Usefulness of glycated albumin in decisions regarding the discontinuation of a diabetes drug and factors associated with poor glycemic control following discontinuation in patients with type 2 diabetes mellitus

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Abstract We studied the usefulness of glycated albumin (GA) for decisions regarding the discontinuation of a diabetes drug in type 2 diabetic patients with good glycemic control, and the factors associated with increases in GA following discontinuation of a diabetes drug in patients with type 2 diabetes mellitus. Sixteen patients (12 males and 4 females) were enrolled in the present study and discontinued one diabetes drug. When the change in GA was less than 1 % at 4 weeks after the discontinuation of the diabetes drug ($\Delta\text{GA}_{4\text{w}}$), discontinuation was continued (the continuous group, $n = 10$), but when the change in GA was more than a 1 %, the discontinued diabetes drug was resumed (the resume group, $n = 6$). In the continuous group, HbA1c at 12 weeks after discontinuation (6.2 ± 0.6 %) remained unchanged from its value at discontinuation (6.2 ± 0.7 %), but it was significantly elevated at 12 weeks after discontinuation in the resume group (changing from 6.3 ± 0.1 to 7.0 ± 0.6 %). Age, duration of diabetes, and GA were significantly lower while body mass index (BMI) was significantly higher in the continuous group than in the resume group, but no significant difference in HbA1c was observed between the groups. The discontinuation of a diabetes drug in patients with low insulin secretion must be performed carefully because factors such as duration of diabetes, BMI, and GA showed

significant differences between the continuous group and resume group in our study, and these indicators are known to be linked with insulin secretion.

Keywords Glycated albumin · HbA1c · Diabetes drug · Discontinuation · Type 2 diabetes mellitus

Introduction

The treatment goals for patients with diabetes mellitus are to prevent the onset and progression of diabetic complications, extend life expectancy, and achieve good quality of life [1]. Suppression of the onset and progression of chronic diabetic complications has been achieved by strict glycemic control, as reported previously in the DCCT study and UKPDS [2, 3]. Therefore, HbA1c levels in patients with diabetes mellitus need to be maintained at less than 7.0 % [1].

Patients with type 2 diabetes mellitus are initially encouraged to improve their lifestyle, such as diet and exercise habits. The administration of diabetes drugs is only initiated when good glycemic control cannot be achieved by lifestyle improvements. Concomitant therapy with diabetes drugs that use different mechanisms of action is recommended when good glycemic control cannot be achieved by the administration of a single diabetes drug. Diabetes drugs with new effects, such as dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-dependent glucose transporter 2 (SGLT2) inhibitors, have recently been introduced [4]. Hypertension and dyslipidemia are closely associated with type 2 diabetes mellitus because obesity is a risk factor not only for type 2 diabetes mellitus, but also for hypertension and dyslipidemia. Combination therapy with antiplatelet, antihypertensive, and/or lipid-lowering

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drugs in addition to strict diabetes therapy was previously shown to suppress the onset of cardiovascular events in patients with type 2 diabetes mellitus [5].

Polypharmacy is common among diabetic patients complicated with other chronic diseases; therefore, adverse drug events have been reported due to drug interactions, inappropriate prescribing, non-adherence to prescribed medicines, and medication errors [6]. Polypharmacy is also inappropriate due to the financial burden on patients and medical economics. Therefore, a simple prescription is desired in order to minimize dosage errors and the number of drugs taken by diabetic patients.

Dose reduction or the discontinuation of diabetes drugs once good glycemic control is achieved has been attempted in diabetic patients. However, improper dose reduction or discontinuation of diabetes drugs may lead to poor glycemic control and the development of diabetic complications. Therefore, a good biomarker of glycemic control needs to be developed in order to assist in decisions regarding the discontinuation of or reductions in the doses of diabetes drugs, but few studies have attempted to identify good biomarkers.

