RESEARCH

Prevalence of positive islet autoantibody in type 2 diabetes patients: a cross-sectional study in a Chinese community

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Abstract

Background: Islet autoantibodies occur in type 2 diabetes. Our study aimed to investigate the prevalence of positive islet autoimmunity in community patients with type 2 diabetes.

Methods: A total of 495 community patients with type 2 diabetes were recruited using the method of cluster sampling in this cross-sectional study. Three islet autoantibodies including glutamic acid decarboxylase antibody (GADA), insulin autoantibody (IAA) and islet cell antibody (ICA) were measured, and clinical characteristics involved in those individuals were evaluated.

Results: The positive rate of islet autoantibodies was 28.5% in total, while combinations of different autoantibodies were rarely seen. Compared with GADA-negative group, positive counterparts significantly tended to have lower levels of body mass index (BMI), waist-hip ratio (WHR), and urinary microalbumin (mALB) ($P < 0.05$). Adjusted for confounding factors, WHR, triglycerides (TG), and mALB seemed to be negative independent predictors of GADA (OR < 1, $P < 0.05$). Patients with positive IAA tended to receive insulin treatment ($P < 0.0001$). Besides, fasting blood glucose (FBG), serum levels of high-density lipoprotein cholesterol (HDL-CH), aspartate transaminase (AST), and γ-glutamyltransferase (GGT) were more likely to be higher in IAA positive subgroup in comparison with the negative counterparts. While after AST was adjusted by unconditional logistic regression analysis, history of insulin treatment, FBG, HDL-CH, and GGT were confirmed as positive predictors of IAA. Furthermore, in patients who were IAA positive, those treated with exogenous insulin tended to have longer duration of diabetes than non-insulin treatment counterparts ($P < 0.0001$). With regard to ICA, however, there were no significant differences between the two subgroups, except that serum level of AST/ALT seemed to be slightly different ($P = 0.064$).

Conclusion: These data suggested that type 2 diabetic community patients with positive GADA tended to be lean and were able to maintain normal lipid metabolism, while patients with positivity of IAA were frequently accompanied with insulin treatment and more closely associated with diabetic liver damage.

Key Words
► type 2 diabetes
► community patients
► islet autoantibody
► clinical characteristics

Endocrine CONNECTIONS

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Introduction

Diabetes mellitus is an acknowledged global chronic disease affecting multiple organ systems with complications ranging from acute conditions such as hyperosmolar hyperglycemic state (HHS), diabetic ketoacidosis (DKA) to chronic conditions including diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy, nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease (1). The incidence of diabetes is on worrisome rise globally, especially in China (2). Historically, based on positivity of islet autoantibodies, diabetes mellitus had been classified into two clinical types: type 1 diabetes (T1DM) and type 2 diabetes (T2DM) (3, 4). The progressive destruction of islet β cell mass caused by islet autoimmunity was considered to be the main etiology of T1DM (5, 6), whereas T2DM tended to be insulin resistant and islet autoimmunity seemed not to be involved in this progress (7). Besides, there was a special form of diabetes termed as latent autoimmune diabetes in adults (LADA), which had clinical phenotype of T2DM and islet autoimmunity positivity of T1DM, and previous studies suggested that it indeed was a subtype of T1DM (8, 9, 10). However, increasing notable discoveries had provided evidence supporting the notion that islet autoimmunity is also a vital component involved in the pathogenesis and development of classical T2DM (11, 12, 13, 14). Typical islet autoantibodies such as glutamic acid decarboxylase antibody (GADA), insulin autoantibody (IAA), and islet cell antibody (ICA), which were considered as biomarkers of classical T1DM, were also reported to be involved in the prevalence of T2DM in recent years. Moreover, associations between these islet autoantibodies and related clinical features in T2DM were observed (15, 16). Previous researches suggested that the positivity of GADA was associated with thyroid and adrenal autoimmunity (17, 18, 19), and one recent Chinese study reported that ICA was related to systemic inflammation and positivity of IAA was more closely associated with insulin treatment (12).

