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Clinical and biochemical characteristics of nonobese type 2 diabetic patients with glutamic acid decarboxylase antibody in Korea

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Abstract

We evaluated the prevalence of glutamic acid decarboxylase autoantibody (GADA) in nonobese patients with type 2 diabetes mellitus in Korea and investigated the characteristics of GADA-positive and GADA-negative patients. Two years later, we assessed the progression of beta-cell function in these patients. Of the 647 nonobese patients with type 2 diabetes mellitus enrolled in the study, 10.1% was positive for GADA. Glutamic acid decarboxylase antibody–positive patients had lower fasting and stimulated C-peptide levels compared with GADA-negative patients (1.70 ± 0.72 vs 1.24 ± 0.59 μg/L, $P < .001$; 2.59 ± 1.51 vs 1.99 ± 0.82 μg/L, $P < .001$). Patients treated with insulin had lower fasting and stimulated C-peptide levels than those not treated (1.13 ± 0.52 vs 1.66 ± 0.73 μg/L, $P = .002$; 1.85 ± 0.69 vs 2.49 ± 0.91 μg/L, $P = .004$) and had higher titers of GADA (30.5 ± 7.3 vs 6.0 ± 4.8 U/mL, $P < .001$). In terms of progression of beta-cell function, fasting and stimulated C-peptide levels were significantly lower in GADA-positive patients after 2 years (from 1.24 ± 0.59 to 0.95 ± 0.54 μg/L, $P = .004$; from 1.99 ± 0.82 to 1.61 ± 0.77 μg/L, $P = .007$), whereas no such difference was observed in the GADA-negative patients. We demonstrate that a significant proportion of Korean patients may be positive for GADA; this is consistent with studies of white subjects, although disagrees with previous reports on Korean subjects. By assessing the presence of GADA in Korean type 2 diabetic patients, we are able to predict their course of beta-cell function and identify in advance those who are likely to require insulin treatment.

1. Introduction

Type 1 diabetes mellitus (T1DM) is defined as a metabolic disorder featuring insulin deficiency resulting from selective autoimmune destruction of beta cells [1]. However, some diabetic patients are difficult to judge according to the current classification criteria. In particular, many nonobese patients with type 2 diabetes mellitus (T2DM) exhibit features of T1DM [2-4].

Autoantibodies, such as islet cell cytoplasmic antibodies, insulin autoantibody, insulinoma-associated protein 2 autoantibody, and glutamic acid decarboxylase autoantibody (GADA), are markers of beta-cell destruction via an autoimmune mechanism in the pathogenesis of T1DM. Among these, GADA is a strong predictor for T1DM autoimmunity [2-5]. Glutamic acid decarboxylase antibody levels appear to be stable after diagnosis, such that patients with T1DM for 10 years continue to have GADA present in their sera [6,7]. This indicates that GADA is unaffected by the absence of functional beta cells; thus, the GADA assay has become an important tool in predicting a patient's prognosis.

However, in cross-sectional studies of different populations, 1.7% to 16.1% of patients with T2DM [8-19] have been found to be positive for GADA. In patients with new-onset T2DM, 4.2% to 16% had GADA [4,20,21]. Many patients clinically classified as having T2DM cannot be treated with oral hypoglycemic agents and have to be referred for insulin treatment [22,23]. In Australia, it was shown that 73.7% of clinically classified patients with T2DM who needed insulin supplementation were positive for GADA [2]. This special form of slow, progressive autoimmune diabetes is referred to as latent autoimmune diabetes in adults (LADA). Among Korean patients with diabetes, 70% to 80% are nonobese; they are diagnosed with diabetes mellitus (DM) in adulthood, and the incidence

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of T1DM is extremely rare [24,25]. Some Korean patients with T2DM are positive for GADA, indicating a possible relationship of autoimmunity in its pathogenesis; however, the role of GADA in T2DM is unclear.

In this study, we determined the clinical and biochemical characteristics of nonobese patients with T2DM in Korea and compared these characteristics between patients positive for GADA with those without GADA. Patients also underwent follow-up examinations to investigate the role of GADA in the pathogenesis of T2DM in Korea.

