Glycated Albumin Is a Better Glycemic Indicator than Glycated Hemoglobin Values in Hemodialysis Patients with Diabetes: Effect of Anemia and Erythropoietin Injection

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The significance of glycated albumin (GA), compared with casual plasma glucose (PG) and glycated hemoglobin (HbA_{1c}), was evaluated as an indicator of the glycemic control state in hemodialysis (HD) patients with diabetes. The mean PG, GA, and HbA_{1c} levels were 164.5 ± 55.7 mg/dl, 22.5 ± 7.5%, and 5.85 ± 1.26%, respectively, in HD patients with diabetes ($n = 538$), which were increased by 51.5, 31.6, and 17.7%, respectively, compared with HD patients without diabetes ($n = 828$). HbA_{1c} levels were significantly lower than simultaneous PG and GA values in those patients in comparison with the relationship among the three parameters in patients who had diabetes without renal dysfunction ($n = 365$), as reflected by the significantly more shallow slope of regression line between HbA_{1c} and PG or GA. A significant negative correlation was found between GA and serum albumin ($r = -0.131$, $P = 0.002$) in HD patients with diabetes, whereas HbA_{1c} correlated positively and negatively with hemoglobin ($r = 0.090$, $P = 0.036$) and weekly dose of erythropoietin injection ($r = -0.159$, $P < 0.001$), respectively. Although PG and GA did not differ significantly between HD patients with diabetes and with and without erythropoietin injection, HbA_{1c} levels were significantly higher in patients without erythropoietin. Categorization of glycemic control into arbitrary quartile by HbA_{1c} level led to better glycemic control in a significantly higher proportions of HD patients with diabetes than those assessed by GA. Multiple regression analysis demonstrated that the weekly dose of erythropoietin, in addition to PG, emerged as an independent factor associated with HbA_{1c} in HD patients with diabetes, although PG but not albumin was an independent factor associated with GA. In summary, it is suggested that GA provides a significantly better measure to estimate glycemic control in HD patients with diabetes and that the assessment of glycemic control by HbA_{1c} in these patients might lead to underestimation likely as a result of the increasing proportion of young erythrocyte by the use of erythropoietin.

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Strict glycemic control in patients with diabetes decreases the incidence of diabetic complications (1), which can determine the quality of life and prognosis of such patients. Intensive treatment with insulin or oral hypoglycemic agents has been established to delay the onset and slow the progression of diabetic microangiopathy in the patients with types 1 diabetes and type 2 diabetes in the Diabetes Control and Complications Trial (2) and the Kumamoto Study (3), respectively. Furthermore, a reduction of the risk for the development of diabetic microangiopathy in patients with type 2 diabetes by strict glycemic control was demonstrated in the UK Prospective Diabetes Study (4). Recent clinical evidence has suggested the favorable effects of strict glycemic control on cardiovascular disease, a main cause of death in patients with diabetes (5,6). It has been reported that strict glycemic control, as indicated by lower glycated hemoglobin (HbA_{1c}) levels, has beneficial effects on the prognosis of patients who have diabetes with chronic kidney disease and undergo regular hemodialysis (HD) (7,8). However, some reports indicate that HbA_{1c} might not provide a relevant assay for glycemic control in HD patients. Although these have been small-scale studies, because HbA_{1c} is the product of chemical condensation of hemoglobin and glucose, HbA_{1c} values are influenced significantly in HD patients by either shortening of the life span of erythrocytes (9,10) or the changing proportion of young to old erythrocytes by erythropoietin use (11). Recently, serum glycated albumin (GA) was hypothesized to be an alternative marker for glycemic control in patients with diabetes, which is not affected by changes in the survival time of erythrocytes in the case of type 2 diabetes with hemoglobinopathy (12). Furthermore, the new, improved method, which is free of interference by endogenous glycated amino acids, is unaffected by changes in albumin concentration (13). Therefore, the present study was designed to assess

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whether the new assay method of GA might provide a better indicator than HbA_{1c} for glycemic control in HD patients with diabetes.