Nevertheless, most previous studies have mainly focused on inpatients or outpatients based on hospitals or clinics, whose poor representation of the whole population of diabetic patients in a certain region might lead to bias. Furthermore, few studies have addressed the correlation between clinical biochemical features such as lipid metabolism, liver and kidney function, and islet autoimmunity in patients with T2DM. In order to further explore the epidemic and clinical characteristics that are distinctively related to islet autoantibodies in community

patients with T2DM, we performed a cross-sectional study using the method of cluster sampling, with a total of 495 diabetic patients recruited from Wu Jing community (Shanghai, China). Islet autoantibodies including GADA, IAA, ICA, and clinical biochemical characteristics referring to lipid metabolism, liver and renal function were all determined among each participant. Thus, our current study aimed to identify the prevalence of positive islet autoimmunity in community patients with T2DM and its potential correlative factors.

Material and methods

Study population

A total of 495 participants from Wu Jing community, Min Hang district, Shanghai, China were consecutively recruited during the period from January to November, 2017 in this cross-sectional study, we applied the method of cluster sampling which can largely represent the total population of T2DM in Shanghai and even the Yangtze river delta region. All characters were clinically diagnosed as T2DM based on the criteria of Chinese Diabetes Society. Those who were under condition of acute infection, allergic disease or other autoimmune diseases were excluded. Islet autoantibodies including GADA, IAA, ICA and clinical biochemical patterns were measured among each subject. The study protocol was approved by Ethics Committee of Basic Medical College of Fudan University (2016-Y028) and Huashan Hospital affiliated to Fudan University (2016-320), and written informed consent was also obtained from all of individuals.

Autoantibody evaluation

Serum levels of islet autoantibodies including GADA, IAA, ICA were determined by enzyme-linked immunesorbent assay (ELISA) in the Department of Clinical Laboratory in Huashan Hospital (Shanghai, China). All samples were measured in duplicate. GADA was detected by ELISA kit (Euroimmun AG, Lübeck, Germany) according to the instruction of the manufacturer, and its positive criteria were defined as ≥ 5 IU/mL. The sensitivity and specificity of GADA ELISA kit were 92 and 98% respectively based on the Diabetes Autoantibody Standardization Program (DASP 2003). IAA and ICA were determined by ELISA kits (Biomerica, USA). We recorded the spectrophotometric readings (optical density (OD) in absorbance units) from each pore and calculated the average OD reading of the

reference pore, negative pore, and positive controls pore, and then divided the average OD of samples and controls by the average OD of reference. The interpretation of results of ratio value was negative if <0.95, positive if >1.05, and indeterminate (borderline) if 0.95–1.05.

Clinical data collection

The basic epidemiological information such as age, gender, height, weight, body mass index (BMI), waist and hip circumference, duration of diabetes, history of insulin treatment, and diabetic family history were all collected except that the data from 13 cases were not available. Fasting blood samples and random urine samples were collected among each individual, series of biochemical characteristics including fasting blood glucose (FBG), hemoglobin A1c (HbA1C), low-density lipoprotein cholesterol (LDL-CH), high-density lipoprotein-cholesterol (HDL-CH), triglycerides (TG), total cholesterol (TCHOL), alanine aminotransferase (ALT), aspartate transaminase (AST), AST/ALT, γ-glutamyltransferase (GGT), urine creatinine (Ucr), urinary microalbumin (mALB), mALB/Ucr, serum creatinine (CREA), serum uric acid (UA), urea were also evaluated.

Statistical analysis

Quantitative data were presented as mean ± S.D. or median (P25,P75) and categorical data were summarized using frequencies as well as proportions or percentages of patients. To compare the differences between two independent groups divided by whether the autoantibody is positive or not, independent samples *t*-test was used for parametric data and Mann–Whitney *U* test or chi-square test for non-parametric counterpart. Since Spearman correlation analysis cannot be used to assess the correlation between levels in one variable and the qualitative variable, we divided clinical biochemical parameters which were continuous variables into two parts according to their medians, then, they were allowed to become categorical variables. The relationships between islet autoantibodies and clinical features were performed using Spearman correlation analysis. Furthermore, unconditional logistic regression analyses (also called binary logistic regression analysis) was used to analyze the independent factors of islet autoantibodies after adjusting for possible confounding variables. *P* values <0.05 were considered statistically significant. All analyses were performed using SPSS, version 22.0 (IBM).

