Estimation of HbA1c response to sitagliptin by change in glycosylated albumin level for 2 weeks

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ABSTRACT

Aims/Introduction: Since glycosylated albumin (GA) reflects shorter-term (about 2 weeks) control of plasma glucose levels compared with HbA1c, GA is thought to be a useful glycemic control indicator for the early period following commencement of the treatment of diabetes. In this study, we attempted to estimate HbA1c using the change in GA level before and after the first 2 weeks (ΔGA2w) of administration of sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor.

Materials and Methods: The study included 28 patients with type 2 diabetes who were administered sitagliptin at a dose of 50 mg/day for 12 weeks.

Results: At 2 weeks after administration of sitagliptin, GA markedly decreased, while HbA1c had only slightly decreased. A significant positive correlation was observed between the ΔGA2w and the change in HbA1c before and after the first 12 weeks of administration of sitagliptin (ΔHbA1c12w) (R = 0.793, P < 0.0001). The latter was about 0.6 times the former. The estimated HbA1c after 12 weeks of therapy was calculated by adding ΔGA2w × 0.6 to the baseline HbA1c. A significant positive correlation was observed between the estimated HbA1c and the measured HbA1c after 12 weeks (R = 0.735, P < 0.0001) and both were similar levels.

Conclusions: HbA1c in the first 12 weeks after administration of sitagliptin could be estimated from the formula using the ΔGA2w.

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KEY WORDS: Glycosylated albumin, HbA1c, Incretin

INTRODUCTION

Glycation of various proteins increases in diabetic patients compared to nondiabetic subjects, and some of these glycosylated proteins may take part in the onset and progression of chronic diabetic complications. Of the glycosylated proteins, HbA1c is used clinically as an indicator for chronic control of plasma glucose levels. It is recommended that HbA1c should be <7.0% based on the result of the Diabetes Control and Complications Trial (DCCT) in order to prevent the onset and progression of chronic diabetic complications. Since the lifespan of erythrocytes is about 120 days, HbA1c reflects plasma glucose levels for the preceding 2–3 months. Therefore, 2–3 months are needed for judging whether or not HbA1c reaches target-to-treat levels after starting treatment of diabetes. HbA1c does not acutely reflect glycemic control state at early phase starting treatment for diabetes, because HbA1c changes slowly. Therefore, according to the American Diabetes Association (ADA) guideline, the therapeutic effect should be judged using HbA1c 3 months after initiating treatment of diabetes.

Glycosylated albumin (GA) is also used as a glycemic control indicator. Since the half-life of serum albumin is about 14 days, GA reflects shorter-term (about 2 weeks) control of plasma glucose levels. The change in GA is assumed to be about three times larger compared to HbA1c, because albumin is more sensitively glycated than hemoglobin. Thus, GA is thought to be a useful glycemic control indicator for early period after starting treatment for diabetes. It has also been shown that GA is a suitable indicator in diabetic patients on insulin therapy who have large glycemic fluctuations, and in patients with a shortened lifespan of erythrocytes (e.g., hemolytic anemia and hemodialysis).

Sitagliptin is a highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor indicated for the treatment of type 2 diabetes. Sitagliptin increases plasma concentration of active glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) two- to three-fold in patients with type 2 diabetes. The effect of sitagliptin on GLP-1 and GIP result in lower fasting and postprandial plasma glucose levels through increases in glucose-dependent insulin release and suppression of glucagon secretion.
In this study, we attempted to estimate HbA1c using the change in GA level before and after the first 2 weeks (ΔGA2w) of administration of sitagliptin.

**MATERIALS AND METHODS**

**Study Patients**

The study included 28 outpatients with type 2 diabetes who were receiving sitagliptin (15 males and 13 females). HbA1c levels have been evaluated to confirm the stability of the glycemic control in all of these patients before initiation of sitagliptin treatment. Eight of these cases were administered sitagliptin alone and twelve cases were administered the drug concomitantly with another oral hypoglycemic agent. The mean age was 63.4 ± 13.3 years, and BMI was 24.1 ± 4.3 kg/m². The baseline HbA1c and GA were 9.4 ± 1.8 and 26.9 ± 7.7%, respectively. Sitagliptin was administered at a dose of 50 mg/day for at least 12 weeks. HbA1c and GA were measured at before and 2, 4, 8 and 12 weeks after administration of sitagliptin. Patients complicated with chronic liver disease, chronic renal disease or anemia were excluded from the study. Rebound cases whose GA levels decreased during the therapy and after then increased by ≥0.5% were also excluded from the study. This study was approved by the Ethics Committee at each study hospital, and the purpose of the study was explained to all the patients and all patients provided written informed consent.

