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CLINICAL STUDY

Autoimmune thyroid diseases in patients with diabetes mellitus

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Abstract: *Background and objectives:* Autoimmune thyroid diseases are frequent in patients with type 1 diabetes mellitus. The aim of our study was to determine the incidence of autoimmune thyroid diseases (AIT) in the different groups of patients with DM (DM type 1 – classical form, DM type 1 – subtype LADA, DM type 2) and compare the incidence of AIT among the groups as well as to the control group of non-diabetics. We also focused our attention on the factors that influence the risk of thyroid diseases incidence in diabetics.
Patients and methods: We examined 79 diabetics (38 women and 41 men, x=55.4±2.8). Diabetic patients were divided into three groups. The control group consisted of 30 non-diabetics.
Results: Chronic autoimmune thyroiditis was diagnosed in 8 (40 %) patients in the first group, in 6 (50 %) in the 2nd group of patients and finally in 20 (43 %) patients with type 2 diabetes mellitus – 3rd group. A significantly higher prevalence of chronic autoimmune thyroiditis was observed in female diabetics and in diabetics with positive family history of thyroid diseases.
Conclusion: Results of paper confirm an increased prevalence of chronic autoimmune thyroiditis in patients with all types of diabetes mellitus resulting in recommendation of careful follow-up of all diabetic patients for presence of thyroid autoimmunity *(Tab. 5, Ref, 13).* Full Text (Free, PDF) www.bmj.sk.
Key words: chronic autoimmune thyroiditis, diabetes mellitus type 1, diabetes mellitus type 2.

Abbreviations: AIT – autoimmune thyroid disease, AITD – chronic autoimmune thyroiditis, anti-GAD – antibodies against glutamate decarboxylase, anti-Tg – antibodies against thyroglobulin, anti-TPO – antibodies against thyreoperoxidase, BMI – body mass index, DM – diabetes mellitus, fT3-free – triiodthyronine, fT4-free – thyroxine, LADA – latent autoimmune diabetes in adults, oGTT – oral glucose tolerance test, OAD – oral antidiabetic drugs, TSH – thyroid stimulating hormone, USG – ultrasound.

Thyroid diseases affect approximately 10–15 % of patients with diabetes mellitus (in comparison: in non-diabetics the prevalence of thyroid diseases is approximately 6 %). Mechanisms of interaction between diabetes mellitus (DM) and thyroid diseases are complex and still unclear. Neither DM nor thyroid diseases present a homogenous nosologic unit, pathogenesis of different types of DM as well as thyroid diseases is diverse. Therefore even the relations between them are also different (1).

Clinical relationship between DM and thyroid diseases can not be explained merely by direct effect of shortage or excess in the thyroid hormones.

Various experimental, clinical as well as genetic and epidemiological studies showed immunological and genetic base of relationship between DM and thyroid diseases. Currently there is a lot of evidence about the importance of genetic factors in autoimmune diseases. In the mean time most of the thyroid diseases and DM type 1 that occur in our population are classical organ specific autoimmune diseases (2).

DM type 1 is often accompanied by other autoimmune diseases. Autoimmune thyroid diseases are among the most common (3).

In the literature there is much less data about thyroid diseases in patients with type 2DM. Recent publications confirm an increased incidence of autoimmune thyroid diseases even in type 2 DM (4, 5).

The aim of our study was to determine the incidence of autoimmune thyroid diseases (AIT) in the different groups of patients with DM (DM type 1 – classical form, DM type 1 – subtype LADA, DM type 2) and compare the incidence of AIT among the groups as well as to the control group of non-diabetics. We also focused our attention on the factors that influence the risk of thyroid diseases incidence in diabetics.

Patients and methods

We evaluated 79 patients with DM (38 women and 41 men, average age 55.4±2.8), from the dispensary care of a diabetes out-patient clinic. The diabetics were divided into 3 groups, as shown in the Table 1.

The first group consisted of diabetics type 1, with classical, juvenile form of DM (Group 1). This group was composed of patients with a history of sudden beginning and fully developed

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Tab. 1. Subgroups of patients with diabetes mellitus (n=79).

