

Improved Monitoring of the Hyperglycemic State in Type 1 Diabetes Patients by Use of the Glycoalbumin/HbA1c Ratio

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■ Abstract

AIM: Generally, the level of glycoalbumin (GA) is approximately 3 times higher than that of HbA1c. However, in type 1 diabetic patients, we often find an even higher GA/HbA1c ratio of nearly 3.5. Therefore, this study was performed to examine the significance of a higher GA/HbA1c ratio. **METHODS:** 17 type 1 diabetic patients were enrolled in part 1 of the study and divided into two groups, one with a higher and the other with a lower GA/HbA1c ratio. In both groups, the correlation between GA or HbA1c level and each “4-point” capillary glucose level was analyzed. 80 type 1 diabetic patients were enrolled in part 2 of the study and the relationship between mean GA/HbA1c ratio in the past year and degree of diabetic

retinopathy was analyzed. **RESULTS:** In part 1 of the study, we found positive correlations between GA and bedtime capillary glucose levels and between HbA1c and bedtime capillary glucose levels in the higher GA/HbA1c group ($r = 0.86$, $p = 0.023$; $r = 0.95$, $p = 0.012$, respectively), but not in the lower GA/HbA1c group. In part 2 of the study, a significant positive correlation between GA/HbA1c ratio and severity of retinopathy could be observed ($r = 0.269$, $p = 0.017$). **CONCLUSIONS:** A higher GA/HbA1c ratio may reflect a postprandial hyperglycemic state and simultaneous monitoring of GA and HbA1c may improve the management of diabetic patients.

Keywords: postprandial hyperglycemia · glycoalbumin · HbA1c · diabetes management

Introduction

he results of the Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS) have demonstrated that it is important to control the level of HbA1c as measure of long-term glycemic control in order to prevent the development and progression of diabetic complications [1, 2]. Glycoalbumin (GA) is a glycated product of albumin, which is used as an alternative marker of glycemic control. Albumin is known to be glycated 10 times faster than hemoglobin [3] and its half-life is 17 days. While HbA1c reflects the average glycemic state of the last 2 to 3 months, GA is considered to cover the past few weeks. Therefore, GA may

be more useful than HbA1c in evaluating short-term changes in glycemic control.

It is possible to measure HbA1c and GA levels in routine clinical practice in Japan (i.e. not only for diabetes patients), and it is recognized that, in general, the level of GA is about 3 times higher than that of HbA1c [4-6]. However, we often find a higher GA/HbA1c ratio (nearly 3.5) in patients with type 1 diabetes. This observation is of interest because a higher than usual GA/HbA1c ratio may reflect recent fluctuations in glucose levels and indicate recently increased postprandial glucose levels. This study was performed to examine the significance of a higher GA/HbA1c ratio by analyzing the relationship between GA or HbA1c level and daily glucose levels.

Materials and methods

A total of 17 type 1 diabetic patients was enrolled in the first part of the study. The group consisted of 9 men and 8 women (mean age 54.6 ± 9.0 years, mean duration of diabetes 10.2 ± 8.8 years, mean HbA1c level $7.2 \pm 0.6\%$, mean GA level $24.4 \pm 3.5\%$). All patients received intensive insulin therapy, i.e. regular and adjusted insulin supply. Type 1 diabetes was defined by insulin dependency (determined by measurement of random serum C-peptide immunoreactivity (CPR) < 0.2 ng/ml or serum CPR < 1.0 ng/ml upon maximum insulin stimulation by the glucagon loading test), with or without GAD antibody positivity (measured by radioimmunoassay, RSR, Cardiff, UK). 9 of 17 patients were GAD antibody positive (mean 47.9 U/ml, range $1.7 - 195$ U/ml). Patients with anemia, liver cirrhosis or renal failure (serum creatinine > 2.0 mg/dl) were excluded because these conditions may influence the levels of GA and HbA1c. Informed consent was obtained from all patients.

