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ORIGINAL ARTICLE

Glycated albumin (GA) and the GA/HbA1c ratio are higher in diabetic patients positive for insulin antibodies with high binding capacity and low affinity

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Abstract

Patients with diabetes mellitus having insulin antibodies (InsAb) with properties of high binding capacity and low affinity, which are observed in insulin autoimmune syndrome (IAS), are known to have greater plasma glucose fluctuations. Glycated albumin (GA) and the GA/HbA1c ratio have been demonstrated to reflect plasma glucose fluctuations. Hence, we hypothesized that GA or the GA/HbA1c ratio in diabetic patients having InsAb with properties of high binding capacity and low affinity may be higher than those in InsAb-negative diabetic patients, and we verified this hypothesis. Subjects were 12 diabetic patients who had InsAb noted while being treated with insulin and were subjected to Scatchard analysis and whose InsAb had properties similar to those of patients with IAS (affinity constant $K1 < 0.24 \times 1/10^{-8}$ M, number of binding sites $R1 \geq 11.5 \times 10^{-8}$ M) [four cases of type 1 diabetes (T1D) and eight cases of type 2 diabetes (T2D)]. The control group consisted of T1D and T2D cases matched to the T1D and T2D cases, respectively, according to sex, age, BMI, and HbA1c. GA and the GA/HbA1c ratio were compared between both groups. GA and the GA/HbA1c ratio in InsAb-positive patients was significantly higher than that in the control group for both T1D and T2D patients. Diabetic patients having InsAb with properties of high binding capacity and low affinity had higher GA and the GA/HbA1c ratio than those of InsAb-negative patients. Greater plasma glucose fluctuations were suggested in InsAb-positive diabetic patients.

Keywords Diabetes · Insulin antibodies · Insulin autoimmune syndrome · Glycated albumin · HbA1c

Introduction

Insulin antibodies (InsAb) are divided into antibodies against exogenous insulin that are produced because of insulin therapy [1] and autoantibodies against endogenous insulin produced in patients with type 1 diabetes and patients with insulin autoimmune syndrome (IAS) [2]. Diabetic patients receiving insulin therapy may produce InsAb against exogenous insulin, the presence of which can be confirmed using the InsAb binding rate. Their properties are assessed using Scatchard analysis. As InsAb produced during insulin therapy usually has the properties of low binding capacity and high affinity, the antibodies cannot be bound to a large amount of insulin, and the bound insulin is not readily released. Thus, these antibodies hardly affect plasma glucose fluctuations [3, 4].

However, InsAb with high binding capacity and low affinity may only rarely be produced, the properties of which are similar to those of autoantibodies produced in IAS patients [5]. These antibodies are capable of being bound to a large amount of insulin and readily released for any reason; therefore, they greatly affect glycemic control to pose clinical problems, such as repeated early morning hypoglycemia and daytime hyperglycemia [6, 7]. Patients with IAS have common HLA alleles such as HLA DRB1 *04:06 [8]. Moreover, some patients with IAS have taken the drugs, most of which contain the sulphydryl group [8, 9]. However, patients with InsAb produced during insulin therapy do not have these characteristics.

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For glycemic control, HbA1c and glycated albumin (GA) are used as indices. While HbA1c reflects mean plasma glucose, GA reportedly reflects not only mean plasma glucose but also plasma glucose fluctuations [10–12]. Therefore, the GA/HbA1c ratio is reported to be useful as an index of plasma glucose fluctuations [13, 14]. It was reported that the GA/HbA1c ratio in patients with type 1 diabetes (T1D), whose plasma glucose fluctuations was greater than that in patients with type 2 diabetes (T2D), was significantly higher than the ratio in T2D patients [15]. IAS is a disease where InsAb with high binding capacity and low affinity is present and induce hypoglycemia [16]. We demonstrated that GA and GA/HbA1c ratio in IAS patients were significantly higher than those in cases with normal glucose tolerance [17]. Here, we hypothesized that GA or the GA/HbA1c ratio in diabetic patients having InsAb with high binding capacity and low affinity increased compared to diabetic patients without InsAb, and we verified this hypothesis.