Patient groups	n	male/female
Group 1	20	12/8
Group 2	12	6/6
Group 3	47	22/25

clinical symptoms of DM already at the emergence of the disease. They had low or even missing levels of C-peptide (C peptide <206 pmol/l). The average age in this group was 31.7±2.6. The average duration of DM type 1 in this group was 15±3.8 years.

The second group consisted of diabetics type 1 – subtype LADA (Group 2). The criteria for patient inclusion into this group were: age at manifestation of DM >35 years, BMI <27 kg/m^2, clinical manifestation same as in patients with DM type 2, history of acceptable initial compensation of DM with diet or oral antidiabetic drugs (OAD), development of insulin dependency 1–3 years after manifestation of DM, low levels of C-peptide, persisting positivity of anti-GAD auto-antibodies. The average age of patients in this group was 52.7±3. The average duration of diabetes in this group was 7.5±3.2 years.

The third group consisted of diabetics type 2 (Group 3). This group was composed of patients with negative anti-GAD findings, preserved secretion of C-peptide. The average age of patients in this group was 66±1.2. The average duration of diabetes type 2 in this group was 9.8±1.4 years.

The control group consisted of 30 non-diabetics that fulfilled the following criteria. Fasting glycemia in venous blood was repeatedly lower than 5.6 mmol/l, and glycemia in the 120th minute of oGTT was lower than 7.8 mmol/l. The control group consisted of 17 women and 13 men, with average age 53±2 years.

All diabetic patients were tested for C-peptide levels (reference range: 206–934 pmol/l) and levels of antibodies against glutamate decarboxylase (anti-GAD, reference range <1 IU/ml) by RIA kits (Immunotech, France). Repeated testing of fasting glycemia in venous blood as well as oral glucose tolerance test (oGTT) were used to rule out diabetes in the control group.

All patients with diabetes as well as from the control group had tests for thyroid function. Thyroidal functions were evaluated by measuring serum levels of thyroid stimulating hormone (TSH), free-triiodthyronine (fT3), and free-thyroxine (fT4). Levels of fT3 and fT4 were measured in automatic analyzer Stratec with RIA method. Ultrasensitive TSH was measured with IRMA method (reference ranges – TSH: 0.17–4.05 mIU/l, fT3: 2.5–5.8 pmol/l, fT4: 11.0–25.0 pmol/l).

Thyroid autoimmune disorders were evaluated by detection of auto-antibodies against thyroidal antigens. We analyzed auto-antibodies against thyreoperoxidase (anti-TPO, reference range <25 IU/ml) and antibodies against thyroglobulin (anti-Tg, norm: <190 IU/ml). Anti-TPO levels were measured by RIA kits (Immunotech, France), anti-Tg levels were measured by IRMA method (Brahms comp.) and antibodies against TSH receptor by kits from Immunotech firm.

All patients underwent an ultrasound (USG) examination of the thyroid, focused on location, echogenity, echostructure and size of the organ. USG examination was done on Sonoline G50 machine with linear probe of 10 MHz.

The thyroid volume was counted according to Brunn formula:

V = a.b.c. 0.479,

where a, b, c represent length, width and height of a lobe.

A careful history was taken to find out about presence of thyroid diseases in firsthand relatives.

All patients were tested for basic lipid status (total cholesterol, LDL-cholesterol, HDL-cholesterol, triacylglycerols).

Chronic autoimmune thyroiditis (AITD) was defined as positivity of antibodies against thyreoperoxidase or antibodies against thyroglobuline or levels of TSH >4.05 mIU/l, together with typical USG image of AIT (5).

Subclinical hypothyroidism was defined as increased levels of TSH >4.05 mIU/l, with normal levels of fT3, fT4. Subclinical hyperthyroidism was defined as decreased level of s-TSH <0.17 mIU/l with normal levels of fT3, fT4. Manifest hypothyroidism was defined as increased level of TSH with low levels of fT3, fT4. Manifest hyperthyroidism was defined as suppressed level of TSH with high levels of fT3 or fT4 (6).

Patient groups were statistically evaluated. Average values of the quantitative parameters were listed as x±SEM. We used simple sorting dispersion analysis (ANOVA) to test the hypotheses of equal mean values of the individual parameters among different patient's groups. In areas with statistically significant difference we further verified differences between different groups of patients with Tukey-Kramer method of contrasts. We used the method of main components as well as multiple regression analysis to evaluate the influence of various risk factors, which influence the incidence of thyroid diseases in diabetics.

