperglycemic effect and subtle changes in thyroid hormone levels might interfere with these actions, thereby increasing the risk of hypoglycemia (Mohn *et al.* 2001, Berant *et al.* 1993, Prager *et al.* 1990). Overt hypothyroidism can thus cause prolonged severe hypoglycemia. By causing secondary hyper-cholesterolemia it can also enhance the development of macroangiopathic complications.

Diagnostic criteria for autoimmune thyroiditis include the presence of thyroid antibodies and thyroid function assessment. For screening purposes, the detection of autoantibodies is the most effective in diagnosing preclinical endocrine dysfunction. Anti-TPO and/or anti-TG antibodies can be detected long before the changes of TSH and thyroid hormone levels occur. Thus the determination of these antibodies might be useful for early diagnosis of the disease before thyroid dysfunction develops. However, thyroid antibodies in the serum do not always appear in autoimmune thyroid diseases (Sostre and Reyes 1991). There is a need for alternative approaches to confirm the diagnosis – ultrasound imaging and fine needle biopsy in some cases.

The objective of this study was to estimate the frequency of thyroid antibodies among adult patients with type 1 diabetes diagnosed in childhood, young and older adulthood and type 2 diabetes patients. We were also interested if type 1 diabetes patients with preserved beta-cell autoimmunity are at higher risk of developing thyroid autoimmune diseases. We therefore compared the frequency of autoimmune thyroiditis in subgroups of patients according to the presence of glutamic acid decarboxylase antibodies (anti-GAD).

Methods

Subjects

We tested 210 sera from patients with type 1 diabetes mellitus (101 females and 109 males) and 83 sera from patients with type 2 diabetes mellitus (39 females and 44 males). These patients were selected by the Outpatients Department of the Department of Internal Medicine III, General Hospital in Prague.

The patients with Type 1 diabetes were divided into three groups (A, B and C) according to the age of diagnosis: group A – 34 patients with type 1 DM diagnosed up to 18 years of age, group B – 72 patients with type 1 DM with the onset in early adulthood (18-35 years of age), and group C – 109 patients with type 1 DM diagnosed in later adulthood (after 35 years of age). Ninety-two patients with type 2 diabetes comprised group D (onset after 35 years of age). The clinical data of the patients are summarized in Table 1.

Table 1. Characterization of groups of patients: means (S.D.).

Groups: **Type of DM**	**A (n=34)** **DM 1 <18**	**B (n=72)** **DM 1 18-35**	**C (n=104)** **DM 1 >35**	**D (n=83)** **DM 2 >35**
Age at diagnosis (years)	10.7 ± 4.1	25.6 ± 5.2	47.5 ± 8.3	52.5 ± 10.4
Actual age (years)	29.8 ± 9.2	33.1 ± 9.7	54.6 ± 8.7	56.3 ± 9.1
Duration of diabetes (years)	19.1 ± 10.4	7.5 ± 7.4	7.3 ± 5.7	3.8 ± 4.6
BMI (kg/m^2)	24.7 ± 2.7	23.6 ± 3.3	26.1 ± 4.4	28.7 ± 4.1
HbA1c (%)	8.8 ± 1.7	8.6 ± 2.6	8.6 ± 1.9	8.0 ± 2.1
Fasting C-peptide (nmol/l)	0.06 ± 0.09	0.13 ± 0.13	0.32 ± 0.25	1.10 ± 0.56
Postprandial C-peptide (nmol/l)	0.03 ± 0.09	0.18 ± 0.25	0.50 ± 0.36	2.18 ± 1.28

Data are means ± S.D.

The patients with type 1 diabetes had lower fasting and postprandial C-peptide levels, and a lower body mass index (BMI) than patients with type 2 diabetes. They were also presenting clinical symptoms at diagnosis more often than patients classified as type 2 diabetes. All of 210 patients with type 1 diabetes were being treated with insulin at the time of the study. The majority of type 2 patients (64 out of 83) were treated with diet alone or with oral hypoglycemic agents. Nineteen patients with type 2 diabetes were treated with insulin in combination with metformine. The metabolic control was slightly better in type 2 diabetic patients than in type 1 patients (HbA1c 8.03 % as compared to 8.68 %).