Subjects and methods

Subjects

We performed the present study in a retrospective manner. We measured InsAb in diabetic patients receiving insulin therapy aged 20 years or older who were inpatients or outpatients of Kobe University Hospital within the period between April 2009 to June 2015. Scatchard analysis was performed in cases that tested positive for InsAb (InsAb binding rate $\geq 0.4\%$) and assessed as having great plasma glucose fluctuations by their attending physicians based on self-monitoring of blood glucose (SMBG). Cases with an affinity constant (K1) $< 0.24 \times 10^{-8}$/M and a number of binding sites (R1) $\geq 11.5 \times 10^{-8}$ M obtained by Scatchard analysis were defined to be cases having InsAb positive for antibodies with high binding capacity and low affinity [1, 3], a property similar to InsAb in IAS. Patients with T1D and patients with T2D were analyzed separately because patients with T1D have significantly higher GA/HbA1c ratios than patients with T2D [13]. Subjects in the present study were 12 patients with their HbA1c and GA measured at the same time (four T1D patients and eight T2D patients).

Within diabetic patients aged 20 years or older receiving insulin therapy who visited our outpatient clinic (249 T1D patients and 162 T2D patients) in the period the same as that of the subjects, cases that matched the subjects for age, sex, BMI, and HbA1c were defined as controls (12 T1D patients and 24 T2D patients).

We obtained information on the subject cases and controls, such as age, sex, presence/absence of InsAb, type of diabetes, duration of insulin therapy, HbA1c, and, GA and calculated the GA/HbA1c ratio. The main outcomes were defined as the difference in GA or the GA/HbA1c ratio and compared between subject cases and controls for each of T1D and T2D.

Measurement

HbA1c, expressed in the National Glycohemoglobin Standardization Program (NGSP) value [18], was measured by high-performance liquid chromatography (HPLC). GA was determined by the enzymatic method using albumin-specific proteinase, ketoamine oxidase, and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan) [19].

The insulin binding rate was measured by the radioimmunoassay (RIA)-polyethylene glycol (PEG) method using the Insulin Antibody Kit Yamasa (Yamasa Corporation, Tokyo, Japan). ^{125}I-labelled insulin was added to the patient's serum and incubated, a 25% polyethylene glycol solution was then added, and bound/free insulin was separated. The radioactivity of the sediment portion was measured, and binding rate was indicated as (bound/total) a percentage.

Scatchard analysis of InsAb was conducted by adding ^{125}I-labelled human insulin (5.6×10^{-12} mol/L) to deinsulinized serum, measuring the amount of antibody-bound insulin, and calculating K1 and R1 by a computer analysis program [3, 4]. We used the already defined criteria to define insulin antibodies with high binding capacity and low affinity [3].

Statistical analyses

We calculated that a sample size of 4 per group was required to provide 80% power to detect a difference with a significance level of 0.05, as previously described [17]. All data are shown as means ± SDs. For statistical analyses, the unpaired Student's *t*-test or the χ^2 test were performed for the comparison of the two groups as appropriate with the SPSS Statistical Software 22.0 (SPSS Inc., Chicago, IL). Multivariable logistic regression analysis was carried out to correct the background factors. The objective variable was the presence or absence of insulin antibody, and the explanatory variables were the GA / HbA1c ratio, age, BMI, gender, and HbA1c. *P* values less than 0.05 were considered statistically significant.

Results

The number of InsAb-positive T1D patients and T2D patients used was four and eight, respectively (Table 1). The Ins binding rate, K1, and R1 of the InsAb-positive T1D patients were $78.9 \pm 5.1\%$, $0.015 \pm 0.006 \times 1/10^{-8}$ M, and $70.3 \pm 31.1 \times 10^{-8}$ M, respectively. The Ins binding rate, K1, and R1 of the InsAb-positive T2D patients