Materials and Methods

Patients

HD patients at Inoue Hospital, Shirasagi Hospital, Ohno Memorial Hospital, and Okada Clinic and patients with diabetes and normal renal function at Osaka City University Hospital were enrolled in this study. All patients provided written informed consent before participation in this study, which was approved by institutional ethics committees (Osaka City University Graduate School of Medicine) and was conducted in accordance with the principles of the Declaration of Helsinki. This study was composed of 538 HD patients with type 2 diabetes, 828 HD patients without diabetes, and 365 patients with type 2 diabetes and normal renal function, which was defined as diabetes and non–chronic renal failure (non-CRF) on the basis of serum creatinine levels of <1.2 mg/dl. The diagnosis of diabetes was based on a history of diabetes or on the criteria in the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (14). The inclusion of patients with type 1 diabetes was negated by a history of diabetes, because of the very small number of patients with type 1 diabetic in Japan (15,16). Patients with diabetes were restricted to those whose diabetes treatment had not been altered during the preceding 6 mo before the determination of GA and HbA_{1c}. Information on weekly doses of erythropoietin, which had not been changed during the 3 mo before determination of GA and HbA_{1c}, also was obtained.

Assay of GA and HbA_{1c}

GA was measured by an enzymatic method using the Lucica GA-L kit (Asahi Kasei Pharma Corp., Tokyo, Japan) (13). GA was hydrolyzed to amino acids by albumin-specific proteinase and then oxidized by ketoamine oxidase to produce hydrogen peroxide, which was measured quantitatively. The GA value was calculated as the percentage of GA relative to total albumin, which was measured with new bromocresol purple method using the same serum sample (13). GA assay was not influenced by the physiologic concentrations of ascorbic acid, bilirubin, and up to 1000 mg/dl glucose (17). HbA_{1c} was measured by routine HPLC and latex agglutination immunoassay, which was standardized according to the Japan Diabetes Society (18).

Biochemical Measurements

Blood was drawn immediately without overnight fasting, before the morning Monday/Tuesday session of HD, to measure serum parameters in HD patients, as described previously (15,16). In patients with diabetes and without CRF, blood samples were collected in the morning.

The mean values of the three monthly measurements of casual plasma glucose (PG) that were obtained during the 2 mo before determination of serum GA and HbA_{1c} were used in the analysis. Serum GA and HbA_{1c} were measured once, concomitant with the determination of red blood cells, Hb, hematocrit, total protein, albumin, blood urea nitrogen, and creatinine.

Statistical Analyses

Data are expressed as means ± SD. Correlation coefficients were calculated by simple regression analysis, and the differences in means between the two groups were analyzed by t test. A χ^2 test was performed to compare the various distributions. Multiple logistic regression analysis assessed the independent contribution of PG, HbA_{1c}, and GA to the occurrence of diabetes. Multiple regression analyses were performed to explore the association of PG, hemoglobin, and erythropoietin dose with HbA_{1c} and GA. Comparison of two regression slopes was performed as described previously (16,19). All analyses were performed using statistical software for Windows (Stat View 5; SAS Institute, Cary, NC).

Results

Variation of Casual PG Levels during Study Period of 2 Months

PG from HD patients with diabetes ($n = 538$) at 2 mo before, 1 mo before, and the time of GA and HbA_{1c} measurements were 162.7 ± 67.4, 162.1 ± 64.8, and 163.1 ± 67.9 mg/dl, respectively. The correlation coefficients for PG between 2 and 1 mo before, between 2 and 0 mo before, and between 1 and 0 mo before were $r = 0.620$ ($P < 0.001$), $r = 0.571$ ($P < 0.001$), and $r = 0.588$ ($P < 0.001$), respectively. These data suggested that glycemic control of our patients with diabetes was stable during the study period.

Effect of a Single HD Session on GA and HbA_{1c}

Serum GA values were almost identical between before and after a single HD session in HD patients ($r = 0.998$, $P < 0.001$); serum HbA_{1c} also correlated significantly in a positive manner ($r = 0.992$, $P < 0.001$) but to a lesser degree. These data clearly indicated that the substances that accumulated into uremic serum did not affect GA values at all.