Results

Prevalence of three islet autoantibodies individually or in combination among community patients with T2DM

In the present cross-sectional study, total 495 T2DM patients in a Chinese community were enrolled, islet autoantibody measurement were collected and presented in Table 1. The percentage of patients who had GADA was 8.28%, IAA 20.8% and ICA 3.03%, with 28.3% (*n* = 141) having at least one of them. The combination of different autoantibodies occur as a relative lower proportion with GADA + IAA (2.22%, *n* = 11), IAA + ICA (1.21%, *n* = 6) and GADA + ICA (0.20%, *n* = 1). Patients positive for all these three autoantibodies were not observed (Table 1).

Clinical and biochemical features of individual islet autoantibodies positive or negative subgroup

Epidemic and clinical characteristics of 482 patients (including 211 males and 271 females) were grouped in Table 2 according to positivity of individual islet autoantibody, 13 cases were excluded because of missing basic epidemiological information. Compared with GADA-negative group, GADA-positive counterparts tended to have significant lower levels of BMI, WHR, and mALB (*P* < 0.05). Moreover, the levels of TG (*P* = 0.056), Ucr (*P* = 0.077) and UA (*P* = 0.093) in GADA-positive group were trending lower compared with those in GADA-negative group, in spite of no statistical significance. As presented in Table 2. The percentage of patients who received insulin treatment in IAA-positive group (29.1%) was markedly higher than that in IAA-negative group (7.14%) (*P* < 0.0001), as well as the level of FBG, HDL-CH, AST, GGT (*P* < 0.05). Furthermore, in order to exclude the interference of exogenous insulin use, we divided 103 IAA-positive patients into two groups according to whether they received insulin treatment to see if there are any differences. Among all 103 IAA-positive patients, 30 patients received insulin treatment and the other 73 patients did not. All clinical and biochemical characteristics detected above were compared between the two groups except for Ucr, mALB, U-mALB/Ucr (because of quite amount of missing data in insulin treatment group). As shown in Supplementary Table 1 (see section on supplementary data given at the end of this article), the duration of diabetes was longer among the 30 IAA positive patients that received exogenous insulin treatment as compared with the 73 who were not insulin treated. Other variables showed no significant

Table 1 Detection of serum islet autoantibodies individually or its combination in community diabetic patients.

Islet autoantibody or its combination	Number of positive	Positive rate (%)
GADA (individual)	41	8.28
IAA (individual)	103	20.8
ICA (individual)	15	3.03
GADA + IAA	11	2.22
IAA + ICA	6	1.21
GADA + ICA	1	0.20
GADA + IAA + ICA	0	0
GADA/IAA/ICA	141	28.5
Total number of cases	495	–

'+' means simultaneously positive; '/' means at least one autoantibody positive.
GADA, glutamic acid decarboxylase autoantibodies; IAA, insulin autoantibodies; ICA, islet cell cytoplasmic autoantibodies.

differences between the two groups. No significant differences of biochemical characteristics between ICA-positive and -negative subgroups were observed, except that the serum level of AST/ALT in positive participants seemed slightly higher than that in negative counterparts ($P=0.064$). Differences between two subgroups divided by positivity of individual autoantibody were presented more intuitively in Fig. 1.

Correlation of islet autoantibodies with clinical characteristics in community diabetic patients

In order to explore the potential factors which might be related with islet autoimmunity in community patients with T2DM, we performed the Spearman correlation analysis between individual islet autoantibody and clinical features. As indicated in Table 3, BMI, WHR, TG, levels of mALB were significantly correlated with the levels of GADA in positive patients ($r<0$, $P<0.05$). Besides Ucr, UA levels were slightly negatively related to the levels of GADA in GADA-positive patients ($P=0.074$, $P=0.059$ respectively). With regard to IAA, history of insulin treatment, levels of FBG, HDL-CH, AST, GGT were positively correlated with the levels of IAA in IAA-positive patients ($r>0$, $P<0.05$). However, there were no factors that are related to the positivity of ICA, except for that serum level of AST/ALT which seemed mildly correlated ($r=0.083$, $P=0.078$).

