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Superiority of glycated albumin over glycated hemoglobin as indicator of glycemic control and predictor of all-cause mortality in patients with type 2 diabetes mellitus receiving peritoneal dialysis

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ABSTRACT

Background: Glycated albumin (GA), in contrast to glycated hemoglobin (HbA1c), precisely reflects glycemic control and predicts all-cause mortality in hemodialysis (HD) patients with diabetes mellitus (DM). However, whether those associations exist in DM patients receiving peritoneal dialysis (PD) remains unclear.

Methods: This was a retrospective cross-sectional and longitudinal observational study. We measured GA, HbA1c, and casual plasma glucose (CPG) for 2 months in DM-PD (n=44) and DM-HD (n=88) patients (age-, gender-matched). The DM-PD patients were followed for 3 years to monitor occurrence of all-cause mortality.

Results: GA and GA/CPG ratios, but not CPG, HbA1c, or HbA1c/CPG, were significantly lower in the DM-PD as compared to the DM-HD patients. The regression lines between CPG and GA showed a significant parallel shift downwards in DM-PD as compared with DM-HD patients, while the slope did not differ significantly between the groups, resulting in underestimation of glycemic control by 4.5%. Kapan-Meier analysis of the DM-PD patients revealed that higher GA (median >18.0%), but not HbA1c (median >6.6%), indicated significantly elevated risk for all-cause mortality, which occurred in 15 patients (34.1%), as compared to those with a lower GA level. Higher GA level was also significantly and independently associated with all-cause mortality in

multivariate Cox proportional hazards analysis.

Conclusions: GA, in contrast to HbA1c, more precisely reflects glycemic control in DM-PD patients, based on its significant association with all-cause mortality. Furthermore, adjustment of the true GA level by adding 4.5% might provide a more precise measurement for determining glycemic control in such patients.

Key words: Peritoneal dialysis; glycated albumin; glycated hemoglobin; glycemic control; all-cause mortality

Background

Glycated hemoglobin (HbA1c) is widely used as a marker of glycemic control, though known to be influenced by the lifespan of red blood cells ¹. In patients with advanced chronic kidney disease (CKD) or receiving dialysis, it is becoming increasingly recognized that HbA1c measurement might underestimate glycemic condition due to anemia, use of erythropoiesis stimulating agents (ESA), and/or iron, independent of glycemic control ². We previously demonstrated that glycated albumin (GA), which is not influenced by the lifespan of red blood cells, provides a significantly better estimate of glycemic control in hemodialysis (HD) patients with diabetes mellitus (DM) as compared to HbA1c ^{3,4}. On the other hand, subjects with increased albumin metabolism are considered to have lower GA values, due to the shortened time of serum albumin exposure to glucose in plasma ⁵. Patients receiving peritoneal dialysis (PD) lose protein in peritoneal dialysate or urine, thus it is possible that increased albumin turnover can falsely suppress GA in PD patients with DM, making it unclear whether GA and/or HbA1c are reliable markers of glycemic control in DM-PD patients.

Strict glycemic control has favorable effects not only on diabetes complications ⁶⁻⁸ but also cardiovascular disease, a leading cause of death in DM patients ⁹⁻¹¹. We previously found that GA, but not HbA1c, is independently and positively associated

with pulse wave velocity and peripheral vascular calcification in DM-HD patients ^{12, 13}. In addition, we reported that GA predicts all-cause mortality ¹⁴, which confirmed other studies that clearly demonstrated that GA, rather than HbA1c, precisely predicts all-cause mortality in DM-HD patients ¹⁵, likely because it accurately reflects glycemic control status. Although a recent study showed that GA, but not HbA1c, predicts all-cause mortality in DM-PD patients ¹⁶, no comparisons of GA with HbA1c or plasma glucose were performed because of a lack of simultaneous measurements of the 3 markers. In the present investigation, those 3 glycemic markers were simultaneously determined, thus this is the first study to precisely assess the clinical significance of GA as a marker for glycemic control as well as predictor of all-cause mortality in DM-PD patients.