Correlation between PG and GA or HbA_{1c} in HD Patients with Diabetes and in Patients with Diabetes and without CRF

As shown in Figure 1, there were significant and positive correlations between PG and serum GA ($r = 0.539$, $P < 0.001$; Figure 1A) or HbA_{1c} ($r = 0.520$, $P < 0.001$; Figure 1B) in HD patients with diabetes. Figure 1, C and D, indicates the correlation of PG with GA ($r = 0.498$, $P < 0.001$; Figure 1C) and HbA_{1c} ($r = 0.630$, $P < 0.001$; Figure 1D) in patients with diabetes and without CRF. As shown, the relationship between PG and GA was identical between the HD patients with diabetes and patients with diabetes and without CRF, although HbA_{1c} values in comparison with those of PG seemed to be significantly lower in HD patients with diabetes than in patients with diabetes and without CRF. In fact, the regression slope between HbA_{1c} and PG was significantly lower in HD patients with diabetes than in patients with diabetes and without CRF ($P < 0.001$), although the slope between GA and PG did not differ significantly between the two groups of patients ($P > 0.10$).

Correlation between Serum GA and HbA_{1c} Levels in HD Patients with Diabetes in Patients with Diabetes and without CRF

There was a significant and positive correlation between serum GA and HbA_{1c} levels in both HD patients with diabetes ($r = 0.777$, $P < 0.001$; Figure 2A) and patients with diabetes and without CRF ($r = 0.732$, $P < 0.001$; Figure 2B). The GA/HbA_{1c} ratio in patients with diabetes and without CRF was 2.93, which was consistent with the previous report of GA/HbA_{1c} ratio of approximately 3.0 (20). The GA value relative to HbA_{1c} was

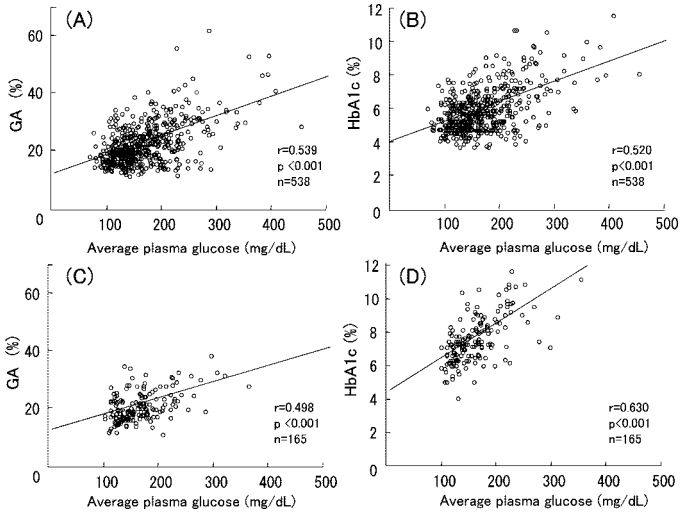

Figure 1. Correlation between the average plasma glucose (PG) values and glycated albumin (GA) or glycated hemoglobin (HbA_{1c}) in hemodialysis (HD) patients with diabetes and in patients with diabetes and without chronic renal failure (CRF). The PG levels correlated significantly and positively with the GA ($r = 0.539$, $P < 0.001$; A) and HbA_{1c} ($r = 0520$, $P < 0.001$; B) levels in HD patients with diabetes. In patients with diabetes and without CRF, the PG levels correlated significantly and positively with GA ($r = 0.498$, $P < 0.001$; C) and HbA_{1c} ($r = 0.630$, $P < 0.001$; D) levels. The regression slope between HbA_{1c} and PG was significantly more shallow in HD patients with diabetes (0.012) compared with patients with diabetes and without CRF (0.021; $P < 0.001$), although that between GA and PG did not differ significantly between the two groups of patients (0.068 *versus* 0.058; $P > 0.10$).

increased significantly to 3.81 in the HD patients with diabetes, which also was supported by a significantly more shallow slope of the regression line compared with the patients with diabetes and without CRF ($P < 0.001$).