Out of 210 patients with type 1 diabetes, 9 of them (4.3 %) were treated with levothyroxine due to previously diagnosed autoimmune thyroiditis and subclinical or overt hypothyroidism. One patient was treated with carbimazol because of hyperthyroidism. Out of 83 patients with type 2 diabetes, 7 of them (8.4 %) were treated with levothyroxine for subclinical or overt hypothyroidism.

Measurements

We measured serum levels of thyroid-specific autoantibodies (anti-TG and anti-TPO) as a marker for autoimmune thyroiditis and glutamic acid decarboxylase (GAD65) autoantibodies (anti-GAD) as a marker of beta-cell autoimmunity in all four groups of patients. The antibodies were measured by validated, commercially available ELISA assays (Combi Kit TG/TPO, Dialab, Austria and Diaplets antiGADplus, Germany). Normal range for anti-TG was < 100 kU/l, for anti-TPO < 120 kU/l, and for anti-GAD < 32 ng/ml. C-peptide (normal range 0.21-0.93 nmol/l) as a marker for residual beta-cell function was measured in the fasting state and one hour after a standard breakfast containing 50 g sacharides (postprandial C-peptide). It was measured with commercially available RIA (Immunotech, France). HbA1c was determined by high-pressure liquid chromatography (HPLC). The normal population range is 4.0-6.0 %. Serum levels of the thyroid stimulating hormone (TSH) (normal range 0.3-5 mIU/l) was determined by electrochemoluminiscence (ELEXIS 2010).

Statistical analysis

The statistical analysis was preformed by StatSoft software (Tulsa, OK, USA). The statistical significance of the differences between group frequencies was tested by the Fisher's Exact Test and the significance was two-tailed. The means and standard deviations were calculated for continuous variables. The differences between groups were then tested by the t-test for independent samples with normal data distribution or by the Mann-Whitney non-parametric test. $P<0.05$ value was regarded as statistically significant.

Results

Anti-GAD was found to be elevated in 12/34 (35 %) patients with type 1 DM diagnosed up to 18 years of age (group A), 44/72 (61 %) patients diagnosed at 18 to 35 years of age (group B), and 41/104 (39 %) patients diagnosed after 35 years of age (group C). In summary, a total of 97 adults with type 1 diabetes out of 210 were anti-GAD-positive (46 %). The female to male ratio was 1.4 (56/41). None of 83 patients with type 2 diabetes in the group D was anti-GAD positive (Fig. 1).

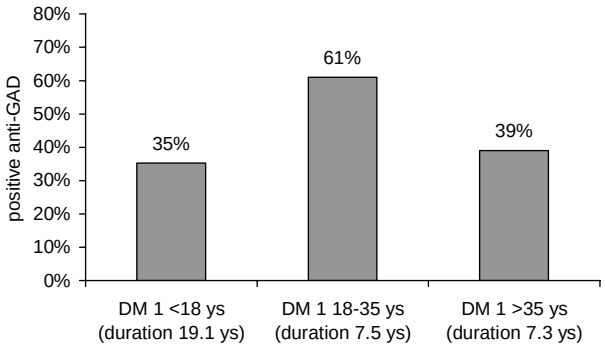

Fig. 1. Prevalence of anti-GAD in adults with type 1 diabetes mellitus.

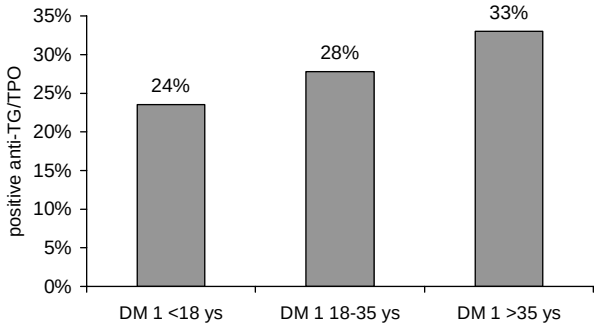

Fig. 2. Prevalence of anti-TG/anti-TPO in adults with type 1 diabetes mellitus.