Table 1 Clinical characteristics of study patients

Type	T1D	T1D	*P*	T2D	T2D	*P*
InsAb	–	+		–	+	
n	12	4	–	24	8	–
Age (years)	62.2 ± 6.7	55.0 ± 22.4	0.316	67.2 ± 10.3	66.8 ± 18.4	0.936
Male (%)	4 (33.3)	2 (50.0)	0.582	7 (29.2)	4 (50.0)	0.298
BMI (kg/m^2)	20.2 ± 1.4	18.6 ± 1.4	0.061	25.3 ± 2.2	25.0 ± 3.2	0.764
Duration of insulin therapy (years)	18.2 ± 12.7	2.8 ± 1.5	0.03	10.2 ± 8.2	2.5 ± 3.1	0.02
InsAb binding rate (%)	n.d	78.9 ± 5.1	–	n.d	80.3 ± 10.6	–
K1 (1/10^{-8} M)	n.d	0.015 ± 0.006	–	n.d	0.040 ± 0.039	–
R1 (10^{-8} M)	n.d	70.3 ± 31.1	–	n.d	61.6 ± 59.9	–
HbA1c (%)	7.8 ± 0.5	8.1 ± 2.3	0.68	8.0 ± 0.7	8.8 ± 2.1	0.131
Insulin administration method						
MDI	9	1		7	5	
CSII	3	2		0	0	
Premixed insulin	0	1		5	3	
Basal insulin only	0	0		11	0	
Antidiabetic medications						
DPP-4 inhibitors	0	0		11	0	
GLP-1 receptor agonists	0	0		9	0	
Sulfonylureas	0	0		6	2	
Biguanides	0	1		19	4	
Thiazolidinediones	0	0		1	1	
SGLT-2 inhibitors	0	0		5	0	
Alpha-glucosidase inhibitors	0	4		10	4	

InsAb insulin antibody, *T1D* type 1 diabetes, T2D type 2 diabetes, *K1* affinity constant, *R1* binding site number, *MDI* Multiple daily injection, *CSII* Continuous subcutaneous insulin infusion. The unpaired Student's *t*-test was performed to compare two groups (Age, BMI, InsAb binding rate, K1, R1, and HbA1c). In addition, the $\chi 2$ test was performed for the comparison of gender between two groups. P values less than 0.05 were considered statistically significant

were $80.3 \pm 10.6\%$, $0.040 \pm 0.039 \times 1/10^{-8}$ M, and $61.6 \pm 59.9 \times 10^{-8}$ M, respectively. Regarding age, BMI, gender, and HbA1c, there were no significant differences between the InsAb-positive and the InsAb-negative in both T1D and T2D patients.

In both the InsAb-positive T1D patients and T2D patients, GA values were significantly higher than those in the controls (Fig. 1). Furthermore, the GA/HbA1c ratio in InsAb-positive T1D patients and T2D patients were both significantly higher than that in the controls (Fig. 2). In the control group, the GA/HbA1c ratio was significantly higher in the T1D patients than in the T2D patients. We performed logistic regression analyses. As result, in type 1 diabetes, GA / HbA1c ratio was statistically significantly higher in the InsAb-positive group even when adjusted by age, BMI, gender, and HbA1c (odds ratio 36.1, 95% confidence interval 1.63–800, $p = 0.023$). In type 2 diabetes, GA/HbA1c ratio was statistically significantly higher in the InsAb-positive group, even when adjusted for age, BMI, gender, and HbA1c (odds ratio 4.8, 95% confidence interval 1.35–17.1, $p = 0.016$).

Discussion

In the present study, differences in GA and the GA/HbA1c ratio were examined between diabetic patients having InsAb with properties of high binding capacity and low affinity and diabetic patients without InsAb. It was first demonstrated that GA and the GA/HbA1c ratio were significantly higher in patients having InsAb with the properties of high binding capacity and low affinity whether in T1D patients or T2D patients.

It was reported that diabetic patients having InsAb with properties of high binding capacity and low affinity had their plasma glucose fluctuations increased [20, 21], which made it difficult to control plasma glucose and required the switching of therapy. Treatments with glucocorticoids [22–24], immunosuppressive therapy [20, 25], plasmapheresis [20, 24], the addition of antidiabetic drug [26, 27], and switching of insulin product [28, 29] have been reported. Within these reports, plasma glucose fluctuations were improved by the therapies in the case reports