Comparison of the Degrees of Glycemic Control on the Basis of HbA_{1c} and GA Values

The mean PG, GA, and HbA_{1c} levels in the HD patients with diabetes were 164.5 ± 55.7 mg/dl, 22.5 ± 7.50%, and 5.85 ± 1.26%, respectively, all of which were significantly higher than the corresponding values of 108.6 ± 26.8 mg/dl, 17.1 ± 4.35%, and 4.97 ± 0.83% in the HD patients without diabetes (Figure 3). The mean PG, GA, and HbA_{1c} levels in the patients with diabetes were increased by 51.5, 31.6, and 17.7%, respectively, of the corresponding values in patients without diabetes. The mean weekly doses of erythropoietin were significantly greater in HD patients with diabetes compared with the HD patients without diabetes (5385.7 ± 3182.3 *versus* 4955.7 ± 3270.7 U, $P < 0.05$), although Hb and albumin did not differ significantly between the two groups of patients (HD patients with diabetes *versus* HD patients without diabetes 9.95 ± 1.30 g/dl *versus* 9.89 ± 1.25 g/dl [$P = 0.387$]; 3.55 ± 0.42 g/dl *versus* 3.54 ± 0.36 g/dl [$P = 0.836$]).

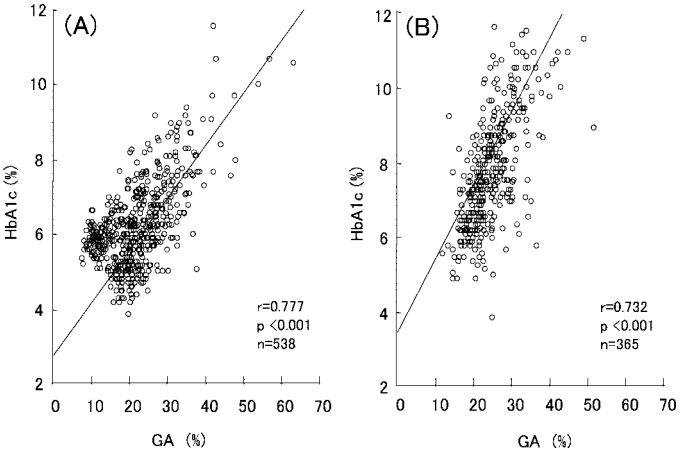

Figure 2. Correlation between the GA and HbA_{1c} levels in HD patients with diabetes and in patients with diabetes and without CRF. The GA values correlated significantly and positively with the HbA_{1c} values in HD patients with diabetes ($r = 0.777$, $P < 0.001$; A) and patients with diabetes and without CRF ($r = 0.732$, $P < 0.001$; B). The regression slope between GA and HbA_{1c} levels was significantly more shallow in HD patients with diabetes (slope 0.141) compared with patients with diabetes and without CRF (slope 0.197; $P < 0.001$).

Logistic Regression Analysis of PG, GA, and HbA_{1c} with Diabetes in HD Patients

The independent contribution of PG, GA, and HbA_{1c} to the probability of diabetes in HD patients was assessed after adjustment for serum albumin and Hb by multiple logistic regression analysis. PG (per 10 mg/dl; odds ratio [OR] 1.486; $P < 0.001$), GA (per 1.0%; OR 1.242; $P < 0.001$), and HbA_{1c} (per 1.0%; OR 2.479; $P < 0.001$) were independent risk factors associated with diabetes in HD patients (Table 1).

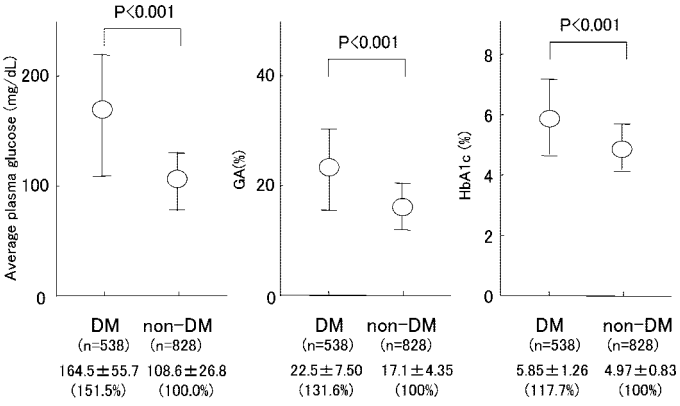

Figure 3. Mean PG, GA, and HbA_{1c} levels in patients with and without diabetes. The means of the average PG, GA, and HbA_{1c} levels all were significantly higher in patients with diabetes that without diabetes by *t* test ($P < 0.001$). The mean PG, GA, and HbA_{1c} levels in patients with diabetes were increased by 51.5, 31.6, and 17.7%, respectively, of the corresponding value in patients without diabetes.