Frequencies of thyroid antibodies in all groups of patients are shown in Table 2. At least one of thyroid antibodies (anti-TG and/or anti-TPO) was found in 8/34 (24 %) patients in group A, 20/72 (28 %) in group B, and 34/104 (33 %) in group C (Fig. 2). Overall anti-TG and/or anti-TPO was found to be elevated in 62 (30 %) out of 210 type 1 diabetic patients and in 22 (27 %) out of 83 type 2 patients (group D). The difference in the frequency of thyroid antibodies between type 1 and type 2 diabetic patients was not significant. The female to male ratio for thyroid antibodies in type 1 diabetes was 1.95 (41/21) and in type 2 diabetes 2.7 (16/6).

The groups with and without thyroid antibodies in both type 1 and type 2 diabetic patients did not differ in actual age, the age at diabetes onset, duration of diabetes, BMI, postprandial C-peptide, or HbA1c level (Tables 3 and 4). They also did not differ in their daily insulin dose (type 1 diabetic patients), and the need of insulin treatment (type 2 diabetic patients). The group with elevated thyroid antibodies had significantly higher levels of TSH than the group without thyroid antibodies in both type 1 and type 2 diabetic patients. Furthermore, patients with type 2 diabetes (but not type 1) and elevated thyroid antibodies were found to have higher level of fasting C-peptide than patients without thyroid antibodies.

Table 2. Frequencies of thyroid antibodies in 4 groups of diabetic patients.

	anti-TG	**anti-TPO**	**anti-TG and TPO**	**anti-TG and/or TPO**
Group A (n=34)	5 (15 %)	1 (3 %)	2 (6 %)	8 (24 %)
Group B (n=72)	4 (6 %)	12 (17 %)	4 (6 %)	20 (28 %)
Group C (n=104)	8 (8 %)	11 (11 %)	15 (14 %)	34 (33 %)
Group D (n=83)	5 (6 %)	6 (7 %)	11 (13 %)	22 (27 %)
Total	22	30	32	84

TSH was available in 154 type 1 diabetes patients and 39 type 2 diabetes patients. Subclinical hypothyroidism (TSH over 5 mIU/l and normal T4 and T3 level) was newly found in 4 out of 154 patients with type 1 DM, all of whom had elevated thyroid antibodies. TSH range was 6.7-13.2 mIU/l. Including 10 patients already treated (one with hyperthyroidism and nine with hypothyroidism), the prevalence of thyroid dysfunction in the whole group was 9 % (14/154). Subclinical hypothyroidism was also newly diagnosed in 5/39 subjects with type 2 diabetes, all of had positive thyroid antibodies. Their TSH range was 5.4-12.1 mIU/l. Including seven patients already receiving treatment for hypothyroidism, the prevalence of thyroid dysfunction was 12/39 (31 %).

Table 3. Characterization of type 1 diabetic patients with and without positive thyroid antibodies.

	DM 1 with negative anti-TG/TPO		DM 1 with positive anti-TG/TPO		
	Mean	**S.D.**	**Mean**	**S.D.**	**p**
Actual age (years)	42.40	14.66	45.18	14.35	ns
Age at diagnosis (years)	32.93	15.79	36.58	15.59	ns
Duration of DM (years)	9.46	8.57	8.81	8.25	ns
BMI (kg/m^2)	25.09	3.79	24.81	4.37	ns
Fasting C-peptide (nmol/l)	0.21	0.23	0.21	0.21	ns
Postrandial C-peptide (nmol/l)	0.32	0.35	0.30	0.35	ns
HbA1c (%)	8.82	2.23	8.22	1.98	ns
TSH (mIU/l)	1.86	0.98	3.22	6.33	0.04
Units of insulin/day	40.10	17.84	36.60	17.09	ns
Anti-GAD-positive	59/148 (40 %)		38/62 (61 %)		0.006

Data are means ± S.D.

Table 4. Characterization of type 2 diabetic patients with and without positive thyroid antibodies.

	DM 2 with negative anti-TG/TPO		DM 2 with positive anti-TG/TPO		
	Mean	**S.D.**	**Mean**	**S.D.**	**p**
Actual age (years)	55.46	8.83	58.68	9.81	ns
Age at diagnosis (years)	51.54	9.72	55.14	12.01	ns
Duration of DM (years)	3.90	4.69	3.55	4.53	ns
BMI (kg/m^2)	28.56	3.81	29.12	4.91	ns
Fasting C-peptide (nmol/l)	1.02	0.43	1.31	0.81	0.04
Postprandial C-peptide (nmol/l)	2.11	1.33	2.37	1.17	ns
HbA1c (%)	8.03	2.10	8.03	2.23	ns
TSH (mIU/l)	2.06	1.26	4.89	4.06	0.003
Insulin treatment	15/61 (25 %)		4/22 (18 %)		ns

Data are means ± S.D.