2. Patients and methods

2.1. Patients

In this study, 1197 patients (622 males and 575 females; age range, 35-86 years) with T2DM were recruited at our affiliated hospitals and clinics from January 2000 to December 2002. Among them, subjects with clinical findings suggestive of T1DM were excluded based on the following criteria: (1) less than 0.6 μg/L of fasting C-peptide and less than 1.5 μg/L of stimulated (2 hours after breakfast) C-peptide; (2) onset of diabetes before the age of 35 years; (3) a history of diabetic ketoacidosis (DKA); and (4) insulin use within the first 6 months after the initial diagnosis of DM. Obese patients (with a body mass index [BMI] of >25 kg/m^2) were also excluded. Moreover, patients with secondary diabetes and those on medications known to influence glucose metabolism were excluded. In all, there remained 647 nonobese patients with T2DM who were then classified as either GADA-positive or GADA-negative. Of the 647 patients, 217 were maintained on a diabetic diet alone, 288 were on oral hypoglycemic agents, and 142 were already being treated with insulin.

In this study, we defined hypertensive patients as those on antihypertensive medication or those with a systolic blood pressure of greater than 140 mm Hg or a diastolic blood pressure of greater than 90 mm Hg. Measurements were taken from these patients and they were then followed up 2 years after the initial examination. The study protocol was approved by the Yonsei University College of Medicine Ethical Committee, and informed consent was obtained from each subject.

2.2. Measurement of anthropometric profiles

Age of onset, duration, family history of diabetes, and history of weight loss (>10% of weight), DKA, and insulin requirements were recorded. Body weight and height were measured in the morning while participants wore light clothing. Body mass index was calculated as the weight in kilograms divided by the square of height in meters. Waist circumference was determined using measuring tape placed midway between the lowest rib and the iliac crest while the participant stood on a flat floor with the feet 30 cm apart. Hip circumference was measured over the widest part of the gluteal region, and the waist-to-hip ratio was calculated accordingly.

2.3. Measurement of biochemical profiles

Blood samples were taken from all subjects after fasting for more than 10 hours. Fasting blood glucose concentration was measured immediately with an autoanalyzer using the hexokinase method (Hitachi 747; Roche, Montclair, NJ). HbA_{1c} was analyzed by high-performance liquid chromatography (Variant II, Bio-Rad, Hercules, CA). C-peptide concentration was measured using an enzyme chemiluminescence immunoassay (Immulite, DPC, Los Angeles, CA).

Total serum cholesterol and high-density lipoprotein cholesterol (HDL-C) were measured using a direct enzymatic method (Hitachi 747; Daiichi, Tokyo, Japan); serum triglyceride levels were measured by an enzymatic colorimetric method (Hitachi 747; Roche, Japan/Germany); and low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald's formula (total cholesterol − triglyceride/5 − HDL-C). Urine ketones were considered positive if 2+ or higher (Uriscan, Yeongdong, Korea; + represents trace quantities or less). Glutamic acid decarboxylase antibody was measured by radioimmunoassay using a commercial kit (RSR, Cardiff, Wales, UK) according to the manufacturer's instructions. Briefly, serum was incubated with ^{125}I-labeled recombinant human GAD65; protein A–sepharose was then added and the mixture was incubated. After centrifugation, the deposit was placed into a gamma scintillation counter. Values for GADA were calculated from a calibration curve prepared using serial dilutions of a positive control serum [26]. The laboratory performing this assay participated in the Diabetes Autoantibody Standardization Program and achieved a sensitivity and specificity for the proficiency GADA measurement of 82% and 89.8%, respectively [27]. Serum samples were considered GADA-positive at levels of 1 U/mL or more, 2 SD above the mean value obtained in the healthy individuals. The follow-up fasting and stimulated C-peptide levels were measured 2 years after the baseline in these participants.

2.4. Statistical analysis

Results are expressed as mean ± SD. A comparison was made between GADA (+) and GADA (−) groups using the independent t test and χ^2 test as was appropriate. Among the patients with GADA, a comparison between patients using insulin and those not using insulin was performed using the unpaired Mann-Whitney U test and χ^2 test as was appropriate. Changes in serum C-peptide levels between the baseline and 2-year follow-up sample were assessed using paired t tests. Statistical analyses were conducted using SPSS for Windows, version 11.0 (SPSS, Chicago, IL); $P < .05$ was set as the level of significance.

3. Results

The mean age at the time of study was 54.8 ± 11.2 years, the mean age at onset was 47.1 ± 9.8 years, the mean duration of diabetes was 7.7 ± 3.0 years, and the mean BMI

was 21.4 ± 3.2 kg/m^2. Of the 647 patients, 70 (10.1%; male-female, 39:31) were positive for GADA.