Table 1. Logistic regression analysis of PG, GA, and HbA_{1c} and other factors associated with diabetes in HD patients[a]

Clinical Variables	Model 1 (OR [95% CI])	Model 2 (OR [95% CI])	Model 3 (OR [95% CI])
Albumin (per 1 g/dl)	1.304 (0.892 to 1.905)	1.292 (0.898 to 1.859)	0.894 (0.617 to 1.295)
Hb (per 1 g/dl)	1.054 (0.941 to 1.181)	1.127 (0.987 to 1.284)	1.079 (0.968 to 1.203)
Average plasma glucose (per 10 mg/dl)	1.486 (1.421 to 1.554)[b]	–	–
GA (per 1%)	–	1.242 (1.208 to 1.278)[b]	–
HbA_{1c} (per 1%)	–	–	2.479 (2.148 to 2.861)[b]

[a]CI, confidence interval; GA, glycated albumin; HbA_{1c}, glycated hemoglobin; HD, hemodialysis; OR, odds ratio; PG, plasma glucose.
[b]$P < 0.001$.

Distribution of the Degrees of Glycemic Control on the Basis of the HbA_{1c} and GA Values

The HD patients with diabetes were divided into four arbitrary categories according to serum HbA_{1c} values: Excellent ($HbA_{1c} \leq 6.0\%$), good ($6.0 < HbA_{1c} \leq 7.0\%$), fair ($7.0 < HbA_{1c} \leq 8.0\%$), and poor ($HbA_{1c} > 8.0\%$). There were 307 (57.1%), 128 (23.7%), 65 (12.1%), and 38 (7.1%) of 538 patients in each group, respectively (Table 2). On the basis of previous reports and our data (Figure 2) that GA values were approximately three times greater than HbA_{1c} values, glycemic control also was assessed according to the GA values: Excellent ($GA \leq 18.0\%$), good ($18.0 < GA \leq 21.0\%$), fair ($21.0 < GA \leq 24.0\%$), and poor ($GA > 24.0\%$). There were 152 (28.3%), 106 (19.7%), 84 (15.6%), and 196 (36.4%) patients in each of the respective groups. The proportions of glycemic control that were based on the HbA_{1c} values were significantly different from those that were based on the GA values ($P < 0.001$ by χ^2 test).

Correlation between GA and Serum Albumin and between HbA_{1c} and Hemoglobin Levels in HD Patients with Diabetes

The serum albumin and HbA_{1c} in HD patients with diabetes ranged from 1.5 to 4.8 g/dl and from 4.9 to 14.8 g/dl, respectively. A significant and negative correlation was found between GA and serum albumin levels ($r = -0.131$, $P = 0.002$; Figure 4A), although HbA_{1c} did not correlate with serum albumin levels ($r = 0.010$, $P = 0.853$). In contrast, there was a significant and positive correlation between HbA_{1c} and hemoglobin levels ($r = 0.090$, $P = 0.036$; Figure 4B), although GA did not correlate with serum hemoglobin levels ($r = 0.037$, $P = 0.397$).

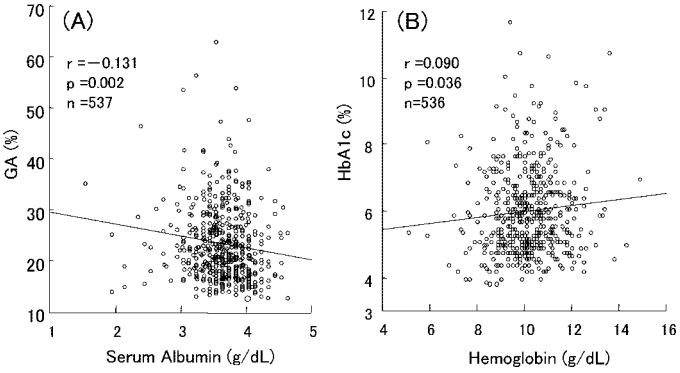

Figure 4. Correlation between serum albumin and GA and between Hb and HbA_{1c}. In patients with diabetes, the GA values correlated significantly and negatively with serum albumin values ($r = -0.131$, $P = 0.002$; A) and HbA_{1c} values correlated positively with hemoglobin ($r = 0.090$, $P = 0.036$; B).