HbA1c, which is widely used as an indicator of glycemic control, reflects the glycemic control of the previous 1–2 months. Glycated albumin (GA) has also been used as a glycemic control indicator in conjunction with HbA1c [7]. Since the half-life of serum albumin is approximately 14 days, GA reflects the short-term (approximately 1–2 weeks) control of plasma glucose levels. Based on these characteristics, GA has been identified as a useful indicator of glycemic control for short periods [8, 9]. We recently predicted the value of HbA1c after 12 weeks by measuring changes in the GA value after the 4-week administration of sitagliptin [10]. It is possible to achieve good glycemic control in a short time by measuring GA because therapeutic efficacy in the early stages may be evaluated. We also demonstrated that GA measurements were useful for predicting deteriorations in glycemic control [11]. Furthermore, while HbA1c levels primarily reflect mean plasma glucose, GA levels have been shown to reflect postprandial plasma glucose/glycemic excursions in addition to mean plasma glucose [7, 12–14].

When patients with good glycemic control have the possibility of discontinuing diabetes drugs, it is important to determine whether this discontinuation is maintainable or if the administration of diabetes drugs needs to resume. Previous studies reported the usefulness of measuring GA early after the administration of diabetes drugs [10]; however, few have investigated the usefulness of GA measurements in the discontinuation of diabetes drugs. Therefore, we herein retrospectively examined the usefulness of GA measurements for decisions regarding the discontinuation of diabetes drugs by type 2 diabetes

mellitus patients with good and stable glycemic control. We also compared various clinical indicators between patients who discontinued a diabetes drug and those who deteriorated following discontinuation.

Methods

Patients

Sixteen patients with type 2 diabetes mellitus whose glycemic control was good and stable and who were attempting to discontinue one diabetes drug were investigated (12 males and 4 females) (Table 1). Good glycemic control was defined as HbA1c < 7.0 %. Stable glycemic control was defined as a difference in HbA1c between 4 weeks before the discontinuation of a diabetes drug and the time point of discontinuation of < 0.5 %. Patients with liver cirrhosis, renal disease (eGFR < 60 mL/min/1.73 m² and/or overt proteinuria), anemia, or administered glucocorticoids that affected the glycemic control index were excluded. The present study was approved by the Ethics Committee at Kawanishi City Hospital according to ethics guidelines concerning epidemiological studies.

Laboratory analysis

HbA1c was measured by an HPLC method, while GA was measured by an enzymatic method. The HbA1c value was indicated according to the scale of the National Glycohemoglobin Standardization Program (NGSP) [15]. HbA1c was measured 4 weeks before the discontinuation of a diabetes drug, at the time-point of discontinuation, and 4 and 12 weeks after discontinuation. GA was measured at the time point of and 4 and 12 weeks after discontinuation. When the GA value increased by less than 1 % in the 4 weeks following discontinuation (Δ GA4w), discontinuation was continued (the continuous group). When the GA value increased by more than 1 %, the discontinued diabetes drug was resumed after 4 weeks (the resume group). Ten out of the 16 patients examined discontinued a diabetes drug, whereas the administration of the discontinued diabetes drug was resumed in the remaining 6 patients (Table 1). We compared various factors such as age, the duration of diabetes, and body mass index (BMI) between the continuous group and resume group, and examined the factors associated with Δ GA4w.

Statistical analysis

The results obtained are shown as the mean $\pm$ standard deviation. The paired Student's *t*-test, unpaired Student's *t*-test, or chi-squared test was used to compare groups. A

Table 1 Characteristics of study patients

	Total	Continuous group	Resume group	<i>p</i> *
<i>n</i>	16	10	6	–
Male (%)	12 (75)	6 (60)	6 (100)	0.074
Age (years)	62 ± 12	58 ± 13	70 ± 4	0.040
BMI (kg/m ²)	25.7 ± 4.6	27.4 ± 4.8	22.8 ± 2.2	0.047
Duration of diabetes (years)	7.4 ± 7.2	4.2 ± 4.9	12.8 ± 7.4	0.014
Number of diabetes drugs	2.1 ± 1.3	1.7 ± 1.1	2.8 ± 1.3	0.080
Number of diabetes drugs (single/double/triple/quadruple)	7/4/1/4	6/2/1/1	1/2/0/3	0.181
HbA1c0w (%)	6.2 ± 0.5	6.2 ± 0.7	6.3 ± 0.1	0.689
GA0w (%)	15.7 ± 1.9	14.8 ± 1.8	17.1 ± 0.9	0.012

* Continuous group vs resume group

univariate regression analysis was performed to analyze the relationship between two parameters. These analyses were performed with the StatView computer program, version 5.0 for Windows (Abacus Concepts, Berkeley, CA, USA). Values of $P < 0.05$ were considered significant.