**Laboratory Methods**

HbA1c was measured by HPLC using ADAMS A1c HA-8160 (Arkray Inc., Kyoto, Japan)17. The value for HbA1c (%) was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%), calculated using the formula HbA1c (%) = HbA1c (Japan Diabetes Society; JDS) (%) + 0.4%, considering the relational expression of HbA1c (JDS) (%) measured according to the previous Japanese standard substance and measurement methods and HbA1c (NGSP)18. Serum GA was determined using a Hitachi 7600 autoanalyzer (Hitachi Instruments Service Co., Tokyo, Japan) employing an enzymatic method using albumin-specific protease, ketoamine oxidase and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan)19.

The estimated HbA1c in the first 12 weeks of administration of sitagliptin was calculated using the following formula.

estimated HbA1c12w (%) = baseline HbA1c (%) + ΔGA2w (%) × 0.6.

Here, ΔGA2w means the difference between baseline GA and GA in the 2 weeks after therapy (baseline GA – GA in the 2 weeks after therapy).

**Statistical Analyses**

All data are shown as means ± SD. For statistical analyses, the paired Student’s t-test was used to compare the two groups. Single linear univariate regression analysis was employed to assess the association between continuous variables using the StatView computer program (Version 5.0 for Windows, Abacaus Concepts, Berkeley, CA, USA). A P value of <0.05 was considered statistically significant.

**RESULTS**

HbA1c and GA decreased from 9.4 ± 1.8 to 26.9 ± 7.7% at baseline to 7.8 ± 0.9 and 21.1 ± 4.5%, respectively, in the first 12 weeks of administration of sitagliptin (Figure 1). The decline curve of GA shifted to the left relative to that of HbA1c. Two weeks after administration of sitagliptin, GA had decreased to 24.3 ± 6.6% from 26.9 ± 7.7%, while HbA1c had only slightly decreased to 9.2 ± 2.4% from 9.4 ± 1.8%. As a result of comparing the change in GA before initiation of therapy and after the first 2 weeks of therapy (ΔGA2w), and the change in HbA1c before initiation of therapy and after the first 12 weeks of therapy (ΔHbA1c12w), a significant positive correlation was observed between them (R = 0.793, P < 0.0001) (Figure 2). The ΔGA2w was −2.6 ± 2.6% and ΔHbA1c12w was −1.6 ± 1.4%; that is, the latter was approximately 0.6 times the former. As a result of estimation of HbA1c after 12 weeks based on these relationships, the measured HbA1c after 12 weeks was 7.8 ± 0.9% and the estimated HbA1c (= baseline HbA1c + ΔGA2w × 0.6) was 7.8 ± 1.4%. The ratio of the estimated HbA1c to the measured HbA1c after 12 weeks was 102 ± 15%. A significant positive correlation was observed between the measured HbA1c and the estimated HbA1c after 12 weeks (R = 0.735, P < 0.0001). The regression line (y = x + 0.17) for both values was close to y = x (Figure 3). Furthermore, the ΔGA4w was −4.5 ± 4.8% and we obtained the formula of ΔHbA1c12w = 0.341 × ΔGA4w (R = 0.965, P < 0.0001; n = 18). Since the ΔGA4w was about three times of ΔHbA1c12w, we could also estimate HbA1c levels after 12 weeks by adding
GA decreased rapidly, while HbA1c decreased gradually. Takahashi et al. have reported similar changes in GA and HbA1c when intensive insulin therapy was introduced to diabetic patients with poor glycemic control. We also reported patients with type 2 diabetes who had poor glycemic control with intensive insulin therapy and compared the change in GA and HbA1c for 2 weeks after the start of therapy. GA decreased by 10.0%, while HbA1c only slightly decreased by 0.9%. In this study GA decreased by 2.7% after 2 weeks of administration of sitagliptin, while HbA1c only slightly decreased by 0.2%. These results confirmed that GA reflects shorter-term plasma glucose levels compared with HbA1c and suggest that GA is useful to estimate the therapeutic effects in the early period of treatment.