Correlation of the Weekly Erythropoietin Dose with HbA_{1c} but Not with GA in HD Patients with Diabetes

As shown in Figure 5, there was a significant and negative correlation between HbA_{1c} and the weekly dose of erythropoietin ($r = -0.159$, $P < 0.001$) in HD patients with diabetes, although GA did not correlate well ($r = 0.055$, $P = 0.201$). The average PG and GA levels in the HD patients with diabetes and without erythropoietin ($n = 73$) were 157.3 ± 60.1 mg/dl and $21.8 \pm 7.8\%$, which were not significantly different from the respective values of 162.8 ± 57.9 mg/dl and $23.0 \pm 7.1\%$ in those who received erythropoietin ($n = 465$). However, the HbA_{1c} values were significantly higher in those who were not

Table 2. Proportion of glycemic control of HD patients with diabetes when assessed by HbA_{1c} and GA[a]

Glycemic Control	HbA_{1c} (%)	GA (%)
Excellent ($HbA_{1C} \leq 6\%$, $GA \leq 18\%$)	307 (57.1)	152 (28.3)
Good ($6\% < HbA_{1c} \leq 7\%$, $18\% < GA \leq 21\%$)	128 (23.7)	106 (19.7)
Fair ($7\% < HbA_{1c} \leq 8\%$, $21\% < GA \leq 24\%$)	65 (12.1)	84 (15.6)
Poor ($8\% < HbA_{1c}$, $24\% < GA$)	38 (7.1)	196 (36.4)

[a]Numbers in parentheses indicate the percentage of whole patients.

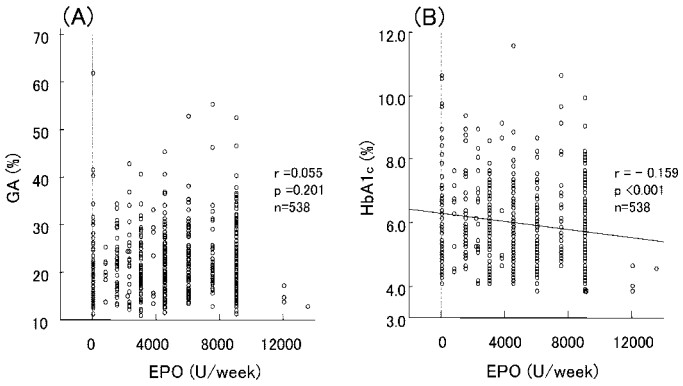

Figure 5. Correlation of weekly doses of recombinant human erythropoietin with GA and HbA_{1c} levels. Although serum GA did not correlate significantly with weekly doses of recombinant human erythropoietin in the HD patients with diabetes ($r = 0.065$, $P = 0.201$; A), HbA_{1c} correlated significantly in a negative manner ($r = -0.159$, $P < 0.001$; B).

treated with erythropoietin compared with those who were treated with erythropoietin (6.26 ± 1.46 *versus* 5.94 ± 1.25%, $P < 0.05$).

Multiple Regression Analysis of Factors for HbA_{1c} and GA in HD Patients with Diabetes

Table 3 represents the results of multiple regression analysis of various clinical variables to evaluate their independent association with HbA_{1c} and GA values in HD patients with diabetes. In model 1, which included average PG, serum albumin, serum creatinine, and hemoglobin, only average PG and hemoglobin were independent factors associated with HbA_{1c}. In model 2, which included the weekly dose of erythropoietin in place of hemoglobin, it emerged as a significant and independent factor associated with HbA_{1c}, in addition to average PG. In model 3, which simultaneously included hemoglobin and erythropoietin dose, erythropoietin dose but not hemoglobin retained a significant and independent association with HbA_{1c}. In fact, the HbA_{1c} values were significantly lower in HD patients who had diabetes and were treated with erythropoietin (5.94 ± 1.25%) than in those without (6.26 ± 1.46%; $P < 0.05$), although PG (162.8 ± 57.9 *versus* 157.3 ± 60.1 mg/dl) and GA (23.0 ± 7.1 *versus* 21.8 ± 7.8%) did not differ significantly between those with and without erythropoietin. In the same model as model 3 for HbA_{1c} to evaluate the independent factors that were associated with GA, the average PG alone exhibited a significant and independent association with GA, although the association with serum albumin was NS.