Results

The age and BMI of the 16 patients that discontinued a diabetes drug were 62 ± 12 years and 25.7 ± 4.6 kg/m², respectively (Table 1). HbA1c and GA at the discontinuation time point were 6.2 ± 0.5 and 15.7 ± 1.9 %, respectively. Regarding the number of diabetes drugs taken, 7, 4, 1, and 4 patients were treated with single, double, triple, and quadruple diabetes drugs, respectively, and the average number of drugs taken for diabetes was 2.1 ± 1.3 . Among the diabetes drugs that patients were attempting to discontinue, DPP-4 inhibitors were being taken by 7 patients, sulfonylurea by 3 patients, biguanide and insulin by 2 patients each, and α -glucosidase inhibitors and thiazolidine by 1 patient each.

In the continuous group, HbA1c at 4 and 12 weeks after discontinuation was unchanged compared to that at the point of discontinuation (6.0 ± 0.6 , 6.2 ± 0.6 , and 6.2 ± 0.7 %, respectively (Fig. 1), but HbA1c was significantly elevated at 4 and 12 weeks after discontinuation (6.7 ± 0.2 and 7.0 ± 0.6 %, respectively, as compared to the value at discontinuation, 6.3 ± 0.1 %) in the resume group. GA was the same value at the point of and at 4 and 12 weeks after discontinuation (14.8 ± 1.8 , 14.9 ± 1.8 , and 15.8 ± 2.8 %, respectively) in the continuous group, but GA was significantly elevated at 4 and 12 weeks after discontinuation in the resume group: 19.4 ± 1.3 and 18.9 ± 1.6 % as compared to 17.1 ± 0.9 % at discontinuation. A significant difference was noted in that

Fig. 1 Changes in HbA1c and GA in the continuous group and the resume group after discontinuation of a diabetes drug. When GA changed by less than 1 % 4 weeks after discontinuation of a diabetes drug (Δ GA4w), discontinuation was continued (the continuous group, filled circles), and when a >1 % increase in GA was observed, the discontinued diabetes drug was resumed (the resume group, open circles). Changes in HbA1c (a) and GA (b) in both groups are shown. *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$ vs 0 week, #: $P < 0.05$, ###: $P < 0.001$; resume group vs continuous group

Δ HbA1c4w was -0.1 ± 0.2 % (-0.4 to 0.1 %) and 0.5 ± 0.2 % (0.2 – 0.8 %) in the continuous group and the resume group, respectively ($P < 0.001$), with the difference between the groups being 0.6 %. The minimum range of HbA1c in both groups (difference between the

maximum value of the continuous group and minimum value of the resume group) was 0.1 %. On the other hand, ΔGA4w was 0.1 ± 0.3 % (-0.3 to 0.5 %) and 2.3 ± 0.7 % (1.6 – 3.2 %) in the continuous group and resume group, respectively, with a significant difference of 2.2 % between the groups ($P < 0.0001$). In addition, the minimum range of ΔGA4w was 1.1 %, which was markedly different from that (0.1 %) of $\Delta\text{HbA1c4w}$. There was no significant difference in the number of diabetes drugs between the two groups (Table 1).

Significant differences in age (58 ± 13 vs. 70 ± 4 years, $p = 0.040$), BMI (27.4 ± 4.8 vs. 22.8 ± 2.2 kg/m², $p = 0.047$), duration of diabetes (4.2 ± 4.9 vs. 12.8 ± 7.4 years, $p = 0.014$), and GA0w (14.8 ± 1.8 vs. 17.1 ± 0.9 %, $p = 0.012$) were observed between the continuous group and resume group (Table 1), whereas no significant difference was observed in HbA1c between the two groups. In addition, correlations were observed between ΔGA4w and BMI ($R = -0.504$, $p = 0.047$), duration of diabetes ($R = 0.596$, $p = 0.015$), and GA0w ($R = 0.570$, $p = 0.021$), but not between ΔGA4w and HbA1c0w ($R = -0.027$, $p = 0.920$) (Fig. 2).