Based on the results of this study, we next examined whether or not HbA1c after 12 weeks could be estimated by GA. A significant positive correlation was observed between the ΔGA2w and the ΔHbA1c12w after administration of sitagliptin (Figure 2). Since the latter was about 0.6 times the former, HbA1c after 12 weeks can be estimated by adding ΔGA2w × 0.6 to the baseline HbA1c. The measured HbA1c levels after 12 weeks were similar to the estimated HbA1c levels (Figure 3).

Since GA and HbA1c levels decreased exponentially after treatment for diabetes, the decreased rate of GA or HbA1c is inversely correlated with the half-life of each. Based on this relationship, we developed an estimation formula for future HbA1c using the change of GA levels over short periods. We investigated the patients with various types of diabetic therapy and confirmed that the estimation formula for HbA1c is adaptable to any patients regardless of the treatment type. In the present study, using the data of GA before and after 2 weeks, estimated HbA1c levels after 12 weeks were 7.7 ± 1.7%, which were similar to measured HbA1c levels (7.8 ± 0.9%). The ratio of the estimated HbA1c to the measured HbA1c after 12 weeks was 102 ± 15%. We already reported that this ratio in patients with diet therapy alone, oral hypoglycemic agents therapy, and insulin therapy were 100 ± 10% (n = 5), 101 ± 8% (n = 17), 103 ± 10% (n = 17), respectively. The ratio in this study was not significantly different from the above data. The HbA1c levels after 12 weeks could, therefore, be estimated using the formula in the present study. Since the formula for estimated HbA1c in the present study is simpler than the formula reported previously, it is clinically useful. However, further study is necessary to confirm whether the formula in the present study can be applied to patients treated with other therapy.

Kanazu et al. have previously reported a formula for estimating HbA1c in the first 12 weeks of administration of sitagliptin. However, their formula requires data for the baseline fasting plasma glucose (FPG) and HbA1c, as well as FPG and HbA1c in the first 4 weeks of administration. The estimation formula we devised for this study uses only the data of the baseline GA and GA in the first 2 weeks after administration, and the calculation formula is simple. The advantage is that therapeutic effects can be evaluated rapidly, i.e., in the first 2 weeks of the introduction of therapy. If the estimated HbA1c after 12 weeks does not reach the target value, the therapy could be

**DISCUSSION**

After the administration of sitagliptin, GA decreased rapidly, while HbA1c decreased gradually. Takahashi et al. have

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\Delta GA_{4w} \times \frac{1}{3} \text{ to the baseline HbA1c (measured HbA1c 8.0 ± 1.0% vs estimate HbA1c 8.1 ± 1.1%; n = 18).}
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**Figure 2** Correlation between the decrease in GA within the first 2 weeks of sitagliptin therapy (ΔGA2w) and the decrease in HbA1c within the first 12 weeks (ΔHbA1c12w).

**Figure 3** Correlation between the estimated HbA1c (= baseline HbA1c + ΔGA2w × 0.6) and the measured HbA1c after 12 weeks of sitagliptin therapy. The dashed line shows the line of the formula \(y = x\).
added to or changed after 2 weeks. We believe that the ability to add to or change the therapy after 2 weeks will enable rapid optimization of glycemic control in most diabetic patients.

We were able to estimate the near future HbA1c after treatment for diabetes by the estimation formula for future HbA1c using the GA value in cases including various hypoglycemic drugs, insulin, or diet therapy alone. Therefore, the estimation formula in the present study is likely to be applicable to not only DPP-4 inhibitors other than sitagliptin, but also to other antidiabetic agents such as sulfonylurea, metformin and thiazolidinedione. It will, however, be necessary to examine drugs other than sitagliptin using similar studies.

In conclusion, the therapeutic effect of sitagliptin could be estimated soon after initiation of therapy by measuring GA before and after 2 weeks of administration of sitagliptin.

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