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The expression of GADA, ZnT8A and IA-2A in patients with type 1 diabetes mellitus with thyroid disease and their correlation with thyroid autoantibodies

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Abstract. – OBJECTIVE: The aim of this research was to study the expression of anti-glutamate decarboxylase antibody (GADA), zinc transporter-8 autoantibody (ZnT8A), and insulinoma-associated protein-2 antibody (IA-2A) in patients with type 1 diabetes (T1DM) with thyroid disease (TD) and its correlation with thyroid autoantibodies.

PATIENTS AND METHODS: 380 patients with T1DM were included in the study, of which 313 patients with T1DM alone were included in the control group. In the TD group, 41 patients with T1DM and Hashimoto's thyroiditis (HT) were included, and 26 cases of T1DM patients with Graves' disease were included in the Graves group. The clinical features of the control group, the HT group, and the Graves group were compared. The positive rates of insulin autoantibodies in the control group and the TD group were analyzed. The clinical characteristics of patients with and without insulin autoantibody positivity were compared. The positive rates of thyroid autoantibodies in T1DM patients with positive GADA, ZnT8A, IA-2A, and different numbers of positive insulin autoantibodies were analyzed.

RESULTS: The levels of total cholesterol (TC) and thyroid stimulating hormone (TSH) in the HT group were significantly higher than those in the control and Graves groups, and the levels of free thyroid hormone (FT4) and low-density lipoprotein cholesterol (LDL-C) were significantly lower than those in the control and Graves groups ($p<0.001$). The levels of TC and TSH in the Graves group were significantly lower than those in the control group, the levels of HbA1c, LDL-C, and FT4 were significantly higher than those in the control group, and the levels of FT3 were significantly higher than those in the control and HT groups ($p<0.001$). The levels of C peptide, triglyceride (TG), and LDL-C of insulin autoantibodies positive patients were significantly lower than those of negative patients ($p<0.05$). The positive rates of GADA, ZnT8A, and IA-2A in the TD group, as well as the positive rates of double antibodies and triple antibodies, were significantly higher than those of the control group ($p<0.05$). In T1DM patients, the positive rates of thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) in GADA and IA-2A-positive patients were significantly higher than those in GADA and IA-2A-negative patients ($p<0.05$). The positive rate of TPOAb in ZnT8A-positive patients was significantly higher than that in ZnT8A-negative patients ($p<0.05$). The positive rates of TRAb, TPOAb, and TGAb in T1DM patients positive for two of the three insulin autoantibodies and three insulin autoantibodies were significantly higher than those positive for one of the three insulin autoantibodies ($p<0.001$).

CONCLUSIONS: TD can exacerbate the disorder of glucose and lipid metabolism in patients with T1DM, and multiple insulin autoantibodies positive T1DM patients it is more likely to have thyroid autoantibody positivity. It is suggested that patients with aggravated glucose and lipid metabolism and multiple insulin autoantibody positivity should be routinely screened for thyroid antibodies to help early diagnosis of TD.

Key Words:
Type 1 diabetes mellitus, Thyroid disease, Glucose and lipid metabolism, Insulin autoantibodies, Thyroid autoantibodies.

Introduction

In patients with type 1 diabetes mellitus (T1DM), the increased levels of glutamic acid decarboxylase antibody (GADA), zinc transporter-8 autoantibody (ZnT8A), and insulinoma-associated protein-2 antibody (IA-2A) can aggravate the immune damage of body, induce dysfunction

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of islet β cells, and lead to the disorders of insulin secretion, ultimately participating in the development of T1DM[1]. Thyroid diseases such as Hashimoto's thyroiditis (HT) and Graves's disease (TD) are comorbidities associated with Type 1 diabetes. The beginning of their occurrence is often less clear. Early clinical diagnosis is difficult, and the occurrence of TD in diabetic patients can further aggravate the disorder of glucose and lipid metabolism and increase the risk of cardiovascular and cerebrovascular diseases[2]. It is currently believed[3] that both patients with T1DM and TD patients exhibit abnormal levels of thyroid autoantibodies, such as thyroid stimulating receptor antibody (TRAb), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TGAb). The levels of insulin autoantibodies such as GADA, ZnT8a, and IA-2A are not only higher in T1DM patients but also significantly increased in TD patients. It is suggested[3] that both insulin and thyroid autoantibodies may be involved in the development of TD in T1DM patients. However, there are few systematic analyses on the expression of GADA, ZnT8a, IA-2A and their correlation with thyroid autoantibodies in T1DM patients with TD.