The correlation between GA or HbA1c and “4-point” mean capillary glucose levels (before breakfast, lunch, dinner and bedtime) was analyzed using Spearman’s rank correlation coefficient. To examine the characteristics of patients with a higher GA/HbA1c ratio, we subdivided all patients into two groups, a higher (GA/HbA1c_{high}) and a lower GA/HbA1c group (GA/HbA1c_{low}) according to the median level of GA/HbA1c (3.37). Afterwards, we analyzed the correlation between GA or HbA1c level and each “4-point” mean capillary glucose level in the two groups using Spearman’s rank correlation coefficient again. Capillary glucose level was measured using Glutest Pro R (Sanwa Kagaku Research Institute, Nagoya, Japan), which contains an auto-memorizing function for the previous 100 measurements. The mean duration of blood glucose measurements was 63.5 days.

We measured GA by using an enzymatic method and HbA1c with the HPLC method. For each patient, the mean levels of GA and HbA1c at every visit during the study period were used. Since this study was performed in a routine clinical practice setting, daily capillary glucose levels were measured by self-monitoring of blood glucose 4 times a day before insulin injections.

To examine whether a higher GA/HbA1c ratio is associated with a particular degree of diabetic complications, we analyzed the relationship between mean GA/HbA1c ra-

tio over the past year and the degree of diabetic retinopathy in 80 “classical” type 1 diabetic patients in the second part of the study (36 men and 44 women, mean age 47.0 ± 14.8 years, mean duration of diabetes 13.0 ± 9.5 years, mean HbA1c level $7.5 \pm 1.3\%$, mean GA level $25.3 \pm 5.1\%$). “Classical” type 1 diabetes was defined by rapid onset and insulin dependency according to the thresholds specified above, with or without GAD antibody positivity. 51 of 80 patients were classical type 1 diabetics with positive GAD antibodies (mean GAD antibody measurement was 85.2 U/ml, range $0.6 - 1610$ U/ml).

Fourteen patients (17.5%) had hypertension. The degree of retinopathy was scored as follows: 0 (none), 1 (simple), 2 (preproliferative), 3 (proliferative). The correlation between GA/HbA1c ratio and degree of retinopathy was analyzed using non-parametric tests.

All data are given as mean \pm SD. The statistical analyses were performed using StatView 5.0™ (SAS Institute Inc., Cary, NC).

Results

Correlation between GA/HbA1c ratio and glucose levels (part 1 of the study)

The mean GA/HbA1c ratio in part 1 of the study was 3.31 ± 0.37 and the median level of GA/HbA1c was 3.37. Clinical and laboratory parameters in the GA/HbA1c_{high} and the GA/HbA1c_{low} group are shown in Table 1. In the overall study cohort, there was no correlation between GA and each “4-point” capillary glucose level. Nor did we observe a correlation between HbA1c and capillary glucose levels in the whole cohort, except for a weak correlation between HbA1c and lunch time capillary glucose levels ($r = 0.53$, $p = 0.036$).

When both groups, GA/HbA1c_{high} and GA/HbA1c_{low}, are considered separately, a significant positive correlation was found between GA and bed-

Table 1. Clinical and laboratory variables in the two patient groups

Parameter	GA/HbA1c _{high} (n = 9)	GA/HbA1c _{low} (n = 8)	p
Age (yr)	55.00 ± 10.00	54.10 ± 9.00	ns
Diabetes duration (yr)	10.20 ± 7.40	10.10 ± 10.60	ns
GA (%)	26.00 ± 2.20	21.20 ± 3.00	0.0061
HbA1c (%)	7.30 ± 0.50	7.00 ± 0.50	ns
GA/HbA1c	3.55 ± 0.13	3.03 ± 0.33	0.0005

Legend: Data are mean \pm SD. p values were determined by Mann-Whitney U test. ns: not significant. GA: glycoalbumin. HbA1c: glycated hemoglobin.