3.1. Clinical characteristics according to GADA detection

There were no significant differences in family history of DM (P = .408) or duration of DM (P = .837) between GADA-negative and GADA-positive patients. Compared with GADA-negative patients, GADA-positive patients were significantly younger (P < .001). The age at the onset of DM, BMI, waist circumference, waist-to-hip ratio, and prevalence of hypertension were significantly lower in the GADA-positive group than in the GADA-negative group (P < .001, P = .048, P = .003, P = .023, and P = .016, respectively). The history of weight loss and ketonuria was significantly higher in the GADA-positive group than in the GADA-negative group (P < .001 and P < .001, respectively). The GADA-positive group also required insulin more frequently than the GADA-negative group (P < .001) (Table 1).

We also analyzed the number of patients with GADA according to the duration of diabetes (Fig. 1). The frequency of GADA in patients were 12.3% (29/235), 9.5% (21/220), 10.7% (15/138), and 9.3% (5/54) for the durations of 5 or less, 6-10, 11-15, and more than 15 years of DM, respectively. The frequency of GADA was independent of the duration of diabetes (P = .784, using the χ^2 test).

3.2. Biochemical characteristics according to GADA detection

There were no significant differences in fasting blood glucose and HbA_{1c} levels between GADA-negative and GADA-positive patients (P = .329 and P = .287, respectively). Glutamic acid decarboxylase antibody–negative patients had higher levels of total cholesterol (P = .042), triglyceride (P = .006), and LDL-C (P = .006) than GADA-positive patients, but the levels of HDL-C were lower in GADA-negative patients (P = .003). Glutamic

Table 1
Comparison of baseline characteristics between GADA (+) and GADA (−) groups

	GADA (−) (n = 577)	GADA (+) (n = 70)	P
Sex (M/F)	309/268	39/31	.732
Age at study (y)	55.4 ± 9.2	49.7 ± 9.4	<.001
Age at onset (y)	47.7 ± 9.6	42.1 ± 9.5	<.001
Duration of DM (y)	7.7 ± 3.8	7.6 ± 4.1	.837
Family history of DM (%)	51.0	45.7	.408
Hypertension (%)	46.6	31.4	.016
History of weight loss (%)	20.5	55.7	<.001
Ketonuria (%)	13.5	44.3	<.001
Insulin requirement (%)	15.1	78.6	<.001
BMI (kg/m^2)	21.5 ± 3.2	20.7 ± 3.1	.048
Waist circumference (cm)	86.1 ± 9.3	82.6 ± 8.0	.003
Waist-to-hip ratio	0.89 ± 0.21	0.83 ± 0.19	.023
Fasting blood glucose (mmol/L)	9.10 ± 2.65	9.43 ± 2.84	.329
HbA_{1c} (%)	8.5 ± 2.2	8.8 ± 2.4	.287
Fasting C-peptide (μg/L)	1.70 ± 0.72	1.24 ± 0.59	<.001
Stimulated C-peptide (μg/L)	2.59 ± 1.51	1.99 ± 0.82	<.001
Total cholesterol (mmol/L)	5.15 ± 1.84	4.68 ± 1.63	.042
Triglyceride (mmol/L)	1.91 ± 1.49	1.50 ± 1.11	.006
HDL-C (mmol/L)	1.14 ± 0.84	1.43 ± 0.79	.003
LDL-C (mmol/L)	3.13 ± 1.35	2.62 ± 1.22	.006

Values are mean ± SD, except for the frequency data.

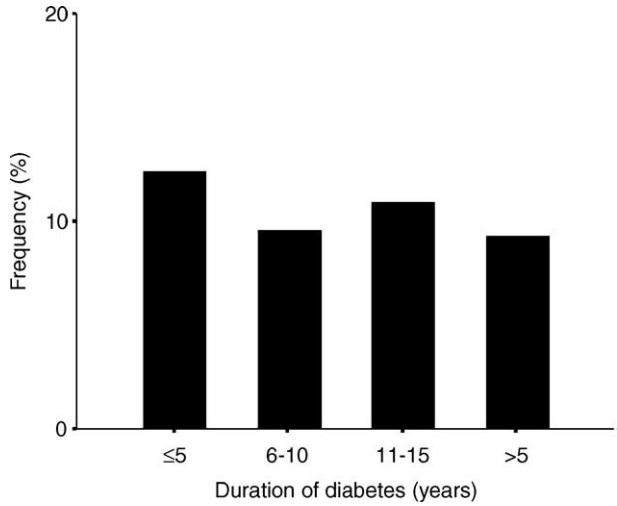

Fig. 1. Percentage of patients positive for GADA with a different duration of diabetes onset. There were no significant differences among the groups (P = .784, using a χ^2 test).