In the current study, we sought to select T1DM patients treated in our hospital from January 2018 to December 2020 as the research object and explored the expression of anti-glutamate decarboxylase antibody (GADA), zinc transporter-8 autoantibody (ZnT8A) and insulinoma-associated protein-2 antibody (IA-2A) in patients with T1DM and TD, as well as their correlation with thyroid autoantibodies. Thus, this study may provide a relevant reference for the diagnosis and management of T1DM patients with TD in clinical practice.

Patients and Methods

General Data

A total of 380 patients with T1DM admitted to our hospital from January 2018 to December 2020 were enrolled, including 143 males and 237 females, aged 5-57 years, with a median age of 30 years. Among them, 313 patients with T1DM were included in the control group, and 67 T1DM patients with TD were included in the TD group. In the TD group, there were 41 patients with HT (HT group) and 26 patients with Graves (Graves group). All adult patients gave their informed consent. For children with T1DM, the consent was provided by their parents. The study was approved by our hospital's Medical Ethics Committee (AKCCH2018002). Inclusion criteria: patients diagnosed with T1DM[4]; patients in the Graves group and HT group clinically diagnosed by endocrinologists and confirmed by clinical symptoms, abnormal thyroid hormone and TRAb, TPOAb and/or TGA autoantibody levels, ultrasound examination, and met the diagnostic criteria for Graves' disease and HT, respectively[5]; patients with normal cognitive functions. Exclusion criteria: other autoimmune diseases, abnormal liver and kidney function, blood system diseases, malignant tumors, infectious diseases, pregnant or lactating women, recent application of lipid-lowering drugs or iodine, associated with other endocrine diseases.

Observation Indicators

(1) Clinical characteristics of the three groups. The general data of all patients were collected, including age, sex, and body mass index (BMI). Fasting venous blood was also drawn from all patients. After centrifugation, the serum levels of HbA1c, fasting plasma glucose (FPG), C-peptide, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), free triiodothyronine (FT3), free thyroid hormone (FT4), thyroid stimulating hormone (TSH) levels were determined. The levels of FPG, TC, TG, HDL-C and LDL-C were measured using a HITACHI7020 automatic biochemical analyzer (Hitachi, Tokyo, Japan), and FT3, FT4, TSH and C-peptide were measured using an Abbott I-2000 automatic chemiluminescence immunoassay analyzer (Abbott Diagnostics, Abbott Park, IL, USA). HbA1c was measured using the American Bio-Rad D-10 analyzer (Bio-Rad Laboratories, Inc., Hercules, CA, USA).

(2) The positive rates of GADA, ZnT8A, and IA-2A were determined by the radioligand method, and the index of GADA, ZnT8A, and IA-2A was higher than 0.05, 0.011, and 0.007, respectively. The positive rate of insulin autoantibody was analyzed in the control group and TD group.

(3) Clinical characteristics of patients with and without insulin antibody positivity were analyzed, including age, sex, BMI, HbA1c, FPG, C-peptide, TC, TG, HDL-C, LDL-C, FT3, FT4, and TSH levels.

(4) The positive rates of thyroid autoantibodies in T1DM patients with different positive insulin autoantibodies were sampled, and the positive

rates of TRAb, TPOAb and TGAb were measured by automatic chemiluminescence immunoassay. The positive rate of thyroid autoantibodies and insulin autoantibodies in T1DM patients was analyzed.

Statistical Analysis

SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used to process the data of this study. In the measurement data, univariate analysis of variance or *t*-test was used for the data of normal distribution, which was represented by (x±s); for the data of non-normal distribution, it was represented by median. χ^2 test was used for counting data, expressed as [n (%)], and test standard α=0.05. p<0.05 was considered statistically significant.

Results

Comparison of Clinical Features Between Control Group, HT Group, and Graves Group

There were no significant differences in BMI, C-peptide, TG, and HDL-C levels among the three groups (p>0.05). The age, female proportion, and FPG level in the HT and Graves groups were significantly higher than those in the control group (p<0.05). The levels of TC and TSH in the HT group were significantly higher than those in the control group and Graves group, while the levels of FT4 and LDL-C were significantly lower than those in the control group and Graves group. The levels of TC and TSH in the Graves group were significantly lower than those in the control group, while the levels of HbA1c, LDL-C, and FT4 were significantly higher than those in the control group. The level of FT3 was significantly higher than that of the control group and HT group (p<0.001). There were no significant differences in age, FPG, and HbA1c between the HT group and the Graves group (p>0.05) (Table I).