Results

The average values of quantitative parameters (age, BMI, C-peptide, anti-GAD, basic lipid status) in control group (n=30), in the group 3 (n=47), in the group 2 (n=12) and in the group 1 (n=20) are listed in Table 2.

Tab. 2. Average values of the quantitative parameters (age, BMI, C-peptide, anti-GAD, basic lipid status) in the control group and the groups of patients with DM.

	Control group	Group 3	Group 2	Group 1
Age	53±2	66±1.2*	52.7±3	31.7±2.6*
BMI	27.4±1	29.3±0.5	24.2±0.3	23.5±0.6
anti-GAD	-	<0.1±0*	5.2±0.6*	3.1±0.7*
C-peptide	-	969±83*	165±40*	41.4±18*
Total cholesterol	5.8±0.2*	5.8±0.2**	5.2±0.4**	4.6±0.2*
Triacylglycerols	1.8±0.3	1.9±0.1	1.9±0.3	1.48±0.1
LDL cholesterol	3.4±0.2*	3.5±0.1*	3.1±0.3	2.5±0.1**
HDL cholesterol	1.4±0.1*	1.3±0.1	1.2±0.1*	1.4±0.1

* p<0.05. ** p<0.01

Tab. 3. Average values of the thyroid functional parameters in the control group and the groups of patients with DM.

	Control group	Group 3	Group 2	Group 1
anti-TPO	15.6±4.3*	39.5±14.5	71.3±33*	24.8±5.8
anti-Tg	41.8±7*	237±112*	55±15*	36.3±4*
TSH	4.3±1.5	2.4±0.2	2.7±0.5	2.9±0.6
fT4	15.6±0.8	16.6±1.4	16.6±0.6	14.8±0.4
fT3	3.6±0.2	5.8±1.5	3.9±0.2	3.7±0.2
thyroid volume	8.2±0.7*	11.1±0.9*	10.7±1.5	9.2±0.7

Tab. 4. Absolute numbers and proportion of subclinical thyroid malfunction, manifest thyroid malfunction, incidence of antibodies anti-TPO, anti-Tg, Ultrasound changes typical for chronic autoimmune thyroiditis and occurrence of chronic autoimmune thyroiditis in the different patients groups.

	Control group	Group 3	Group 2	Group 1	Statistical significance
Family history of thyroid diseases	7/23 %	11/23 %	6/50 %	6/30 %	NS
anti-TPO	4/13 %	12/25 %	6/50 %	6/30 %	p<0.05*
anti-Tg	1/3 %	3/6.4 %	1/8 %	0/0 %	NS
Subclinical malfunction of thyroid	7/23 %	9/19 %	3/25 %	3/15 %	NS
Manifest malfunction of thyroid	1/3 %	1/2,1 %	0/0 %	0/0 %	NS
USG finding (AITD)	10/33 %	20/43 %	6/50 %	8/40 %	NS
Dg AITD	10/33 %	20/43 %	6/50 %	8/40 %	NS

* Statistical significance between the control group and the group of patients with DM type 1 — subtype LADA

There were statistically significant differences detected in the levels of antibodies against glutamate decarboxylase (anti-GAD) between individual groups of patients (p<0.01). Patients in the group 3 did not have positive levels of these autoantibodies and there were also significant differences between group 2 and group 1 (p<0.01). The lowest values of C-peptide were in group 1, they were slightly higher in group 2 and the highest in group 3.

Control group as well as group 3 had significantly increased total cholesterol compared to groups 1 and 2.

There were no significant differences in the levels of triacylglycerols between individual groups. LDL-cholesterol in group 1 was significantly lower in comparison with the control group (p<0.01) and also in comparison with group 3 (p<0.01). There were differences in the levels of HDL-cholesterol only between group 2 and the control group (p<0.05).

Average values of the quantitative parameters of thyroid function (anti-TPO, anti-Tg, TSH, fT3, fT4, thyroid volume) in the control group and groups of patients are listed in Table 3.

The lowest values of anti-TPO were observed in the control group, slightly but not significantly higher were in group 1 and 3 and the highest values were detected in group 2 (p<0.02).