Independent factors that associated with islet autoimmunity

Next, in order to further address the independent factors associated with islet autoimmunity, we conducted the

unconditional logistic regression analysis. All indexes with statistical significance ($P<0.05$) or obvious tendency in the correlation analysis ($P<0.1$) were incorporated into the regression analysis model, besides, clinical factors such as age, gender, and BMI were also included. As Table 4 showed, after adjustment for age, gender, BMI, Ucr and UA, WHR (OR=0.40, 95% CI (0.17–0.95), $P=0.037$), TG (OR=0.36, 95% CI (0.17–0.79), $P=0.010$), and mALB (OR=0.36, 95% CI (0.17–0.79), $P=0.011$) remained independently associated with the positivity of GADA. As for IAA, after confounding factors were adjusted, insulin treatment (OR=18.94, 95% CI (8.49–42.24), $P<0.0001$), and serum levels of FBG (OR=4.13, 95% CI (2.15–7.94), $P<0.001$), HDL-CH (OR=2.30, 95% CI (1.34–3.96), $P=0.003$), and AST (OR=1.64, 95% CI (1.00–2.69), $P=0.05$) were independently associated with the positivity of IAA. Furthermore, among all epidemical and biochemical features analyzed, no significant factors were observed as independently associated with ICA.

Discussion

Several studies reported that islet autoimmunity, including T cell-mediated cellular immunity (20, 21) and humoral immunity in which autoantibodies played a vital role (10, 11, 12), both contributed to the pathogenesis and development of not only T1DM, but also T2DM. Furthermore, a series of evidence clued that the associations between islet autoimmunity and clinical features in T2DM occurs to some extent (18, 22, 23).

In this cross-sectional study, we carried out the method of cluster sampling and a total of 495 patients clinically diagnosed T2DM from Wu Jing community (Shanghai, China) were recruited as a representative of type 2 diabetic population in the Yangtze River delta region. Approximately 28.5% of those participants were at least one islet autoantibody positive, with 8.28% for individual GADA, 20.8% for individual IAA and 3.03% for individual ICA, which was roughly consistent with previous domestic and foreign studies (10, 12, 24). However, rare combinations of two or more autoantibodies were simultaneously observed in our study, which is in line with the previous report that the incidence of islet autoimmunity in Asians was lower than that in Northern Europeans (25, 26). The differences in dietary habits, environmental factors, ethnic factors and phenotypic characteristics could explain the heterogeneity in the prevalence and other characteristics of islet autoimmunity.