Discussion

The results of the present study revealed that the discontinuation of a diabetes drug was possible for more than half of our patients without any deterioration of glycemic control by continuing discontinuation in patients with $\Delta\text{GA4w} < 1$ %. HbA1c 4 weeks after discontinuation was higher than at the discontinuation time point in the resume group. In addition, age, duration of diabetes, and GA0w were significantly lower in the continuous group than in the resume group, and BMI was significantly higher in the continuous group than in the resume group, whereas no significant difference was noted in HbA1c at the discontinuation of a diabetes drug between the two groups.

Differences in $\Delta\text{HbA1c4w}$ and ΔGA4w between the continuous group and resume group were 0.6 and 2.2 %, respectively, which demonstrated that changes in ΔGA4w were markedly larger than those in $\Delta\text{HbA1c4w}$. Furthermore, the minimum ranges of $\Delta\text{HbA1c4w}$ and ΔGA4w were 0.1 and 1.1 %, respectively; therefore, the changes in ΔGA4w were markedly larger than those in $\Delta\text{HbA1c4w}$. The difference in $\Delta\text{HbA1c4w}$ between the continuous

Fig. 2 Relationship between the change in GA 4 weeks following discontinuation and various factors. Correlations were observed between the change in GA 4 weeks following discontinuation (ΔGA4w) and BMI (a), duration of diabetes (b), HbA1c0w (c), and GA0w (d)

group and the resume group was small, whereas a clear difference in $\Delta\text{GA}4\text{w}$ was observed between both groups. We recently reported a strong correlation between $\Delta\text{GA}4\text{w}$ and $\Delta\text{HbA1c}12\text{w}$ in type 2 diabetic patients taking sitagliptin, in which HbA1c at 12 weeks after the treatment was predicted using the value of $\Delta\text{GA}4\text{w}$ [10]. HbA1c and GA at 12 weeks after discontinuation were significantly higher than at the time of discontinuation in the resume group. Among 6 patients in the resume group, HbA1c was elevated at 12 weeks after discontinuation in 3 patients despite them resuming the discontinued drug, which suggests that deteriorated glycemic control may occur due to the discontinuation of a diabetes drug. Therefore, it was considered that the period of discontinuation of a diabetes drug should be kept shorter than 4 weeks for these patients.

We also demonstrated the usefulness of GA for predicting poor glycemic control after patients had been discharged from diabetes education hospitalization [11]. The rebound of HbA1c could not be evaluated at the time of the GA rebound. The rebound of HbA1c can only be confirmed by measuring HbA1c at the next outpatient visit. As described above, the evaluation of glycemic control by GA is more useful than its evaluation by HbA1c. In the present study, it was possible to judge the discontinuation of a diabetes drug with $\Delta\text{GA}4\text{w}$ appropriately because HbA1c was almost unchanged even when the discontinuation of a diabetes drug was continued in the case of $<1\%$ $\Delta\text{GA}4\text{w}$ after discontinuation.

$\Delta\text{GA}4\text{w}$ of 1% or more was used as an indicator of deterioration of glycemic control in the present study, and it was able to discriminate the continuous group from the resume group in the $\Delta\text{GA}4\text{w}$ range $0.6\text{--}1.5\%$. Since $\Delta\text{GA}4\text{w}$ was approximately threefold that of $\Delta\text{HbA1c}12\text{w}$ in a previous study on sitagliptin [10], a 1% change in $\Delta\text{GA}4\text{w}$ was equal to an approximately 0.3% change in $\Delta\text{HbA1c}12\text{w}$. Setting $\Delta\text{GA}4\text{w}$ to 1% or more was considered appropriate for evaluating deteriorations in glycemic control because an increase in HbA1c to 0.3% or more reflects significantly deteriorated glycemic control.