Comparison of the Positive Rate of Insulin Autoantibody Between Control Group and TD Group

The positive rates of GADA, ZnT8A, IA-2A, double antibody, and triple antibody in the TD group were significantly higher than those in the control group, while the positive rate for one of the three insulin autoantibodies in the TD group was significantly lower than that in the control group (p<0.001) (Table II).

Comparison of Clinical Characteristics Between Patients with Insulin Autoantibodies Positivity and Negativity

There were no significant differences in age, sex, BMI, HbA1c, FPG, TC, HDL-C, FT3, FT4, and TSH levels in patients with and without insulin antibody positivity (p>0.05). The levels of C-peptide, TG and LDL-C in patients with positive insulin autoantibody were significantly

Table I. Comparison of clinical characteristics of patients in the control group, HT group, and Graves group.

Clinical features	Control group (n = 313)	HT group (n = 41)	Graves group (n = 26)	χ^2/F	p
Age	29.56 ± 12.38	32.44 ± 14.28*	33.19 ± 14.67*	9.131	0.007
Male (%)	185 (59.11)	31 (75.61)*	21 (80.77)*	8.234	0.016
BMI (kg/m^2)	19.43 ± 5.37	19.55 ± 5.59	19.20 ± 5.18	1.071	0.231
HbA1c (%)	10.89 ± 2.74	11.42 ± 3.29	12.11 ± 3.40*	9.786	< .001
FPG (mmol/L)	9.84 ± 3.16	11.39 ± 3.37*	10.98 ± 3.24*	7.943	< .001
C peptide (pmol/L)	102.46 ± 32.17	96.74 ± 29.27	99.01 ± 31.45	1.291	0.146
TC (mmol/L)	4.82 ± 1.14	5.98 ± 1.76*	3.55 ± 1.04*#	12.381	< .001
TG (mmol/L)	0.98 ± 0.23	1.07 ± 0.31	0.92 ± 0.25	1.083	0.132
HDL-C (mmol/L)	1.27 ± 0.40	1.44 ± 0.49	1.18 ± 0.37	1.190	0.287
LDL-C (mmol/L)	2.87 ± 0.86	1.70 ± 0.78*	3.69 ± 1.22*#	12.381	< .001
FT3 (pmol/L)	4.68 ± 1.52	4.57 ± 1.68	6.78 ± 2.11*#	6.704	< .001
FT4 (pmol/L)	14.56 ± 4.13	9.89 ± 3.24*	18.65 ± 4.97*#	19.085	< .001
TSH (μU/ml)	2.03 ± 0.61	4.70 ± 1.65*	0.02 ± 0.01*#	23.406	< .001

Compared with the control group, *p < 0.05; Compared with HT group, #p < 0.05. Body mass index (BMI), fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), free triiodothyronine (FT3), free thyroid hormone (FT4), thyroid stimulating hormone (TSH).

Table II. Comparison of a positive rate of insulin autoantibody between the control group and TD group (n, %).

Group	Number of cases	GADA positive	ZnT8A positive	IA-2A positive	Positive for one of the three insulin autoantibodies	Positive for two of the three insulin autoantibodies	Positive for three insulin autoantibodies
The control group	313	163 (52.08)	39 (12.46)	97 (30.99)	160 (51.12)	50 (15.97)	13 (4.15)
TD group	67	56 (83.58)	35 (52.23)	37 (55.22)	18 (26.87)	25 (37.31)	20 (29.85)
χ^2		22.434	55.687	14.197	13.036	15.863	45.955
p		< .001	< .001	< .001	< .001	< .001	<.001

Anti-glutamate decarboxylase antibody (GADA), zinc transporter-8 autoantibody (ZnT8A), insulinoma-associated protein-2 antibody (IA-2A), thyroid disease (TD).

lower than those in patients with negative insulin autoantibody (p<0.05) (Table III).

Positive Rate of Thyroid Autoantibodies in T1DM Patients with Different Positive Insulin Autoantibodies

In T1DM patients, the positive rates of TPOAb and TGAb in GADA and IA-2A-positive patients were significantly higher than those in GADA and IA-2A-negative patients (p<0.05). The positive rate of TPOAb in ZnT8A-positive patients was significantly higher than that in ZnT8A-negative patients (p<0.05) (Table IV).

Among patients with positive insulin autoantibodies, the positive rates of TRAb, TPOAb, and TGAb in T1DM patients with positive double and triple antibodies were significantly higher than those in patients with positive single antibodies (p<0.05) (Table V).