Methods

Subjects and study design

This was a retrospective cross-sectional and longitudinal observational study. The entry criteria for this study included diagnosis of DM-PD in patients who had been treated while in a stable condition at Inoue Hospital, and whose therapeutic regimen for DM had not been altered during the preceding 6 months and weekly dose of ESA had

not been changing during the preceding 3 months prior to simultaneous determination of GA and HbA1c (n=51). Those who had been receiving dialysis therapy for less than 6 months were excluded (n=2). Furthermore, patients with liver cirrhosis, malignancy, infection, acute illness, or history of peritonitis were also excluded from analysis (n=5). As a result, 44 DM-PD patients (32 males, 12 females) were enrolled as subjects in the present study. We previously performed a cross-sectional study (Osaka CKD Expert Research) that included 538 DM-HD patients who also underwent simultaneous measurements of GA and HbA1c, and whose therapeutic regimen for DM and weekly dose of ESA had not been altered during the preceding 6 and 3 months, respectively, prior to those measurements. That study aimed to assess whether GA might provide a better indication as compared to HbA1c of glycemic control in DM-HD patients ³. Corresponding to the present 44 enrolled patients, we sequentially selected 88 age- and gender-matched DM-HD patients from the Osaka CKD Expert Research cohort for analysis. The diagnosis of DM was based on history of diabetes or criteria presented in the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus ¹⁷.

The present study was conducted in accordance with the principles of the Declaration of Helsinki and retrospectively approved by the Ethics Committee of Inoue Hospital

(approval No. 219). Institutional approval for an opt-out consent method was given because of the observational nature (retrospective analysis) of this study.

Laboratory measurements

Blood was drawn without overnight fasting from DM-PD patients between 8:00-10:00 am, and from DM-HD patients just prior to starting their first dialysis session of the week. GA was measured with an enzymatic method using a Lucica GA-L kit (Asahi Kasei Pharma Corp., Tokyo, Japan), as previously reported ¹⁸. Briefly, GA was hydrolyzed to amino acids by albumin-specific proteinase and then oxidized by ketoamine oxidase to produce hydrogen peroxide, which was quantitatively measured. The GA value was calculated as the percentage of GA relative to total albumin, which was measured using the new bromocresol purple method ¹⁸. GA assay findings are not influenced by the physiologic concentrations of ascorbic acid, bilirubin, or glucose up to 1000 mg/dL. HbA1c was measured by routine HPLC and latex agglutination immunoassay techniques, then standardized according to method of the Japan Diabetes Society. HbA1c values were converted to National Glycohemoglobin Standardization Program equivalent values, according to the recommendations of the Japanese Diabetes Society and International Federation of Clinical Chemistry ¹⁹. The mean values of 3

measurements of casual plasma glucose (CPG) obtained during the 2 months prior to determination of serum GA and HbA1c were used in the present analyses. We calculated Geriatric Nutritional Risk Index (GNRI) values based on serum albumin and body weight, as follows ²⁰⁻²²:

$$\text{GNRI} = [14.89 \times \text{albumin (g/dL)}] + [41.7 \times (\text{body weight/ideal body weight})]$$

Outcome data collection

The DM-PD patients were followed for 3 years. At the end of the follow-up period, 18 patients were alive and receiving PD, 11 were transferred to HD, and the remaining 15 had died.

Statistical analysis

Data are expressed as the mean $\pm$ standard deviation. A non-repeated t-test (continuous variables with normal distribution) and Fisher's exact test (categorical variables) were used to compare variables between groups. To compare variables between the 3 measured factors, we used one-way analysis of variance (ANOVA), followed by a Tukey-Kramer post-hoc test. Pearson's correlation test was used to determine correlations between continuous variables. Analysis of covariance was used

to compare regression lines. Survival curves were estimated using the Kaplan-Meier analysis method with a log-rank test. A receiver operator characteristic (ROC) curve was constructed to identify the optimum cutoff value for predicting all-cause mortality. Prognostic variables for survival were examined using a Cox proportional hazards regression model. All statistical analyses were performed using the Statistical Package for the Social Sciences software package (PASW Statistics version 22.0). All reported p values are 2-tailed and were considered to be statistically significant at <0.05 .

RESULTS

Clinical characteristics of patients on DM-PD and DM-HD patients

Table 1 shows the clinical characteristics of the 44 DM-PD and 88 DM-HD patients. The DM-PD group exhibited significantly lower levels of serum albumin and significantly shorter dialysis durations as compared to the DM-HD group, and also tended to have higher hemoglobin levels and body mass index (BMI). Although the average CPG level was not significantly different between the groups, GA was significantly lower and HbA1c tended to be higher in the DM-PD group. In addition, the GA/CPG and GA/HbA1c ratios were significantly lower in the DM-PD patients, while HbA1c/CPG ratio was not significantly different between the groups.