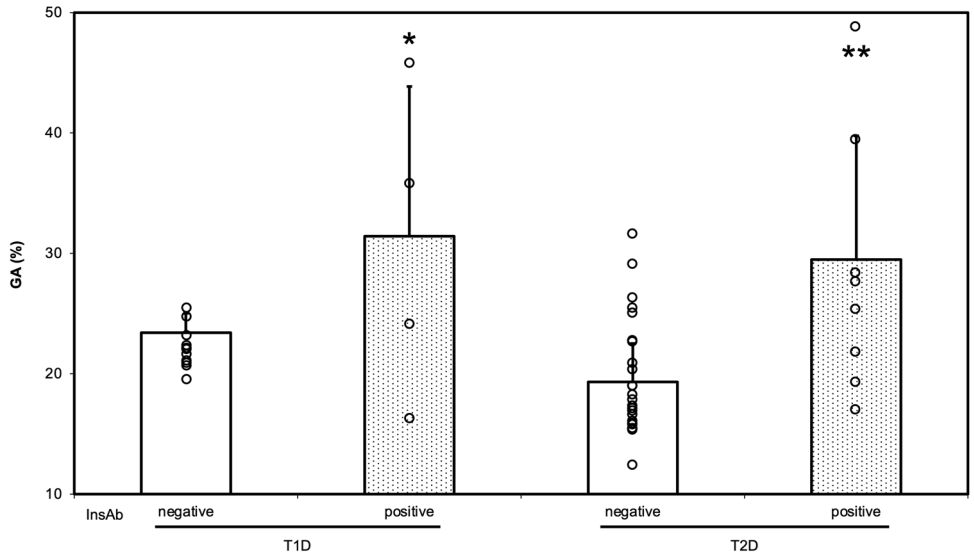

Fig. 1 Comparison of GA between InsAb negative (open columns) and InsAb positive (shaded columns) diabetic patients, left panel for type 1 diabetes, right panel for type 2 diabetes, respectively. The figure shows the individual plots of GA values. In left panel, in type 1 diabetes, $n=12$ for InsAb negative patients (GA = 23.4 ± 1.6%), $n=4$ for InsAb positive patients (GA = 31.4 ± 12.4%). The unpaired Student's *t*-test was performed for the comparison of two groups. As a result, the *P* value is 0.03. In right panel, in type 2 diabetes, $n=24$ for InsAb negative patients (GA = 21.1 ± 4.7%), $n=8$ for InsAb positive patients (GA = 29.5 ± 10.3%). The unpaired Student's *t*-test was performed for the comparison of two groups. As a result, the *P* value is 0.003. $^{*}P<0.05$, $^{**}P<0.01$, *InsAb* insulin antibody, *T1D* type 1 diabetes, *T2D* type 2 diabetes

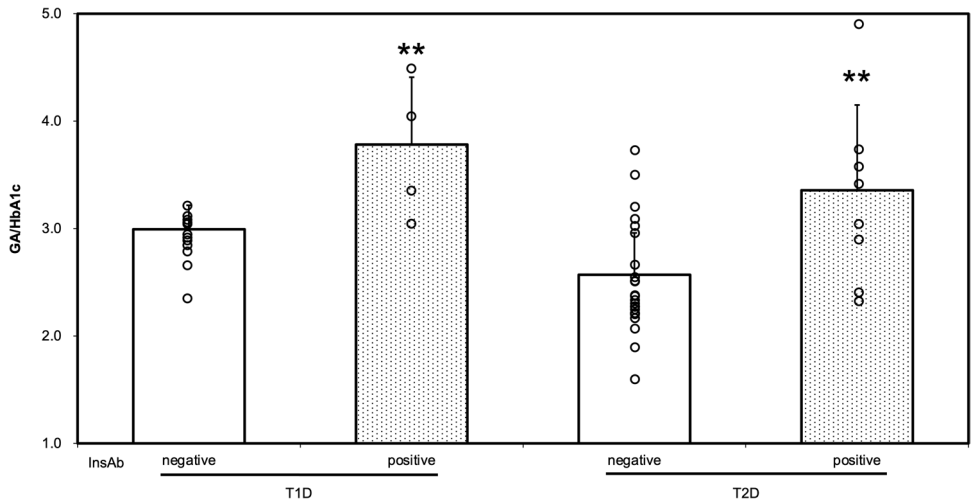

Fig. 2 Comparison of the GA/HbA1c ratio between InsAb negative (open columns) and InsAb positive (shaded columns) diabetic patients, left panel for type 1 diabetes, right panel for type 2 diabetes, respectively. The figure shows the individual plots of GA/HbA1c values. In left panel, in type 1 diabetes, $n=12$ for InsAb negative patients (GA/HbA1c = 2.99 ± 0.22), $n=4$ for InsAb positive patients (GA/HbA1c = 3.78 ± 0.63). The unpaired Student's *t*-test was performed for the comparison of two groups. As a result, the *P* value is 0.001. In right panel, in type 2 diabetes, $n=24$ for InsAb negative patients (GA/HbA1c = 3.36 ± 0.79), $n=8$ for InsAb positive patients (GA/HbA1c = 2.61 ± 0.48). The unpaired Student's *t*-test was performed for the comparison of two groups. As a result, the *P* value is 0.003. $^{*}P<0.05$, $^{**}P<0.01$, *InsAb* insulin antibody, *T1D* type 1 diabetes, *T2D* type 2 diabetess