Discussion

The incidence of TD in T1DM patients is approximately 15-30%, which may be related to the similar genetic mechanism and immune deficiency between the two groups[6]. At present, it is believed[7] that the bioactive substances produced in the hyperglycemia environment of T1DM patients can significantly affect the thyroid cell function, resulting in the change of thyroid autoantibodies such as TRAb, TPOAb, and TGAb. A high thyroid antibody level can cause abnormal thyroid follicular function and affect the secretion of thyroid hormones. In turn, changes in thyroid function in T1DM patients occur, and TD is promoted[7]. Some studies[8] have found that the positive rate of insulin autoantibodies in T1DM patients is related to ethnicity, genetics, gender, disease course, and other factors, but

Table III. Comparison of clinical characteristics between patients with positive and negative insulin autoantibodies.

Clinical features	Patients with insulin autoantibody positivity (n = 286)	Patients without insulin autoantibody positivity (n = 94)	χ^2/F	p
Age	30.29 ± 13.29	29.60 ± 12.87	0.572	0.604
Male (%)	181 (63.29)	56 (59.57)	0.415	0.519
BMI (kg/m^2)	19.51 ± 5.69	19.18 ± 5.24	1.231	0.135
HbA1c (%)	11.09 ± 3.17	10.85 ± 2.80	0.956	0.217
FPG (mmol/L)	10.22 ± 3.22	9.68 ± 3.05	1.309	0.115
C-peptide (pmol/L)	103.68 ± 31.87	95.30 ± 28.96	3.491	0.006
TC (mmol/L)	4.90 ± 1.25	4.73 ± 1.18	0.867	0.245
TG (mmol/L)	1.04 ± 0.28	0.82 ± 0.19	5.683	< .001
HDL-C (mmol/L)	1.26 ± 0.37	1.35 ± 0.41	0.905	0.124
LDL-C (mmol/L)	2.98 ± 0.91	2.25 ± 0.73	9.930	< .001
FT3 (pmol/L)	4.79 ± 1.58	4.88 ± 1.62	0.453	0.671
FT4 (pmol/L)	14.47 ± 3.98	13.93 ± 3.34	1.446	0.097
TSH (μU/ml)	2.13 ± 0.64	2.33 ± 0.70	1.102	0.132

Body mass index (BMI), fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), free triiodothyronine (FT3), free thyroid hormone (FT4), thyroid stimulating hormone (TSH).

Table IV. Positive rate of thyroid autoantibodies in T1DM patients with different positive insulin autoantibodies n (%).

Insulin autoantibody		The number of cases	TRAb (n = 32)	TPOAb (n = 52)	TGAb (n = 38)
GADA	Positive	219	23 (10.50)	49 (22.37)	32 (14.61)
	Negative	161	9 (5.59)	3 (1.86)[a]	6 (3.73)[a]
ZnT8A	Positive	74	8 (10.81)	21 (28.38)	11 (14.86)
	Negative	306	24 (7.84)	31 (10.13)[b]	27 (8.82)
IA-2A	Positive	134	16 (11.94)	39 (29.10)	27 (20.15)
	Negative	246	16 (6.50)	13 (5.28)[c]	11 (4.47)[c]

[a]$p < 0.05$ compared with GADA positive; Compared with ZnT8A positive, [b]$p < 0.05$; [c]$p < 0.05$ compared with positive IA-2A. Anti-glutamate decarboxylase antibody (GADA), zinc transporter-8 autoantibody (ZnT8A), insulinoma-associated protein-2 antibody (IA-2A), thyroid stimulating receptor antibody (TRAb), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TGAb).

the correlation between it and TD and thyroid autoantibodies is not completely clear. The study on the expression of GADA, ZnT8A, and IA-2A in T1DM patients with TD and their correlation with thyroid autoantibodies is conducive to the early diagnosis and clinical intervention of TD in T1DM patients.

In this study, it was found that female T1DM patients were more likely to be complicated with TD, which may be related to the correlation between the level of estradiol and autoimmunity in the female body[9,10]. In this study, the age of T1DM patients with TD was significantly higher, which may be related to the course of T1DM. Studies[11,12] have found that long-term hyperglycemia can promote abnormal thyroid hormone secretion and increase the risk of TD. In this study, it was found that the FPG level in T1DM patients with TD was significantly higher than that in the control group, the HbA1c level was significantly higher in the Graves group, while the TC and LDL-C levels were significantly lower, and the TC and LDL-C levels were significantly higher in the HT group, which further indicated that the occurrence of HD could affect the control of blood glucose and lipid in T1DM patients, especially for patients with Graves. Graves' disease is often clinically characterized by hyperthyroidism, which significantly increases thyroid hormone levels and glycogenolysis and aggravates pancreatic β cell damage. It also accelerates lipid metabolism, increases LDL-C receptor expression, and thus increases HbA1c level and significantly decreases TC and LDL-C levels[13]. It is suggested[14] that thyroid function screening should be included in routine examination for patients with T1DM with significantly abnormal and poorly controlled lipid levels, so as to contribute to the early diagnosis of TD.