CPG level variations during 2-month study period in DM-PD and DM-HD patients

CPG levels in the DM-PD patients obtained at 2 months and 1 month before, and at the time (0 months) of the GA and HbA1c measurements were 162.5 ± 48.0 , 165.3 ± 56.1 , and 147.7 ± 40.6 mg/dl, respectively. Findings of one-way ANOVA did not indicate significant differences ($p=0.192$), while those of the Tukey-Kramer post-hoc test also showed that CPG in DM-PD patients was not significantly different among the 3 measurement time points (-2 vs. 0 months, $p=0.335$; -1 vs. 0 months, $p=0.208$; -2 vs. 1 month; $p=0.962$). In the DM-HD patients, CPG levels were 152.6 ± 68.0 , 144.0 ± 55.2 , and 152.2 ± 63.3 mg/dl, respectively, at the 3 measurement time points. One-way ANOVA did not show significant differences ($p=0.537$), and post-hoc Tukey-Kramer test findings also showed that CPG in DM-HD patients was not significantly different among the 3 measurement time points (-2 vs. 0 months, $p=0.999$; -1 vs. 0 months, $p=0.654$; -2 vs. 1 month; $p=0.631$). These results suggested that glycemic control in both the DM-PD and DM-HD patients during the 2 month examination period, which might have significant effects on HbA1c and GA, were stable enough to determine the association of the average CPG value during the prior 2 months with GA or HbA1c in such patients.

Correlation of CPG with GA and HbA1c in DM-PD and DM-HD patients

Figure 1 shows simple correlations of CPG with GA (Fig. 1A) and HbA1c (Fig. 1B) in DM-PD and DM-HD patients. Although the slope of the regression lines between CPG and GA did not differ significantly between the groups ($p=0.772$), those lines for the DM-PD patients showed a significant downward direction as compared with those for the DM-HD patients ($p<0.001$) (Fig 1A). On the other hand, the slope or position of the regression lines between CPG and HbA1c in both groups was nearly identical (Fig. 1B).

Correlation of clinical parameters with GA in DM-PD patients

Among the clinical parameters examined, CPG ($r=0.538$, $p<0.001$) and HbA1c ($r=0.500$, $p=0.001$) were significantly and positively correlated with GA, whereas there was no correlation shown for age ($r=0.110$, $p=0.478$), gender ($r=-0.039$, $p=0.802$), dialysis duration ($r=-0.015$, $p=0.925$), serum albumin ($r=-0.116$, $p=0.455$), serum creatinine ($r=-0.055$, $p=0.723$), hemoglobin ($r=-0.190$, $p=0.216$), BMI ($r=-0.174$, $p=0.260$), or GNRI ($r=-0.190$, $p=0.217$).

Association of clinical parameters with all-cause mortality in DM-PD patients

During the follow-up period of 36 months, 15 of 44 DM-PD patients died, including 7 from cardiovascular causes [cardiovascular disease (n=3), cerebrovascular disease (n=4)] and 8 from non-cardiovascular causes [infectious disease (n=6), malignancy (n=2)]. When the DM-PD patients were divided into 2 subgroups based on the median levels of GA (18.0%), HbA1c (6.6%), and CPG (155 mg/dL), Kaplan-Meier analysis (Figure 2) showed that a higher GA value was positively associated with all-cause mortality, whereas higher HbA1c and CPG were not. ROC analysis also showed that GA had a greater AUC (AUC=0.711, p=0.023) to predict all-cause mortality as compared to that of HbA1c (AUC=0.602, p=0.271) and CPG (AUC=0.632, p=0.155) (Figure 3). The cut-off value for greatest sensitivity and specificity for GA was 18.0% (sensitivity 0.800, specificity 0.345), which was consistent with the median value of GA. To confirm the independent association of higher GA with all-cause mortality in DM-PD patients, multivariate Cox proportional hazards analyses were performed (Table 2). In model 2, which included higher GA and albumin as covariates, higher GA level and lower albumin level were significantly associated with all-cause mortality. When age, gender, dialysis duration, BMI, hemoglobin, past cardiovascular disease events, dose of erythropoietin, serum creatinine and GNRI were sequentially added to model 2

(models 3-11, respectively), higher GA remained significantly associated with greater mortality in all of the models.

DISCUSSION

In the present study, GA level and GA/CPG ratio were significantly lower in DM-PD as compared to DM-HD patients, while CPG was not significantly different between the groups. This suggests that GA was significantly low for CPG in the DM-PD patients as compared to the DM-HD patients. Interestingly, the regression lines between CPG and GA for the DM-PD and DM-HD patients were parallel, though shifted significantly downwards in the former as compared to the latter group. It seems that GA value may reflect glycemic control in DM-PD patients as precisely as seen in DM-HD patients, although measured GA in DM-PD patients may lead to underestimation of glycemic control (Figure 1). Furthermore, the present study showed that impaired glycemic control in DM-PD patients determined by GA, but not HbA1c value is able to independently predict all-cause mortality (Table 2).