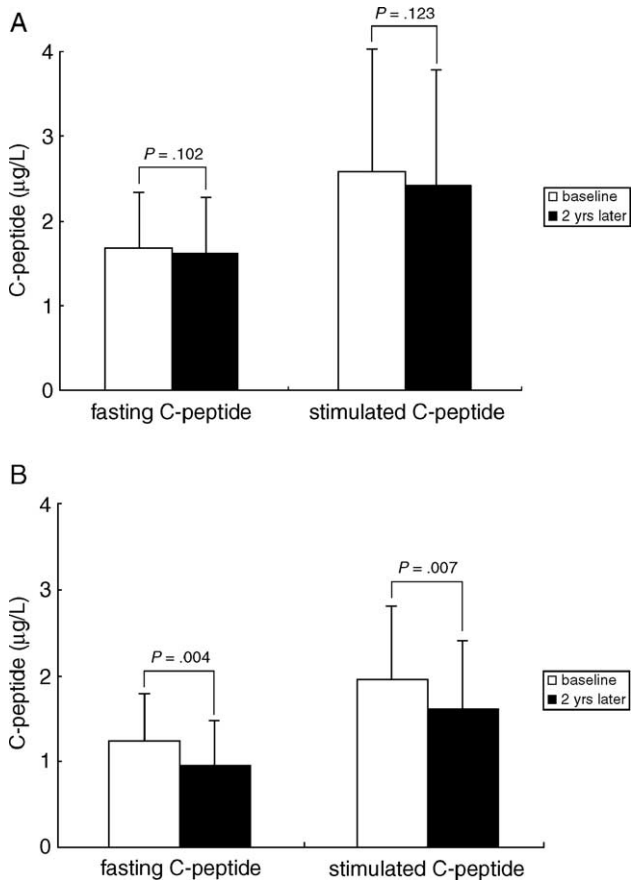

Fig. 2. Comparison of serum C-peptide levels at baseline and after 2 years in the (A) GADA-negative and (B) GADA-positive groups.

Table 2
Clinical characteristics of the insulin (−) group and the insulin (+) group among GADA-positive patients

	Insulin (−) (n = 15)	Insulin (+) (n = 55)	*P*
Sex (M/F)	9/6	30/25	.706
Age at study (y)	53.9 ± 9.8	48.4 ± 9.3	.048
Age at onset (y)	46.9 ± 10.0	40.6 ± 9.6	.029
Duration of DM (y)	7.0 ± 4.1	7.8 ± 4.6	.544
BMI (kg/m^2)	22.1 ± 2.9	20.3 ± 2.8	.032
Fasting blood glucose (mmol/L)	9.30 ± 2.52	9.62 ± 2.89	.698
HbA_{1c} (%)	8.6 ± 2.4	9.0 ± 2.7	.605
Fasting C-peptide (μg/L)	1.66 ± 0.73	1.13 ± 0.52	.002
Stimulated C-peptide (μg/L)	2.49 ± 0.91	1.85 ± 0.69	.004
GADA (U/mL)	6.0 ± 4.8	30.5 ± 7.3	<.001

Values are mean ± SD, except for the frequency data.

acid decarboxylase antibody–positive patients had significantly lower fasting and stimulated C-peptide levels (1.70 ± 0.72 vs 1.24 ± 0.59 μg/L, $P < .001$; 2.59 ± 1.51 vs 1.99 ± 0.82 μg/L, $P < .001$, respectively), suggesting that GADA-positive patients have a significantly lower insulin secretion capacity (Table 1).

Fasting and stimulated C-peptide levels were significantly lower in GADA-positive patients after 2 years (n = 62, from 1.24 ± 0.59 to 0.95 ± 0.54 μg/L, $P = .004$; from 1.99 ± 0.82 to 1.61 ± 0.77 μg/L, $P = .007$, respectively), but not in GADA-negative patients (n = 517, from 1.70 ± 0.72 to 1.63 ± 0.69 μg/L, $P = .102$; from 2.59 ± 1.51 to 2.45 ± 1.48 μg/L, $P = .123$, respectively) (Fig. 2).

3.3. Clinical and biochemical characteristics of GADA-positive patients according to the requirement of insulin therapy

In the GADA-positive group, 55 patients (male-female, 30:25) were using insulin as a treatment modality, whereas 15 patients (male-female, 9:6) did not need insulin to control glucose. When we compared the current age and the age at the onset of diabetes between these 2 groups, the insulin-dependent group was significantly younger ($P = .048$ and $P = .029$, respectively), whereas no significant differences were observed in the duration of DM between the 2 groups ($P = .544$).