In this study, it was found that the positive rates of GADA, ZnT8A, and IA-2A in T1DM patients with TD were significantly higher than those in patients with T1DM alone, which may be due to the presence of glutamate decarcarboxylase in many tissues and organs, such as thyroid and pancreas and was significantly related to the abnormal expression of thyroid epithelial cells[15]. ZnT8A can be expressed in thyroid follicular cells, and thyroid hormones can regulate the expression of zinc ions and zinc transporters, and the level of ZnT8A increases with abnormal thyroid function in patients[16].

Table V. The positive rate of thyroid autoantibodies in T1DM patients n (%).

Insulin autoantibody	The number of cases	TRAb	TPOAb	TGAb
Positive for one of the three insulin autoantibodies	178	10 (5.62)	18 (10.11)	11 (6.18)
Positive for two of the three insulin autoantibodies	75	15 (20.00)*	24 (32.00)*	21 (28.00)*
Positive for three insulin autoantibodies	33	7 (21.21)*	10 (30.30)*	6 (18.18)*
χ^2		14.755	20.677	22.582
p		< .001	< .001	< .001

*$p < 0.001$ compared with positive monoantibody. Thyroid stimulating receptor antibody (TRAb), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TGAb).

IA-2A is a specific marker of islet β cell damage, and islet β cell damage in T1DM patients with TD is often higher than that in patients with T1DM alone, which leads to a significantly higher positive rate of IA-2A in T1DM patients with TD[17]. In addition, this study found that the positive rates of double antibody and triple antibody were significantly higher in the TD group, which further suggested that close follow-up of thyroid function should be conducted for T1DM patients with multiple positive insulin antibodies. In this study, the levels of C-peptide in patients with positive insulin autoantibody were significantly lower than those in patients with negative insulin autoantibody, suggesting that insulin autoantibody may have a significant correlation with pancreatic islet function impairment. This may be due to the injury of islet β cells in T1DM patients, which can cause antigen exposure, activate the immune system in the body, and promote the production of insulin antibodies and other factors. In this study, it was found that TG and LDL-C levels in patients with positive insulin autoantibody were significantly lower than those in patients with negative insulin autoantibody, suggesting that the metabolic disorder in patients with positive insulin autoantibody was mild, which was similar to the results of previous studies[18].

In this study, patients with positive GADA, ZnT8A, and IA-2A were more likely to be combined with positive TPOAb, and patients with multiple positive insulin autoantibodies had higher positive rates of TRAb, TPOAb, and TGAb, which was similar to the results of related reports[19]. Some studies[20] have found that TD patients with high TPOAb titer have higher insulin autoantibody-positive rate, and TPOAb titer in TD patients with positive insulin autoantibody is significantly higher than that in patients with negative insulin autoantibody, which may be caused by the similarity of the immunological mechanism of TD and T1DM, but the specific mechanism still needs further study.

Limitations

There are several limitations in the current study: first, not all of the T1DM patients in this study were newly diagnosed with T1DM, and different treatment times and strategies may have a certain impact on the study results. Second, the study did not exclude patients with thyroid diseases who were already using medications to control thyroid dysfunction. Third, the sample size of this study was limited. Thus, we will conduct in-depth research in the future to enrich the current content further.

Conclusions

The occurrence of TD can aggravate the disorder of glucose and lipid metabolism in T1DM patients, and T1DM patients with multiple positive insulin autoantibodies are more likely to be combined with positive thyroid autoantibodies. It is suggested[21] that routine thyroid antibody screening should be performed in clinical practice for patients with increased abnormal glucose and lipid metabolism and multiple positive insulin autoantibodies, which is helpful for the early diagnosis of TD.

Conflict of Interest

The authors declare that they have no conflict of interests.

Informed Consent

All subjects provided written informed consent for inclusion before they participated in the study.

Ethics Approval

The study was carried out after being approved by the Medical Ethics Committee of Ankang City Central Hospital (AKCCH2018002).

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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None.

Authors' Contribution

Jun Chen: Data curation; Methodology; Software; Validation; Investigation; Writing-Original Draft. Chen Bao: Conceptualization; Data curation; Formal analysis; Methodology, Investigation, Supervision; Software; Validation. All authors have read and approved the final version of the manuscript.

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