Other studies including ours ^{3,4} have accumulated results indicating that GA provides a more precise measurement to indicate glycemic control than HbA1c in DM-HD patients. This conclusion is based on findings showing that suppression of HbA1c by

renal anemia, as well as use of ESA and/or iron independent of glycemic control can lead to an underestimation of glycemic control in DM-HD patients. On the other hand, large-scale cohort study of 850 DM-PD patients reported that HbA1c values were influenced not only by mean CPG but also by hemoglobin ²³. Therefore, since HbA1c may be suppressed by anemia independent of glycemic control in DM-PD patients, glycemic control might be underestimated in anemic DM-PD patients as compared to non-anemic DM patients without CKD when estimated based on HbA1c. In the present study, the regression lines between HbA1c and CPG did not differ between the DM-HD and DM-PD groups, while the slope of those lines was significantly shallower than a regression line previously reported for non-CKD DM patients ³, suggesting that HbA1c measurements might be falsely reduced by anemia or ESA dosage in both DM-PD and DM-HD patients.

Previously, only a limited number of studies ²⁴⁻²⁶ have examined the clinical significance of GA measurement for evaluation of glycemic control in DM-PD patients. Although GA is not affected by anemia or hemoglobin level, albumin metabolism is known to have an influence ⁵. Low GA values have been observed in subjects with increased albumin metabolism, such as hyperthyroidism ²⁷ and nephrotic syndrome ²⁸, due to the shortened exposure time of serum albumin to glucose in plasma. PD patients

lose protein at a rate of approximately 5 g/day in peritoneal fluid and urine ²⁹, and albumin synthesis in the liver is stimulated to compensate for that loss ³⁰, resulting in a higher turnover of circulating albumin. Therefore, DM-PD patients are considered to exhibit GA levels low for their CPG as compared to DM non-PD patients, because of the shortened half-life of albumin in circulation. As expected, the present study found that GA and GA/CPG were significantly lower in DM-PD as compared to DM-HD patients (Table 1), as previously reported in investigations of DM-PD ^{24, 25}. Interestingly, we found a downward shift of the regression line without a significant change in the DM-PD as compared to the DM-HD group (Figure 1), suggesting that GA measurement retained its significance as a glycemic marker, except for underestimation of glycemic control in those patients. The present findings also confirm those of previous studies showing that serum albumin level was not correlated with GA level in DM-PD patients ^{24, 26}. Considering the parallel downward shift of the regression lines between GA and CPG in the DM-PD as compared to the DM-HD group, it seems that adjustment of the true GA level by adding 4.5% might provide more a precise measurement for determining glycemic control in DM-PD patients.

We previously reported that GA, but not HbA1c, may be a significant measurement for determination of arterial wall stiffening ¹² and peripheral vascular calcification ¹³ in

DM-HD patients. Furthermore, several studies including ours ^{14, 15} have demonstrated that GA, rather than HbA1c, can precisely predict all-cause mortality in those patients. Consistent with a recent study showing that GA ($\geq 20\%$) but not HbA1c level was associated with all-cause mortality in DM-PD patients ¹⁶, the present results also showed that those patients with elevated GA ($>18.0\%$), but not elevated HbA1c have a greater risk for death, which was independent of serum creatinine concentration as a marker of sarcopenic status ³¹ and GNRI as a marker of nutritional status ²⁰⁻²². Furthermore, the adjusted cut-off value increased to 22.5%, when the GA level was adjusted (measured GA level +4.5%). Our previous report ¹⁴ as well as a large-scale epidemiological study ¹⁵ both showed that DM-HD patients with a GA level $>20\text{--}21\%$ have significantly higher risk for all-cause mortality, thus the cut-off GA value to determine increased risk for all-cause mortality might be similar in DM-PD and DM-HD patients.

This study has some important limitations. First, it was retrospective in design and the number of subjects was small. Also, peritoneal transport function and albumin loss were not fully measured. In addition, the study population consisted of nearly exclusively Japanese patients, thus it is unclear whether these findings can be generalized for other ethnic groups. Nevertheless, the present study clearly indicated

that GA is superior than HbA1c as indicator of glycemic control and all-cause mortality in DM-PD patients.

In conclusion, GA, in contrast to HbA1c, more precisely reflects glycemic control in DM-PD patients, although GA level is consistently lower than CPG level in DM-PD patients as compared to DM-HD patients. GA might be a better predictor of all-cause mortality in cases of DM-PD.