Table 2 Clinical and biochemical characteristics of each group classified regarding the positivity of islet autoantibodies.

	GADA negative	GADA positive	P value	IAA negative	IAA positive	P value	ICA negative	ICA positive	P value
Number of patients	454 (91.7%)	41	/	392 (79.2%)	103 (20.8%)	/	480 (97.0%)	15	/
Age (years)	65.0±6.56	64.1±7.82	0.389	64.9±6.42	65.0±7.57	0.894	64.9±6.63	65.1±8.13	0.900
Gender (male/female)	196/246 (44.3/55.7%)	15/25	0.404	170/212 (44.5/55.5%)	41/59	0.530	203/265 (43.4/56.6%)	8/6	0.307
BMI (kg/m²)	24.5±3.06	23.0±2.67	0.006[a]	24.3±2.98	24.5±3.35	0.616	24.3±3.07	24.9±2.64	0.585
WHR	0.91±0.06	0.88±0.05	0.003[a]	0.91±0.05	0.91±0.06	0.833	0.91±0.05	0.92±0.07	0.447
Duration of diabetes (years)	8.00±5.37	8.55±5.52	0.516	8.03±5.31	8.13±5.67	0.911	8.09±5.38	6.79±5.39	0.328
Insulin treatment	51	7	0.267	28	30	<0.0001[b]	57	1	0.568
Diabetic family history	115 (25.3%)	10	0.888	98	27	0.785	121 (25.2%)	4	0.819
FBG (mmol/L)	7.24±1.53	7.55±2.57	0.483	7.23±1.71	7.40±1.32	0.023[c]	7.28±1.65	6.83±0.99	0.373
HbA1C (%)	7.02±1.10	7.27±1.25	0.243	7.02±1.11	7.15±1.12	0.259	7.05±1.11	6.76±1.04	0.367
LDL-CH (mmol/L)	2.33±0.99	2.13±0.72	0.206	2.32±0.98	2.29±0.95	0.740	2.31±0.97	2.48±0.92	0.513
HDL-CH (mmol/L)	1.04±0.41	1.14±0.43	0.125	1.02±0.41	1.15±0.37	0.005[a]	1.05±0.41	1.01±0.28	0.739
TG (mmol/L)	2.09±1.60	1.67±1.12	0.056	2.01±1.45	2.21±1.95	0.749	2.05±1.56	2.10±1.94	0.583
TCHOL (mmol/L)	4.29±1.28	4.00±0.99	0.109	4.23±1.30	4.41±1.08	0.179	4.27±1.27	4.32±0.83	0.915
ALT (U/L)	10.1±6.72	9.44±3.11	0.388	9.97±6.56	10.5±6.26	0.284	10.1±6.56	8.40±3.68	0.202
AST (U/L)	18.4±10.5	17.7±8.10	0.797	17.9±10.7	19.9±8.34	0.002[a]	18.3±10.3	18.8±9.73	0.721
AST/ALT	2.08±0.97	2.03±0.77	0.810	2.05±0.94	2.17±0.98	0.193	2.07±0.96	2.29±0.65	0.064
GGT (U/L)	18.5 (12.3, 29.8)	20.0 (14.0, 28.3)	0.464	20.0 (13.0, 27.0)	22.0 (15.8, 31.3)	0.047[c]	20.0 (14.0, 28.0)	25.0 (16.0, 67.0)	0.113
Ucr (µmol/L)	10127±7147	7498±3778	0.077	10240±7247	8599±5553	0.121	9956±7021	9208±5888	0.694
UREA (mmol/L)	5.24±1.55	5.52±1.35	0.208	5.23±1.58	5.39±1.33	0.295	5.26±1.55	5.27±0.95	0.955
mALB (mg/L)	6.53 (3.75, 22.9)	4.23 (3.00, 10.4)	0.01[c]	6.39 (3.40, 21.3)	5.70 (3.45, 23.7)	0.698	6.30 (3.40, 21.4)	8.75 (3.15, 65.7)	0.498
U-mALB/Ucr (mg/g)	9.17 (4.59, 22.8)	5.85 (4.70, 16.7)	0.221	8.82 (4.48, 21.8)	8.80 (5.28, 23.9)	0.332	8.80 (4.58, 21.9)	13.0 (6.46, 67.2)	0.250
CREA (µmol/L)	64.5±19.4	61.8±17.6	0.406	64.0±19.6	65.3±17.8	0.511	64.3±19.4	65.2±12.7	0.678
UA (µmol/L)	281±88.5	261±107	0.093	281±92.2	273±82.8	0.273	279±91.1	297±59.0	0.286