There were no significant differences in the anti-TG between the control group and groups of patients 1 and 2, whereas in group 3 they were significantly higher in comparison with the other groups (p<0.01).

The thyroid volume was significantly higher in group 3 compared with the control group (p<0.05).

The prevalence of subclinical and overt thyroid dysfunction, incidence of antithyroid antibodies, ultrasound finding of AITDs as well as the final diagnosis of chronic AIT in the individual groups of patients are listed in Table 4.

Significantly higher values of anti TPO were found in group 2 compared with other groups of patients (p<0.05).

Tab. 5. The comparison of selected parameters between the group of diabetics (diabetics type 1 – classical, juvenile form of DM, diabetics type 1 – subtype LADA, diabetics type 2) with AITD and the group of diabetics (diabetics type 1 – classical, juvenile form of DM, diabetics type 1 – subtype LADA, diabetics type 2) without AITD.

	Diabetics with AITD (n=34)	Diabetics without AITD (n=45)	Statistical significance
Age	55.6±2.8	55.1±2.7	NS
Sex-male/female	10/24	31/14	p<0.01
BMI	27.1±0.7	27.0±0.6	NS
anti-GAD	1.6±0.4	1.7±0.4	NS
C-peptide	549.9±95.8	659.1±99.9	NS
Total cholesterol	5.4±0.2	5.4±0.2	NS
Tg	1.8±0.1	1.8±0.1	NS
LDL-cholesterol	3.1±0.1	3.2±1.0	NS
HDL-cholesterol	1.4±0.6	1.2±0.4	NS
anti-TPO	84.2±21.5	7.7±0.8	p<0.01
anti-Tg	322.9±152.9	34.4±2.3	p<0.01
TSH	3.5±0.4	1.8±0.1	p<0.01
fT4	14.9±0.6	17.0±1.5	NS
fT3	4.4±0.5	5.5±1.5	NS
Thyroid volume	11.6±1.2	9.8±0.7	p<0.05
Duration of DM	11.4±1.6	10.0±1.2	NS
Positive FA for thyroid diseases yes/no	16/18	7/38	p<0.01

The comparison of selected parameters between diabetic patients (diabetics type 1-classical, juvenile form of DM, diabetics type 1 – subtype LADA, diabetics type 2) with AITD and diabetic patients (diabetics type 1 – classical, juvenile form of DM, diabetics type 1 – subtype LADA, diabetics type 2) without AITD is listed in Table 5.

A significantly higher incidence of female gender was detected in the group with DM and AITD in comparison to diabetics without AITD ($p<0.01$).

Although all patients with AITD were in euthyreotic state, TSH values were significantly higher in patients with AITD than those without AITD ($p<0.01$).

The thyroid volume was significantly higher in the group of patients with AITD compared with the group of patients without AITD ($p<0.05$). The group of patients with DM and AITD had significantly more frequent positive family history of thyroid diseases in comparison with the group of patients with DM without AITD ($p<0.01$).

In multivariate analysis only female gender and family history were predictive factors indicating an increased risk of thyroid autoimmunity in diabetic patients.

Discussion

Autoimmune thyroid diseases are common in diabetics with DM type 1 (3). The most frequent of them is the chronic autoimmune thyroiditis (AITD).

In our group of 20 patients with classic juvenile form of DM type 1, AITD was diagnosed in 8 (40 %) patients, in patients with diabetes of type LADA in 6 patients (50 %), respectively. Despite high incidence of AITD in the LADA group we did not find statistically significant difference in the incidence of AITD in comparison to the control group, AITD was detected in 10 (33 %) non-diabetics. Our data about high prevalence of AITD in patients with classic juvenile form of DM type 1, especially those with LADA are similar to many other papers which confirm that the incidence of AITD rises significantly with the age of manifestation of DM type 1.