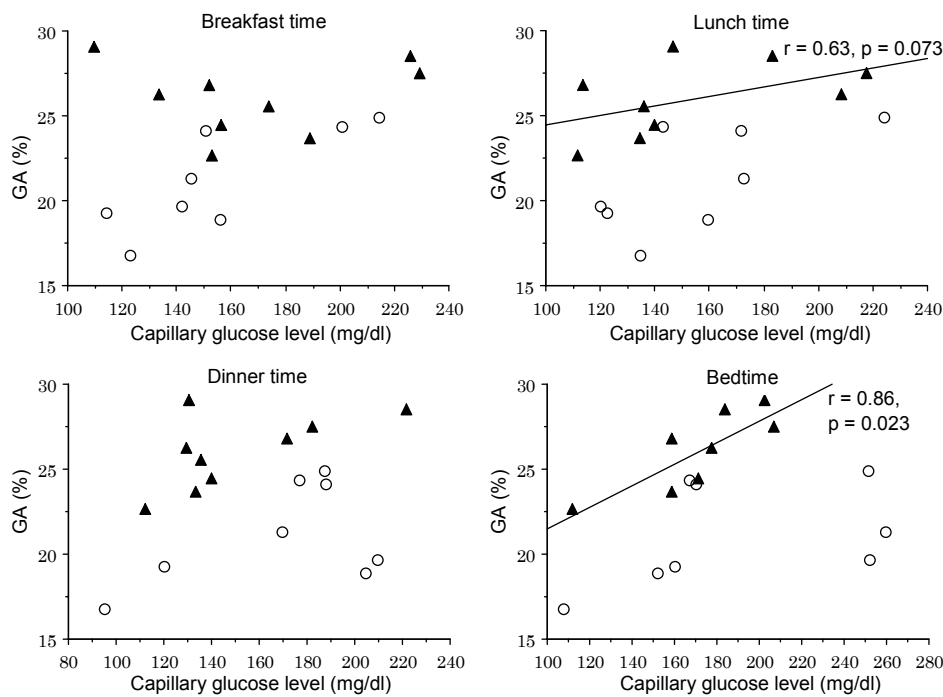


Figure 1. Correlation between GA level and each 4-point capillary glucose level. Black triangles: GA/HbA1c_{high} group. White circles: GA/HbA1c_{low} group.

time capillary glucose levels in the GA/HbA1c_{high} group ($r = 0.86, p = 0.023$, Figure 1), but not in the GA/HbA1c_{low} group. Moreover, a significant positive correlation was found between HbA1c and bedtime capillary glucose levels in the GA/HbA1c_{high} group as well ($r = 0.95, p = 0.012$, Figure 2).

Regarding lunch time capillary glucose levels, a more significant correlation between HbA1c level and capillary glucose level was found in the GA/HbA1c_{high} group ($r = 0.82, p = 0.021$, Figure 2) compared with the overall cohort of patients. Moreover, a similar positive tendency was found between GA and lunch time capillary glucose levels in the GA/HbA1c_{high} group ($r = 0.63, p = 0.073$, Figure 1).

Correlation between GA/HbA1c ratio and diabetic retinopathy (part 2 of the study)

In part 2 of the study, 22 of 80 patients had diabetic retinopathy and there was a significant positive correlation between GA/HbA1c ratio and severity of retinopathy ($r = 0.269, p = 0.017$). Hypertension also affected the severity of retinopathy ($r = 0.657, p = 0.018$), but there was no statistically significant difference in the proportion of patients with hypertension

between the GA/HbA1c_{high} and the GA/HbA1c_{low} group (22.5%, 12.5%, respectively; $p = 0.378$).

Discussion

The results of the DCCT and UKPDS studies have demonstrated that it is important to control the level of HbA1c as a measure of long-term glycemic control in order to prevent the development and progression of diabetic complications [1, 2]. However, patients who received intensive treatment in the DCCT trial had a lower risk of diabetic retinopathy than those who had received conventional treatment, even though the level of HbA1c was

matched between the two groups [7]. Therefore, HbA1c level alone may not be sufficient to evaluate glycemic control and the risk of diabetic complications. Bonora *et al.* previously reported that HbA1c seems to reflect the “preprandial” plasma glucose state [8]. In this context, the DCCT results suggest that the difference in the incidence of diabetic complications between the two groups may have been caused by differences in the “postprandial” glycemic state. In fact, the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study and others have demonstrated the importance of the postprandial glycemic state [9]. However, the oral glucose tolerance test (OGTT) used to evaluate the postprandial state in the DECODE study is impractical for routine medical visits and to date there is no useful marker that reflects the “usual” postprandial glucose state. Therefore, a suitable marker that reflects the postprandial state in daily life is needed.