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Table 1. Patient clinical characteristics

	DM-PD (n=44)	DM-HD (n=88)	p value
Age (years)	62.2±9.8	62.2±10.0	1.000
Male	32 (72.7)	64 (72.7)	1.000
Dialysis duration (years)	2.4±2.2	5.2±4.1	<0.001
History of CVD events	21 (47.7)	-	-
Body weight (kg)	63.3±12.3	59.7±10.7	0.089
Body mass index (kg/m ²)	23.9±3.6	22.8±3.2	0.087
Hemoglobin (g/dL)	10.3±1.2	9.9±1.2	0.066
Albumin (g/dL)	3.4±0.6	3.7±0.4	0.011
Creatinine (mg/dL)	9.7±2.6	10.8±2.6	0.016
GNRI	96.3±11.7	98.0±8.4	0.334
CPG (mg/dL)	157.6±37.1	149.6±51.4	0.359
HbA1c (%)	6.6±0.9	6.3±1.1	0.078
GA (%)	19.0±4.5	23.0±6.3	<0.001
GA/CPG ratio	0.125±0.032	0.163±0.050	<0.001
HbA1c/CPG ratio	0.044±0.012	0.045±0.012	0.657
GA/HbA1c ratio	2.879±0.579	3.655±0.697	<0.001
Dose of erythropoietin (U/week)	5054.0±2964.2	4721.6±2244.6	0.513

Values are presented as the mean ± standard deviation or number (%) of dichotomous variables.

P values are shown for comparisons of mean values between the groups (unrepeated t-test) or categorical variables (Fisher's exact test).

Abbreviations: CVD, cardiovascular disease; CPG, casual plasma glucose; HbA1c, glycated hemoglobin; GA, glycated albumin; GNRI, Geriatric Nutritional Risk Index

Table 2. Independent association of higher GA level with all-cause mortality determined by multivariate cox proportional analysis

Model	Adjustment	HR	95% CI	p
1	GA (high=1, low=0), unadjusted	4.782	1.346-16.998	0.016
2	Model 1+ albumin	4.775	1.334-17.090	0.016
3	Model 2 + age	4.420	1.223-15.982	0.023
4	Model 2 + gender	4.788	1.337-17.147	0.016
5	Model 2 + dialysis duration	4.868	1.352-17.524	0.015
6	Model 2 + body mass index	4.632	1.294-16.576	0.018
7	Model 2 + hemoglobin	4.735	1.321-16.973	0.017
8	Model 2 + past CVD events	4.736	1.317-17.028	0.017
9	Model 2 + dose of erythropoietin	4.978	1.391-17.817	0.014
10	Model 2 + creatinine	4.462	1.229-16.196	0.023
11	Model 2 + GNRI	4.632	1.294-16.576	0.018

Abbreviations: HR, hazard ratio; CI, confidence interval; GA, glycated albumin; CVD, cardiovascular disease; GNRI, Geriatric Nutritional Risk Index

Figure legends

Figure 1. Correlations of CPG with GA and HbA1c in DM-PD and DM-HD patients.

(A)

Linear regression equations used.

1) Patients receiving peritoneal dialysis: $y = 0.065x + 8.76$, $r=0.538$, $p<0.001$

2) Patients receiving hemodialysis: $y = 0.071x + 12.39$, $r=0.578$, $p<0.001$

Analysis of covariance (ANCOVA) findings indicated that the regression line was significantly different between the groups ($p<0.001$).

(B)

Linear regression equations used.

1) Patients receiving peritoneal dialysis: $y = 0.0095x + 5.107$, $r=0.401$, $p=0.007$

2) Patients receiving hemodialysis: $y = 0.012x + 4.473$, $r=0.582$, $p<0.001$

ANCOVA findings indicated that the regression line was not significantly different between the groups ($p=0.134$).

Abbreviations: CPG, casual plasma glucose; GA, glycated albumin; HbA1c, glycated hemoglobin

Figure 1

Figure 2. Findings of Kaplan-Meier analysis of associations of GA, HbA1c, and CPG with all-cause mortality.

The patients were divided into 2 groups according to the median values for GA (18.0%), CPG (155 mg/dL), and HbA1c (6.6%). Probability was analyzed using a log-rank test.

Figure 2

Figure 3. Receiver operating characteristic (ROC) curves for GA, HbA1c, and CPG to predict all-cause mortality.

(A) GA.

(B) HbA1c.

(C) CPG.

Figure 3