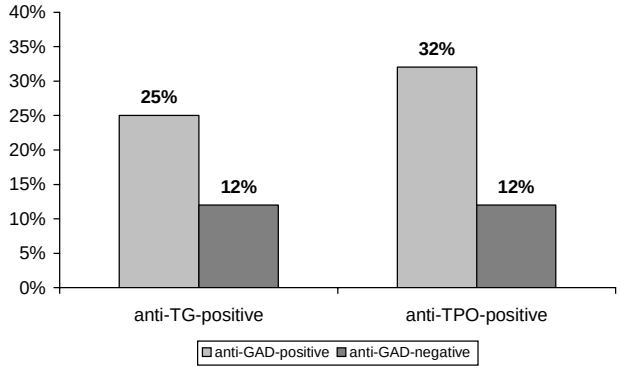

Fig. 3. Frequencies of anti-TG and anti-TPO in anti-GAD-positive and anti-GAD-negative adults with type 1 diabetes mellitus.

The patients with type 1 DM were further grouped according to their anti-GAD status. The anti-GAD-positive patients were found to have a higher prevalence of anti-TG antibodies than anti-GAD-negative patients (24.7 % (24/97) vs. 12.4 % (14/113), p=0.03) as well as anti-TPO antibodies (32.0 % (31/97) vs. 12.4 % (14/113), p<0.001) (Fig. 3). In summary, at least one thyroid-specific antibody was detected in 39.2 % (38/97) of anti-GAD-positive and only in 21.2 % (24/113) of anti-GAD-negative patients with type 1 DM (p=0.006). The frequency of type 1 diabetes patients with positive both anti-GAD and thyroid antibodies was 51 % (21/41)

in group C (diagnosed after the age of 35), and only 34 % (15/44) in group B (diagnosed before the age of 35), but this difference was not significant. The prevalence of thyroid antibodies did not differ significantly between anti-GAD-negative type 1 diabetic patients and type 2 diabetics (24/113 or 21 % vs. 22/83 or 27 %, p=0.4). In contrast, anti-GAD-positive type 1 patients had a significantly higher prevalence of thyroid antibodies than both anti-GAD negative type 1 and type 2 diabetic patients.

Discussion

Many studies demonstrated higher prevalence of thyroid antibodies in children and adolescents with type 1 diabetes mellitus compared with healthy subjects (Radetti *et al.* 1995, Jaeger *et al.* 2001, Mohn *et al.* 2001). In a German study the prevalence of thyroid antibodies in children and adolescents with type 1 DM (median age 12.8 years, range 2-18) was 16.2 % compared with 1.9 % in healthy controls (Hansen *et al.* 1999). In another recent multicenter study of 7097 patients with type 1 DM (mean age 12.4 years, range 0.3-20.0) the prevalence of thyroid antibodies was 21.6 % (Kordonouri *et al.* 2002). Young patients with thyroid antibodies were significantly older and had a longer duration of diabetes than those without antibodies. Furthermore, diabetes in these patients had developed later in life.

Little is known about the prevalence of autoimmune thyroiditis in patients with adult onset of type 1 diabetes and patients with type 2 diabetes. Some studies investigated children, adolescents and adults with type 1 diabetes together. The problem is also the correct classification of diabetes in newly diagnosed adult patients. Spanish authors examined a group of 111 newly diagnosed adolescents and adults with type 1 diabetes (more than 13 years old, with a mean of 26.8 years). Anti-TPO antibodies were found in 27.9 % (Fernandez-Castaner *et al.* 1999). A Thai study investigated 50 patients with type 1 diabetes, most of them (but not all) with the onset in adulthood (mean 36.5 years, range 9-76). The frequency of thyroid antibodies was 32 % (Rattarasarn *et al.* 2000). Several previous studies investigating type 2 diabetic patients divided subjects into insulin-requiring and non-insulin-requiring groups (Groop *et al.* 1988) or anti-GAD-negative and anti-GAD-positive groups (Gambelunghe *et al.* 2000, Tuomi *et al.* 1993), thus analyzing both type 2 and type 1 diabetic adults together. In a study of 312 patients with type 2 diabetes the thyroid antibodies were positive in 34 % of the insulin-treated patients and 20 % of patients treated with a diet or oral hypoglycemic agents (Groop *et al.* 1988). Another study analyzed sera from 600 diabetes patients classified as type 2 and anti-GAD was found in 11 %. Anti-TPO was present in 24 % of anti-GAD-positive patients but only in 5 % of anti-GAD-negative patients (Gambelunghe *et al.* 2000).