Data are showed as n (%), mean ± s.D. or median (P25, P75). P values refer to the comparison of the two subgroups by independent samples t-test or Mann–Whitney U test for continuous variables, and chi-square test for categorical variables. P value <0.05 was considered statistical significance. Significant differences are in bold and the significance level is indicated with superscript letters.

[a]$P < 0.01$, [b]$P < 0.0001$ and [c]$P < 0.05$,

ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CREA, serum creatinine; FBG, fasting blood glucose; GADA, glutamic acid decarboxylase autoantibodies; GGT, γ-glutamyltransferase; HbA1c, hemoglobin A1c; HDL-CH, high-density lipoprotein (cholesterol); IAA, insulin autoantibodies; ICA, islet cell cytoplasmic autoantibodies; LDL-CH, low-density lipoprotein (cholesterol); mALB, urinary microalbumin; TCHOL, total cholesterol; TG, triglycerides; UA, serum uric acid; Ucr, urine creatinine; WHR, waist-hip ratio.
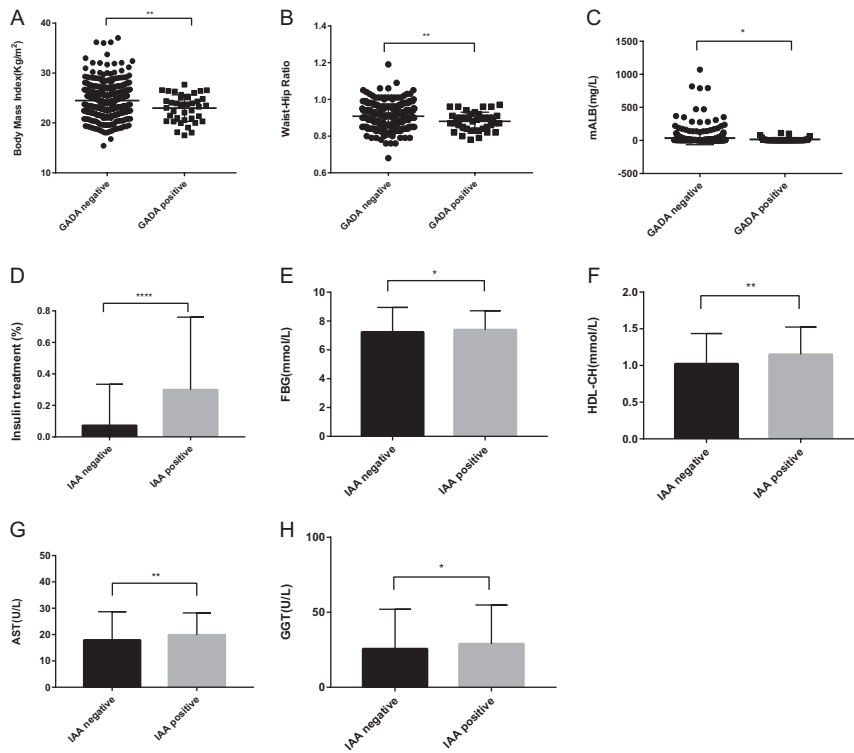
Figure 1
Significant differences between subgroups divided by positivity of GADA or IAA. (A, B and C) GADA-positive group presents lower levels of BMI, WHR and mALB in comparison with negative counterparts; (D, E, F, G and H) IAA-positive group tends to show higher rate of insulin treatment and higher levels of FBG, HDL-CH, AST and GGT than negative ones. All comparison tests between the two groups were performed using the statistical method of Mann–Whitney U test. *$P < 0.05$; **$P < 0.01$, ***$P < 0.001$ and ****$P < 0.0001$. BMI, body mass index; WHR, waist-hip ratio; mALB, urinary microalbumin; FBG, fasting blood glucose; HDL-CH, high-density lipoprotein (cholesterol); AST, aspartate transaminase; GGT, r-glutamyltransferase; GADA, glutamic acid decarboxylase autoantibodies; IAA, insulin autoantibodies.

In agreement with the previous studies (18, 19, 27, 28), our findings presented that patients in GADA-positive subgroup tended to have significantly lower BMI, WHR and TG than those in negative group, suggesting that GADA-positive participants seemed to be leaner and to have less abdominal obesity. T2DM has always been considered as a chronic metabolic syndrome with higher BMI and waist circumference values, low HDL cholesterol levels, higher triglyceride levels, higher blood pressure (29), while we found in the current study that type 2 diabetic patients with positivity of GADA might maintain normal lipid metabolism, thereby avoiding to get fat. The characteristics presented above were much more similar to the phenotype of typical T1DM. Therefore, it was reasonable to believe that type 2 diabetic patients with the positivity of GADA were more likely to develop insulin treatment dependence. Besides, our data also showed that mALBs were negatively correlated with GADA levels ($r=-0.122$, $P=0.007$) and served as an independent negative predictor of GADA (OR=0.36, $P=0.011$). Few previous studies were referred to associations between renal function and islet autoimmunity in T2DM, while a Chinese retrospective study reported that the incidence of microvascular complications including diabetic nephropathy were lower in LADA patients than that in T2DM patients at the early stage of diabetes (30). In this study, we also found GADA positivity is negatively related with the mALB levels. In our opinion, different pre-clinical periods of diabetes might be one reason for this phenomenon. For type 2 diabetic patients with islet autoimmunity, the destruction rate of islet function is more rapid than that of islet autoantibody-negative group, GADA-negative patients tend to undergo longer pre-clinical period and are at an increased risk of developing microvascular complications. Prospective studies about the renal function and GADA positivity is warranted.

The positivity rate of IAA (20.8%) in our study is lower than that in previous reports (12, 31), which could be due to the less insulin treatment in community diabetic patients rather than outpatients or inpatients were recruited in our study. IAA originally referred to autoantibody induced by insulin which are secreted by islet β cell, while it was also induced along with the exogenous insulin treatment. Indeed, in the present study, the prevalence of IAA was largely influenced by exogenous insulin therapy (OR=18.94, $P<0.0001$). Besides, in order to exclude the interference of exogenous insulin use, we divided IAA-positive patients into two groups according to whether they received insulin treatment to see if there were any differences. We found that the duration of diabetes in patients who received exogenous insulin treatment was longer than those non-insulin treatment patients, and it may be that patients with longer course of disease have more severe damage to islet function and

Table 3 Correlation analysis between individual islet autoantibody and clinical features.