where InsAb properties were improved by glucocorticoids, plasmapheresis [22–24], the addition of antidiabetic drug [26, 27], or switching of insulin products [28, 29]. Such cases have been reported regardless of whether in T1D [21–23, 25, 27] or T2D [20, 26, 27, 29]. Therefore, InsAb with properties of high binding capacity and low affinity seemed to be involved in plasma glucose fluctuations regardless of disease type. On the other hand, these reports

were all case reports, while the present study demonstrated the fact using multiple cases.

In the past, there was no measure other than repeating SMBG to demonstrate plasma glucose fluctuations, and identification of nocturnal plasma glucose fluctuations was particularly difficult. In recent years, CGM (continuous glucose monitoring) [30] and isCGM (intermittently scanned continuous glucose monitoring) [31] have become available to confirm plasma glucose fluctuations. However, these test methods are not available in all institutions. On the other hand, HbA1c and GA can be measured at many medical institutions.

The plasma glucose fluctuations index the GA/HbA1c ratio used in the present study reportedly correlated with the plasma glucose fluctuations index (SD) calculated from the CGM data [14]. In addition, there are not enough data in epidemiological studies on the relationship between diabetic complications and glucose fluctuation evaluated by CGM. In the Hisayama Study, the GA / HbA1c ratio as an indicator of blood glucose fluctuation was significantly associated with the risk of Alzheimer's disease with or without impaired glucose tolerance [32]. Thus, the GA/HbA1c ratio is considered to be an important indicator. Furthermore, it was reported that IAS patients had higher GA or GA/HbA1c ratios [17], possibly because InsAb with properties of high binding capacity and low affinity noted in IAS was related to higher GA/HbA1c ratios via enhanced plasma glucose fluctuations. In the results from the present study, the patients having InsAb with properties of high binding capacity and low affinity had higher GA/HbA1c ratio even with insulin therapy, suggesting possible enhancement of plasma glucose fluctuations. It was also suggested that InsAb with high binding capacity and low affinity might enhance plasma glucose fluctuations in patients receiving insulin therapy.

Accordingly, measurement of the GA/HbA1c ratio in diabetic patients can differentiate patients with greater plasma glucose fluctuations, and if InsAb is positive, the antibodies are expected to have the high binding capacity and low affinity. In such cases, it is important to perform the Scatchard analysis to identify InsAb properties. If the analysis reveals that the InsAb has the high binding capacity and low affinity, switching of therapy should be considered. Measurement of the GA/HbA1c ratio is useful as a screening tool to differentiate such patients.

The present study had several limitations. First, the number of cases was relatively few. However, diabetes mellitus having InsAb with properties of high binding capacity and low affinity is a rare disease, and only 42 diabetic patients were reported to have such InsAb as far as we researched. Therefore, the present study accumulated relatively as many as 16 cases. Even if the sample size was actually calculated with reference to the previous reports, the number of subjects in this study was not a major problem. Second, the study also had the limitation that actual plasma glucose fluctuations in the subject cases and controls could not be evaluated by CGM and SMBG. However, previous reports [14, 15] have shown an association between GA / HbA1c ratio and glycemic fluctuations evaluated by CGM and SMBG. Third, although patients receiving insulin therapy having InsAb with high binding capacity and low affinity were known to have the condition improved by glucocorticoids, immunosuppressants, or switching of the type of insulin, no study has been performed on whether these therapies reduced GA or the GA/HbA1c ratio either. Furthermore, insulin secretory capacity is also an important factor in glycemic fluctuation, it was not included in the analysis of this study. These are also issues to be considered in the future.

In conclusion, diabetic patients having InsAb with high binding capacity and low affinity have higher plasma glucose fluctuations indices GA and the GA/HbA1c ratio.

Acknowledgements We conducted this research and observed the Declaration of Helsinki and current ethical codes, and the research was approved by the ethics committee of Kobe University Graduate School of Medicine [approval number of Ethics Committee 180172] at November 26, 2018.

Declarations

Conflict of interest The authors declare no conflicts of interest associated with this manuscript.

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