BMI, the duration of diabetes, and $\text{GA}0\text{w}$, which was correlated with $\Delta\text{GA}4\text{w}$, are known to be linked with insulin secretion. The insulin secretion in patients with type 2 diabetes mellitus decreases by as much as 50% of normal at the onset of diabetes mellitus, and a gradual decline in insulin secretion with increasing duration of diabetes has been reported [16]. HbA1c primarily reflects the mean plasma glucose, while GA has been shown to reflect postprandial plasma glucose/glycemic excursions in addition to mean plasma glucose [7]. Glycemic excursions are enhanced in diabetic patients with low insulin secretion, and changes in GA become greater than those in HbA1c; therefore, the GA/HbA1c ratio shows a negative correlation with insulin secretion [12–14]. GA levels are known to be negatively

correlated with BMI [17]. We previously reported that BMI was positively correlated with insulin secretion in patients with type 2 diabetes mellitus [18]; hence, large glycemic excursions were observed in low-BMI patients because of their low insulin secretion with high GA levels [19].

The results of the present study revealed that the discontinuation of a diabetes drug may worsen glycemic control in patients with low insulin secretion, such as those with a long duration of diabetes, low BMI, or high GA. Patients with low insulin secretion were markedly affected by the discontinuation of one diabetes drug, even if they had good glycemic control. On the other hand, patients with stable insulin secretion were not markedly affected by the discontinuation of one diabetes drug. Therefore, careful consideration prior to the discontinuation of a diabetes drug is needed for patients with low insulin secretion. The number of prescribed diabetes drugs was higher in the resume group than in the continuous group, but this difference was not significant. The number of diabetes drugs was positively correlated with duration of diabetes (data not shown), which suggests that a long duration of diabetes might decrease insulin secretion.

Administration of DPP-4 inhibitors was discontinued in 7 out of 16 patients in the present study. α -Glucosidase inhibitors and glinides do not have potent HbA1c-lowering effects; therefore, the number of patients who were administered these drugs was small in the present study. Since sulfonylurea promotes the secretion of insulin independently of plasma glucose, it may be selected for the discontinuation of drugs in patients with low fasting plasma glucose levels. Therefore, the number of patients administered sulfonylurea was small. DPP-4 inhibitors have been shown to induce weak hypoglycemia [20]. However, DPP-4 inhibitors were previously reported to markedly reduce HbA1c in patients with poor glycemic control [10, 20]. Therefore, it is difficult to determine whether the discontinuation of DPP-4 inhibitors is possible in patients with good glycemic control. Since biguanide and thiazolidinedione are not hypoglycemic drugs like DPP-4 inhibitors, it is difficult to determine the validity of discontinuation. Only two patients in the present study were administered biguanide, and one was given thiazolidinedione. Future studies are needed in order to examine the potential for discontinuation of biguanide and/or thiazolidinedione with this approach.

The usefulness of diabetes drugs (as evaluated by GA measurements) for glycemic control has frequently been reported [7, 8], and the usefulness of GA, which is also an indicator of glycemic control after the discontinuation of a diabetes drug, was demonstrated for the first time in the present study. Even when the diabetes drug was changed, the same evaluation method (using GA measurements) was demonstrated to be applicable.

There are some limitations of the present study. The number of patients was small. Furthermore, decisions regarding which diabetes drug to discontinue were based on the judgment of the attending physician, so there was a bias in the selection of the drug to discontinue. Future studies must include attempts to discontinue various diabetes drugs in a large number of subjects. In addition, the present study was retrospective. Therefore, a prospective study needs to be performed according to a certain protocol. Moreover, we did not determine the presence of essential or discontinued drugs according to patient background because neither insulin secretion nor insulin resistance was measured in any patient. Therefore, the relationship between the effects of discontinuation on glycemic control and the various mechanisms of action of diabetes drugs needs to be examined in a larger number of patients.

In conclusion, Δ GA4w will be a useful indicator for decisions regarding the discontinuation of diabetes drugs. However, the discontinuation of a diabetes drug must be considered carefully for patients with low insulin secretion, such as those with long-term diabetes, low BMI, or high GA, even if they have good glycemic control.

Compliance with ethical standards

Conflict of interest None.

Human rights and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients prior to their participation in this study.

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