	GADA positive (n = 41)	IAA positive (n = 103)	ICA positive (n = 15)
Age (years)			
r	−0.018	0.020	0.042
P	0.700	0.666	0.354
Gender (male/female)			
r	−0.038	−0.029	0.047
P	0.404	0.531	0.307
BMI (kg/m^2)			
r	**−0.167**	0.009	0.025
P	**<0.0001**[a]	0.841	0.583
WHR			
r	**−0.103**	0.016	0.055
P	**0.021**[b]	0.715	0.222
Duration of diabetes (years)			
r	0.002	0.029	−0.118
P	0.965	0.516	0.329
Insulin treatment			
r	0.051	**0.283**	−0.026
P	0.268	**<0.0001**[a]	0.569
Diabetic family history			
r	−0.006	0.012	0.010
P	0.888	0.785	0.820
FBG (mmol/L)			
r	0.065	**0.094**	−0.036
P	0.146	**0.038**[b]	0.428
HbA1C (%)			
r	0.049	0.040	−0.007
P	0.285	0.390	0.876
LDL-CH (mmol/L)			
r	−0.040	−0.004	0.010
P	0.378	0.379	0.824
HDL-CH (mmol/L)			
r	0.033	**0.185**	−0.020
P	0.470	**<0.0001**[a]	0.652
TG (mmol/L)			
r	**−0.111**	−0.046	−0.012
P	**0.014**[b]	0.309	0.788
TCHOL (mmol/L)			
r	−0.053	0.062	0.011
P	0.238	0.171	0.812
ALT (U/L)			
r	0.070	0.047	−0.089
P	0.118	0.295	0.202
AST (U/L)			
r	−0.020	**0.093**	−0.019
P	0.656	**0.039**[b]	0.668
AST/ALT			
r	0.002	0.035	0.079
P	0.967	0.431	0.078
GGT (U/L)			
r	−0.057	**0.049**	0.030
P	0.209	**0.047**[b]	0.510

(Continued)

Table 3 Continued.

	GADA positive (n = 41)	IAA positive (n = 103)	ICA positive (n = 15)
Ucr (μmol/L)			
r	−0.082	−0.059	−0.071
P	0.074	0.199	0.124
UREA (mmol/L)			
r	0.074	0.023	0.016
P	0.100	0.603	0.727
mALB (mg/L)			
r	**−0.122**	−0.051	0.024
P	**0.007**[c]	0.262	0.605
U-mALB/Ucr (mg/g)			
r	−0.090	0.002	0.024
P	0.052	0.959	0.605
CREA (μmol/L)			
r	−0.045	0.001	0.078
P	0.323	0.974	0.683
UA (μmol/L)			
r	−0.085	−0.062	0.056
P	0.059	0.168	0.210

Data of r and P values were calculated from Spearman correlation analysis. A P value <0.05 was considered as statistically significant. Significant correlations were in bold and the significance level is indicated with superscript letters.
[a]$P < 0.0001$, [b]$P < 0.05$ and [c]$P < 0.01$.
ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CREA, serum creatinine; FBG, fasting blood glucose; GADA, glutamic acid decarboxylase autoantibodies; GGT, γ-glutamyltransferase; HbA1c, hemoglobin A1c; HDL-CH, high-density lipoprotein (cholesterol); IAA, insulin autoantibodies; ICA, islet cell cytoplasmic autoantibodies; LDL-CH, low-density lipoprotein (cholesterol); mALB, urinary microalbumin; TCHOL, total cholesterol; TG, triglycerides; UA, serum uric acid; Ucr, urine creatinine; WHR, waist-hip ratio.

become more dependent on insulin therapy. Furthermore, level of FBG also seemed as a positive predictor of IAA (OR=4.13, $P<0.001$), maybe patients with positive IAA tended to be under a condition in which blood glucose was difficult to be controlled in comparison with IAA-negative counterparts. Besides, our study found that HDL-CH were positively associated with IAA ($r=0.185$, $P<0.0001$), as reported in a previous study, type 2 diabetic patients with GADA positive showed higher HDL-CH (32, 33), and whether IAA might also play a crucial role in regulating lipid metabolism and protecting macrovascular terms need to be further elucidated.