Patients receiving insulin had a lower BMI than those not treated ($P = .032$). HbA_{1c} did not differ between the 2 groups ($P = .605$). Patients treated with insulin had significantly lower fasting and stimulated C-peptide levels than those not treated (1.13 ± 0.52 vs 1.66 ± 0.73 μg/L, $P = .002$; 1.85 ± 0.69 vs 2.49 ± 0.91 μg/L, $P = .004$, respectively). Their levels of GADA were also significantly higher (30.5 ± 7.3 vs 6.0 ± 4.8 U/mL, $P < .001$) (Table 2).

4. Discussion

There have been few studies concerning GADA in T2DM in Korea. Previous reports demonstrate that approximately 1.7% to 4% of patients with T2DM in Korea test positive for GADA [8,28]. In our study, 10.1% of the subjects tested positive for GADA, considerably higher than seen in previous studies done in Korea [8,28]. However, we have to take into consideration that our study is not a true population-based study, but rather a hospital-based study; therefore, there is a limitation in stating that this result represents the percentage of LADA in all Korean diabetic patients. Moreover, because obese patients were excluded from our study, the prevalence of LADA might have been overestimated. However, the subjects in previous Korean diabetes studies were relatively obese, whereas the subjects of this study were nonobese diabetic patients (mean BMI of 21.4 kg/m^2), a population that represents as much as 70% to 80% of all diabetic patients in Korea [24,25]. Therefore, there is a possibility that many patients with LADA were excluded in previous studies. Accordingly, our study suggests that the pathogenesis of T2DM in Korean adults is likely to have an autoimmune component.

The frequency of GADA in our study did not significantly differ between those with variable durations of diabetes. These results indicate that the presence of GADA in T2DM may persist, although the mechanism of persistence remains unclear (as is the case with T1DM) [29].

Latent autoimmune diabetes in adults is a special form of diabetes that is clinically similar to T2DM, the difference being that patients are positive for pancreatic autoantibodies. As clinical manifestations slowly progress and typical T1DM features do not occur, the initial treatment is diet control and exercise or oral hypoglycemic agents, like that for T2DM. However, beta-cell destruction progresses, and sooner or later, the patient needs insulin for glucose control [2,30]. Recent studies among young adults in Sweden have shown a high positive predictive value of 92% for GADA presence predicting the need for insulin treatment 3 years after diagnosis [31]. In our study, 78.6% of GADA-positive patients were treated with insulin. Furthermore, insulin secretion of subjects who were GADA-positive significantly decreased after 2 years, but not in GADA-negative subjects, suggesting that GADA may be an indicator of insulin deficiency resulting from immune destruction.

We compared GADA levels between those who used insulin and those who did not among GADA-positive patients; the level in those who used insulin was higher than that in those who did not. These results are similar to results from other studies [11,15,19,32]. Therefore, when a patient is GADA-positive and its titer is high, it can serve as a positive predictor for the future need for insulin therapy. Because insulin is considered to protect the function of remaining beta cells, diminish the potential risk for the development of DKA, and slow down autoimmune destruction [30,33,34], prompt insulin treatment in patients with high titers of GADA in early-stage DM may be helpful in preserving the function of the remaining beta cells. Furthermore, considering the relatively high incidence of LADA and the reluctance to use insulin in Korean patients with DM, many patients may benefit from measuring GADA, as it can promote earlier use of insulin.

The metabolic syndrome induced by insulin resistance is common in T2DM. In our study, compared with GADA-negative subjects, those who were positive for GADA had a significantly lower BMI, prevalence of hypertension, and triglyceride levels, as well as higher HDL-C levels. Thus, patients with GADA have a biochemical profile suggesting a lower risk of a cardiovascular event. These findings are consistent with a current, randomized, double-blind study [20] and with the Botnia study [15,35].

There are some possible limitations to our study. The subjects were not studied at the time of diagnosis; therefore, other pancreatic autoantibodies could not be reliably measured. Although the duration of diabetes for GADA-positive and GADA-negative groups was similar, the changes in C-peptide levels could not be traced from the time of diagnosis, but rather only from the point of recruitment. Moreover, there were no data about the presence of other autoimmune diseases and the reporting of HLA background in the subjects.

In conclusion, we demonstrate that a significant proportion of Korean patients may be positive for GADA, which is consistent with studies in white subjects and in disagreement with previous reports on Korean subjects. Testing for GADA allowed us to identify patients with more deteriorated beta-cell function and those with an earlier need for insulin treatment among Korean DM patients. Further studies should be done on the pathogenesis of insulin deficiency in patients with T2DM and its possible relation to GADA levels, other autoantibodies, and genetic predisposition.

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