In part 1 of the study, the mean interval between breakfast, lunch, dinner, and bedtime was 4-5 h, 6-7 h and 3-4 h, respectively. Given that our results indicate a significant positive correlation between GA or HbA1c level and bedtime capillary glucose level in pa-

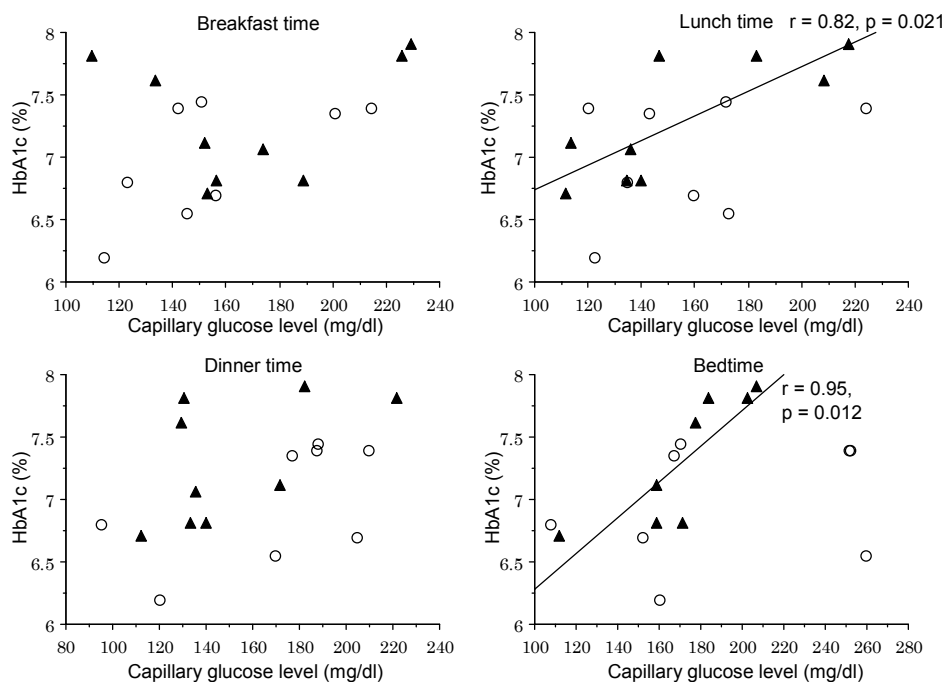


Figure 2. Correlation between HbA1c level and each 4-point capillary glucose level. Black triangles: GA/HbA1c_{high} group. White circles: GA/HbA1c_{low} group.

tients with a higher GA/HbA1c ratio, we speculate that a higher GA/HbA1c ratio than usual may reflect a postprandial hyperglycemic state.

Interestingly, when we instructed part of the patient cohort in this study to increase their bolus insulin dosage, a reduction in postprandial glucose level and GA/HbA1c ratio was observed for several months, although these data are preliminary (data not shown). In order to confirm these results, it is necessary to include measurements of 1-2 h postprandial or continuous glucose levels in a future study. The results of the present study are limited because of the lack of con-

tinuous glucose levels and the small study cohort.

To evaluate the significance of the GA/HbA1c ratio, we analyzed the correlation between GA/HbA1c ratio and the degree of diabetic retinopathy in part 2 of the study. The results suggest that patients with a higher GA/HbA1c ratio had more severe diabetic retinopathy. According to a previous report that postprandial hyperglycemia is a better predictor of diabetic retinopathy than HbA1c [10], GA/HbA1c ratio may reflect the postprandial glycemic state and may be a useful target for the prevention of diabetic complications, rather than HbA1c alone. However, diabetic retinopathy

is affected by various factors. Therefore, we have to follow the patients for longer periods in order to draw more robust conclusions and to correct for confounders.

In conclusion, a higher GA/HbA1c ratio may reflect the postprandial hyperglycemic state and simultaneous measurement of GA and HbA1c may be useful for the management of diabetic patients. As the cohort included in this study was relatively small, further studies are needed to prove the value of glucose monitoring by the additional parameter, GA/HbA1c, in predicting the risk of chronic complications.

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