Discussion

In this study, the measurement of GA was shown to provide a more relevant method to assess glycemic control in HD patients with diabetes. Although PG was measured without overnight fasting, a previous report showed that nonfasting, rather than fasting, PG was a better marker of glycemic control in type 2 diabetes (21). Because the mean values of monthly-determined PG essentially were the same throughout the study period, it was suggested that glycemic control had been stable during the 2 mo before the determination of GA and HbA_{1c} and that a single determination just before the Monday/Tuesday HD session might be representative of glycemic control in HD patients with diabetes. Although HbA_{1c} and GA reflect glycemic control during the preceding 4 to 6 wk and 1 to 2 wk (11), the stable glycemic control during the preceding 2 mo can negate the different impact of acute changes of glycemic control between HbA_{1c} and GA in this study. Supportive of this notion is that the correlation coefficient between PG and HbA_{1c} was similar with that between PG and GA. The correlation coefficients of PG at 2, 1, or 0 mo before with HbA_{1c} were very similar to those with GA (data not shown).

Although the seven-point PG profile during a single day is hypothesized to be ideal as a measure of glycemic control, HD patients showed a higher day-to-day variation of diet intake and physical stress as a result of the HD session three times a week. Although the previous report used the PG sampling scheme to a 14-point scheme during a 7-d period in a small number of HD patients (10), this scheme cannot apply to almost 1400 patients. The degree with which serum GA correlated with PG was identical between the HD patients with diabetes

Table 3. Multiple regression analysis of PG and other factors that were associated independently with HbA_{1c} and GA in HD patients with diabetes

Clinical Variables	HbA_{1c} (%)			GA (%)
	Model 1	Model 2	Model 3	Model 1
Average PG (mg/dl)	0.515[a]	0.515[a]	0.515[a]	0.538[a]
Serum albumin (g/dl)	−0.057	−0.027	−0.055	−0.067
Serum creatinine (mg/dl)	−0.040	−0.048	−0.045	−0.193
Hb (g/dl)	0.103[b]	–	0.039	0.003
Erythropoietin (U/wk)	–	−0.156[c]	−0.128[b]	0.074
R^2	0.285[a]	0.294[a]	0.298[a]	0.365[a]

[a] $P < 0.001$.
[b] $P < 0.05$.
[c] $P < 0.01$.

and patients with diabetes and without CRF (Figure 1, A and C). The significantly lower value of HbA_{1c} relative to PG and GA in HD patients with diabetes compared with the patients with diabetes and without CRF (Figure 1, B and D) might suggest that the measurement of HbA_{1c} would result in the underestimation of glycemic control in HD patients with diabetes. On the basis of the regression line between GA and PG in HD patients with diabetes (Figure 1, A and B), it was shown that a "fair" category of GA of 21.0% and HbA_{1c} of 7.0% results in a PG of 130 and 247 mg/dl, respectively. Therefore, the GA value of 21.0% was reasonably categorized into a fair category, as reflected by the PG value of 130 mg/dl. However, categorization of the HbA_{1c} value of 7.0% into a fair category definitely was an underestimation, as reflected by PG values as high as 247 mg/dl.

The mechanism for the significantly lower HbA_{1c} value in those patients was explained by anemia and/or erythropoietin injection, as reflected by a significant correlation of HbA_{1c} with hemoglobin and the weekly dose of erythropoietin (Figures 4 and 5). Multiple regression analysis demonstrated that erythropoietin use, rather than hemoglobin reduction, was an independent factor that was associated significantly with the HbA_{1c} values (Table 3). In fact, the HbA_{1c} values were significantly lower in HD patients who had diabetes and were treated with erythropoietin compared with those without, although PG and GA did not differ significantly between two groups of patients. The differences of the mean HbA_{1c} values between the HD patients with diabetes and HD patients without diabetes were smaller than those of PG and GA, which is explained partly by a significantly greater erythropoietin dose in the HD patients with diabetes. Importantly, although serum albumin correlated negatively with GA (Figure 4), it failed to be a significant factor associated with GA (Table 3). The only factor that associated independently with GA value was the average PG, which associated to a greater degree with GA compared with HbA_{1c}. Multiple logistic regression analysis showed that PG glucose, GA, and HbA_{1c} were independent risk factors associated with the prevalence of diabetes after adjustment for serum albumin and Hb. A 1% increase of GA value is indicative of 1.242-fold increase to have diabetes in contrast to a 2.479-fold increase per 1% increase of HbA_{1c} value. Because a 3% increase of GA is equal to a 1% increase of HbA_{1c}, it was suggested that an increase of GA might be more highly indicative of diabetes than that of HbA_{1c}.