We divided adult diabetic patients into well-defined groups according to the type of diabetes (type 1 and type 2) and we further subdivided type 1 diabetes patients according to the age of diagnosis (childhood, younger and older adulthood). We found thyroid antibodies in 30 % of adults with type 1 DM, but also in 27 % of adults with type 2 diabetes. In both groups the prevalence was higher among females than among males, which is in agreement with previous studies of diabetic patients. Thyroid antibodies were present in 24 % of adults with type 1 DM diagnosed up to the age of 18 years with long duration of diabetes. Comparable result was found in a US study of a similar cohort of patients, where the frequency of thyroid antibodies was 26.6 % (McCanlies *et al.* 1998). The prevalences of thyroid antibodies among patients with type 1 diabetes diagnosed in adulthood before and after the age of 35 years were not significantly different (28 % vs. 33 %). Unlike the studies of children and adolescents with type 1 diabetes, we found no differences in age, duration of diabetes and age at the onset of diabetes between the thyroid antibodies-positive and -negative groups of diabetic adults.

In this study, the determination of TSH was available only in 66 % of the total cohort. This was due to the different diagnostic approaches among diabetologists participating in this study. Nine patients with type 1 diabetes were already receiving treatment for hypothyroidism and one for hyperthyroidism and four patients were diagnosed for the first time with subclinical hypothyroidism. The prevalence of thyroid dysfunction in the whole group was 9 %. Seven patients with type 2 DM were already treated for hypothyroidism and five were newly diagnosed with subclinical hypothyroidism – the overall prevalence of thyroid dysfunction in this group was thus even higher (31 %).

It has been questioned whether anti-TG provide further diagnostic information as compared to the single use of anti-TPO in the diagnosis of autoimmune thyroiditis. In our study, antibodies were directed against both TG and TPO in 32 out of 84 of antibody-positive

patients. Thirty of 84 patients were only anti-TPO-positive. Additionally, 22 of 84 had only anti-TG indicating that a part of the information is missed if only anti-TPO are measured. Hansen *et al.* (1999) also found similar results among young patients with type 1 diabetes.

We detected elevated anti-GAD antibodies in 46 % of patients with type 1 diabetes. The prevalence was higher among subjects with the onset of the disease in younger adulthood (18-35 years) than in those who were diagnosed after the age of 35 years (61 % vs. 39 %, p=0.006). Both groups were comparable as far as the duration of the disease is concerned (7.5 vs. 7.3 years). On the other hand, the frequency of anti-GAD-positive subjects in the group of patients diagnosed up to 18 years of age was low – only 35 %. We explain this observation by the long duration of diabetes in this group (mean 19.1 years). It is known that anti-GAD is positive in more than 70 % of children with recent onset of type 1 diabetes and its level seems to decrease with the duration of the disease and decreasing number of residual beta cells (Bingley *et al.* 1997, Fajardo *et al.* 2001). While the prevalence of anti-GAD decreases with the age of diabetes onset, thyroid antibodies are more prevalent among diabetic adults than among children, with the highest prevalence among middle-aged women. The differences in the frequencies between our four groups of diabetic adults were not statistically significant. Thyroid antibodies did not correlate with either the actual age, age at DM onset, or duration of diabetes (data not shown).

We found the prevalence of thyroid antibodies among anti-GAD-positive patients with type 1 diabetes to be almost twice as high as among anti-GAD-negative (39.2 vs 21.2 %, p=0.006). We conclude that anti-GAD positivity in diabetic patients can be considered as a predictive factor for thyroid autoimmunity development.

In conclusion, these data support the recommendation for regular examinations of thyroid antibodies and thyroid function assessment in all patients with type 1 and type 2 diabetes.

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