Interestingly, according to our study, both IAA and ICA were positively associated to several biochemical indicators of liver damage, including AST, GGT, AST/ALT. Liver diseases such as autoimmune hepatitis, non-alcoholic steatohepatitis (NASH), cirrhosis even liver cancer were presented to be correlated with diabetes mellitus (34, 35). Nevertheless, the internal correlation

Table 4 Independent factors related to autoantibody positivity by unconditional logistic regression analysis.

	OR (95% CI)	**P value**
GADA		
Age (years)	1.00 (0.95–1.05)	0.945
Gender	1.03 (0.49–2.20)	0.931
BMI (kg/m^2)	0.59 (0.27–1.30)	0.190
WHR	0.40 (0.17–0.95)	**0.037**[a]
TG (mmol/L)	0.36 (0.17–0.79)	**0.010**[a]
Ucr (μmol/L)	1.00 (0.997–1.003)	0.930
mALB (mg/L)	0.36 (0.17–0.79)	**0.011**[a]
UA (μmol/L)	0.64 (0.30–1.36)	0.244
IAA		
Age (years)	1.01 (0.97–1.04)	0.713
Gender	0.94 (0.57–1.55)	0.807
BMI (kg/m^2)	1.19 (0.73–1.95)	0.492
Insulin treatment	18.9 (8.49–42.2)	**<0.0001**[b]
FBG (mmol/L)	4.13 (2.15–7.94)	**<0.001**[c]
HDL-CH (mmol/L)	2.30 (1.34–3.96)	**0.003**[d]
AST (U/L)	1.64 (1.00–2.69)	**0.050**[a]
GGT (U/L)	1.51 (1.00–2.28)	0.052
ICA		
Age (years)	1.00 (0.93–1.09)	0.914
Gender	1.82 (0.62–5.37)	0.277
BMI (kg/m^2)	0.75 (0.26–2.26)	0.608
AST/ALT	2.51 (0.77–8.15)	0.125

OR (95% CI) and *P* value were calculated by unconditional logistic regression and *P* value ≤0.05 were considered statistically significant. Significant correlations were in bold and the significance level is indicated with superscript letters.
[a]$P \leq 0.05$, [b]$P < 0.0001$, [c]$P < 0.001$, [d]$P < 0.01$.
AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; GADA, glutamic acid decarboxylase autoantibodies; GGT, γ-glutamyltransferase; HDL-CH, high-density lipoprotein (cholesterol); IAA, insulin autoantibodies; ICA, islet cell cytoplasmic autoantibodies; mALB, Urinary microalbumin; OR, odds ratio; TG, triglycerides; UA, serum uric acid; Ucr, urine creatinine; WHR, waist-hip ratio.

between islet autoantibodies and diabetic liver damage is poorly understood. In our study, Spearman correlation analysis showed that AST ($r=0.093$, $P=0.039$) and GGT ($r=0.049$, $P=0.047$) were positively associated with IAA. Presumably, the reason might be that increased circulating islet autoantibodies would induce systemic autoimmune and chronic inflammatory status. An Italian study demonstrated that type 2 diabetic patients with presence of GADA were in high risk for thyroid and adrenal autoimmunity (18). Thus, it was most likely that autoimmune liver disease were generated meanwhile under the condition of islet autoimmunity. Moreover, a research referring to children presented that childhood autoimmune hepatitis is associated with a high frequency of ICA and IAA (36), which is in line with our current study among adult patients to some extent.

In this cross-sectional study, we investigated the prevalence of islet autoantibodies in patients with T2DM from one Chinese community and analyzed the correlation between clinical biochemical characteristics and islet autoantibodies, in order to explore the intrinsic factors of islet autoimmunity in T2DM. T2DM tended to be a chronic disorder caused by comprehensive factors of autoimmunity, metabolism dysfunction and systemic inflammation, and so forth. Furthermore, islet autoimmunity is closely related to metabolic syndrome, liver and kidney function. Limited by the small sample size, some of the results illustrated above need to be confirmed by multi-center large sample study. Of course, much more researches need to focus on the islet autoimmune patterns of T2DM, in order to obtain a deeper understanding and provide new ideas for the diagnosis, treatment and prevention of diabetes mellitus.

Conclusion

To conclude, our current study suggested that type 2 diabetic community patients with high prevalence of GADA tended to maintain normal lipid metabolism and avoid metabolic syndrome. However, positivity of IAA was frequently accompanied with insulin treatment and was more closely associated with diabetic liver damage.

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