The nonenzymatic glycation of various proteins is increased in patients with diabetes as a result of sustained higher PG (22). The rate of production also depends on the half-life of each protein (23). HbA_{1c} provides an integrated measure of PG during the previous 2 to 3 mo as a result of the long life span of erythrocytes (120 d) (24,25), whereas GA has been hypothesized to be a glycemic indicator during the immediately previous 2 wk (23). Although a rapid change in glycemic control may reflect a greater change of GA than HbA_{1c}, this study examined the significance of GA compared with HbA_{1c} under stationary state of diabetic control, without any change of antidiabetic drugs during the study period, and compared GA and HbA_{1c} values in patients with diabetes and with and without renal dysfunction. Therefore, the better correlation of average PG during the preceding 2 mo with GA compared with HbA_{1c} cannot be accounted for by a rapid fluctuation of glycemic control in the HD patients with diabetes. Although the HbA_{1c} values correlated significantly with PG and GA in both HD patients with diabetes and patients with diabetes and without CRF, the ratios of HbA_{1c}/PG and HbA_{1c}/GA were significantly lower in the HD patients with diabetes, as indicated by the significantly more shallow slope between the HbA_{1c} and PG or GA in those patients, although the GA/PG ratio retained the same relationship between two groups of patients. A previous report (11) showed that after erythropoietin treatment, HbA_{1c} levels decreased with the increase of hematocrit in 15 HD patients without diabetes, although PG did not change. Conversely, after stopping erythropoietin treatment, HbA_{1c} levels increased. Because erythropoietin accelerates the production of new erythrocytes and the proportion of young erythrocytes in peripheral blood must increase after erythropoietin administration. HbA_{1c} is the product of the chemical condensation of hemoglobin and glucose, and the glycated rate of just-produced young erythrocytes is reported to be lower than that of old cells (26). Therefore, it seems that the decrease of HbA_{1c} levels relative to PG or GA in HD patients who have diabetes and are treated with erythropoietin might be due to the increasing proportion of young erythrocytes over old erythrocytes in peripheral blood of those patients (11). Anemia that results from shorter life span of erythrocytes theoretically suppresses HbA_{1c} values. Withdrawal of erythropoietin administration increases HbA_{1c} values, although it suppresses Hb levels (11). Therefore, a relationship between HbA_{1c} and Hb could be controversial. These data may suggest that HbA_{1c} is not an ideal index for glycemic control in HD patients who have diabetes and receive erythropoietin. Because approximately 90% of dialysis patients undergo erythropoietin treatment, HbA_{1c} might be an unsuitable marker to reflect glycemic control in HD patients with diabetes because of the false reduction of HbA_{1c} values as a result of the increasing proportion of young erythrocytes over old erythrocytes in peripheral blood of those who receive erythropoietin; however, this was not due to improvement of glycemic control, leading to the underestimation of integrated hyperglycemia when assessed by HbA_{1c} value. Among 12 countries in the Dialysis Outcomes and Practice Patterns (DOPPS) study, Japanese HD patients received the lowest weekly dosages of erythropoietin, which was less than one third of the highest dosage in the United States (27). Therefore, it is possible that the seeming erythropoietin-induced reduction of HbA_{1c} values might be greater in the other countries.

GA acquires biologic properties that are linked to the pathogenesis of diabetic vascular complications (28,29), suggesting that GA not only is significant as an indicator of hyperglycemia (30,31) but also contributes directly to vascular injury. As such, GA is better than HbA_{1c} in predicting the development of vascular complications in HD patients with diabetes. However, a limitation of the GA assay also exists. Albumin turnover should change in patients who are maintained on peritoneal dialysis and in patients who have CRF with massive protein-

uria, in whom GA values theoretically should be reduced as a result of shorter exposure to plasma albumin.

Conclusion

It was suggested that GA provides a significantly better measure to estimate glycemic control in HD patients with diabetes and that the assessment of glycemic control by HbA_{1c} in those patients might lead to underestimation.

Disclosures

None.

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