Holl et al and Roldan et al found incidence of AITD: up to 5 % patients in type 1 diabetics with manifestation in pre-school age, 15–25 % in manifestation of DM type 1 in adolescence (7, 8). Vondra et al and Groop et al listed incidence of AITD between 20–51 % in patients with manifestation of DM type 1 in adult age (2, 9). The international literature data about the incidence of AITD in patients with DM type 1 – subtype LADA differ quite a bit from one source to another, which may be caused by ethnic and regional differences (9, 10). We found significantly higher incidence of AITD in women as well as diabetics with positive family history of thyroid diseases in the group of patients with DM and currently present AITD in comparison with the group of diabetics without AITD. These results are in accordance with the finding of others who found that AITD is more 3–5 times more common in women than in men (2). Vondra et al conclude that family history data can be suggestive of increased risk for thyroid diseases in patients with DM. It is mainly accumulation of autoimmune and allergic diseases, and especially thyroid diseases in their consanguineous relatives (2).

There are much less literature data available about the incidence of thyroid diseases in DM type 2. Recently there has been an increase in papers which confirm a higher incidence of AITD even in DM type 2. Krejči et al diagnosed of AITD in 27 % of patients in a group of 83 diabetics with DM type 2 (4). In our group of 47 patients with DM type 2 we diagnosed AITD also in a high proportion of patients (43 %). But even in this case the proportion of AITD was not significantly higher in comparison to the incidence of AITD in our control group.

Epidemiological data in non-diabetics based on very sensitive methods state the prevalence of AITD within 1–5 % in men and 10–24 % in women (2, 6). Prevalence of hypothyroidism with respect to age and sex in non-diabetics is reported to vary from 3 up to 21 % (6). In our control group we found AITD in 10 (33 %) of non-diabetics, subclinical hypothyroidism in 7 (23 %) patients and manifest hypothyroidism in 1 (3 %) patient from the control group of non-diabetics.

Our explanation for the high incidence of AITD as well as AITD complicated by subclinical hypothyroidism in our control group of non-diabetics is that the control group had a high proportion of patients with hypercholesterolemia, which could have been secondary as a result of unrecognized subclinical hypothyroidism.

Thus, in differential diagnosis of any form of dyslipoproteinemias it is necessary to rule out hypothyroidism.

The reason for increased incidence of AITD in DM type 2 is unknown. Possible mechanisms are genetic relationships between DM type 2 and thyroid diseases, however infections and stress could be a triggering factors. Psychological stress, particularly its chronic form is widely discussed in current literature (2, 5, 11).

The risk of increased thyroid volume, which was found in our study, may be explained by frequent low iodine levels in blood, which is considered to be quite frequent in diabetics (5, 12).

AITD is the main cause of hypothyroidism not only in diabetics. The prevalence of subclinical and manifest form of hypothyroidism together is described in between 5–15 % of children and adolescents, in adulthood it reaches as high as 24 %. It is 7x more common in women, with a significant increase in older age (2). Unrecognized hypothyroidism in diabetics can cause an unsatisfying compensation of DM and can result in frequent and prolonged hypoglycemia. Hypothyroidism in diabetics speeds up the development of long-term complications, mainly macroangiopathic (2). Even subclinical hypothyroidism has a negative influence on lipid metabolism and it is an independent risk factor for myocardial infarction (13).

In our group of 20 patients with DM type 1 we found subclinical hypothyroidism in 3 (15 %) patients, in 3 (25 %) of 12 patients with DM type 1 subtype LADA, in 9 (19 %) of 47 patients with DM type 2.

Graves-Basedow disease is a less common form of autoimmune thyroid disease. Graves-Basedow thyrotoxicosis appears most often in young female diabetics, it is a threatening complication mainly postpartum. In patients with DM it leads to in-

creased instability of diabetes, it often leads to acute decompensation and in patients with DM type 1 to decompensation with ketoacidosis. In DM type 1 it has been reported between 8–10 % (8). Its incidence in non-diabetic population is around 2 % (2).

In our group of patients with DM type 1 (the group of patients with DM type 1 – classical form, the group of patients with DM type 1 – subtype LADA) we did not find any case of subclinical or manifest hyperthyroidism, probably because of a relatively small number of patients with DM type 1. We observed T3-toxicosis in one female diabetic with DM type 2.

Based on our data we fully recommend once or twice a year testing for autoantibodies against the thyroid gland and measuring TSH level with the goal of early detection of laboratory manifestation of thyroidal autoimmunity or development of functional disorder. Without such regular and specific laboratory tests is early diagnosis of autoimmune thyroid diseases in routine diabetologic practice a very difficult task.

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