Blood Glucose Levels in Peritoneal Dialysis Are Better Reflected by HbA1c Than by Glycated Albumin

Yusuke Watanabe, Yoichi Ohno, Tsutomu Inoue, Hiroshi Takane, Hirokazu Okada, Hiromichi Suzuki

Introduction

Hemoglobin A1c (HbA1c) is typically used as a glycemic marker in diabetic patients. However, HbA1c is influenced by factors other than blood glucose (1,2). Of those factors, the lifespan of an erythrocyte is particularly important. In patients with chronic kidney disease, HbA1c values are lower because of renal anemia. Furthermore, when erythropoietin is administered to patients with renal anemia, HbA1c levels decline even further because the number of young non-glycated red blood cells in the peripheral blood increases (3,4).

Recently, glycemic control has been reported to be more accurately reflected by glycated albumin (GA) than by HbA1c in hemodialysis patients with diabetes because GA is not affected by renal anemia (5,6). However, only a few studies have assessed how well GA measurements reflect glycemic control in peritoneal dialysis (PD) patients. Furthermore, whether GA is better than HbA1c as a glycemic marker in PD patients remains unclear because the metabolism of albumin is markedly influenced by PD (7).

The aims of the present study were to determine whether GA or HbA1c is a superior indicator of glycemic control in patients undergoing PD and to clarify the factors that, in addition to blood glucose, affect the values of GA and HbA1c.

Methods

Subjects

From January to April 2011, consecutive PD patients at Saitama Medical University Hospital (n = 71; 20 with diabetes (DM), 51 without DM) were enrolled into the study, which was approved by the institutional ethics committee. All patients provided written informed consent before participating. Among the patients with DM, 6 were receiving insulin therapy, and 2 were taking oral hypoglycemic agents. The glucose concentration of the PD fluids used by the patients were in the range 1.35% – 2.5% and did not change during the observation period.

Patients were excluded from the study if they had started on PD within the preceding 2 months; if they were on combination PD and hemodialysis therapy;
if they were using icodextrin solution; if they had received blood transfusions; if their erythropoietin dose had been changed within the preceding 2 months; or if they had liver cirrhosis, hemolytic anemia, or bleeding complications. Table I shows the clinical characteristics of the study patients.

### Measurements
Casual blood glucose levels were measured on 3 occasions, including during the month before study entry, and serum GA and HbA1c levels were determined. The average of each patient’s casual blood glucose values was used for the analyses. In 37 patients (10 with DM, 27 without DM), blood sampling was performed during visits to the outpatient department for fasting blood samples; in 34 patients (10 with DM, 24 without DM) postprandial blood sampling was performed. Blood glucose was also measured in the dialysate reservoir in all cases.

Glycated albumin was measured by an enzymatic method (Lucica GA-L: Asahi Kasei Pharma, Tokyo, Japan; normal range: 12.4% – 16.3%), and HbA1c was measured using a latex agglutination assay (Determiner HbA1c: Kyowa Medex, Tokyo, Japan; normal range: 4.7% – 6.2%) according to National Glycohemoglobin Standardization Program standards. Serum GA and HbA1c were measured concomitantly with hemoglobin, albumin, blood urea nitrogen, and creatinine. Albumin concentrations in urine and dialysate were measured, and urinary and transperitoneal losses of albumin were calculated. The normalized protein catabolic rate was calculated according to the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative guidelines (8). Body mass index [BMI (kg/m²)] was calculated using the formula

\[ \text{BMI} = \frac{\text{weight in kilograms}}{\text{height in meters squared}}. \]

### Statistical analyses
The differences in mean values between groups were analyzed using the Student t-test. The chi-square test was used to compare the proportions of men and women in the DM and non-DM groups. Simple

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Non-DM</th>
<th>DM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>71</td>
<td>51</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.9±10.8</td>
<td>64.6±11.5</td>
<td>65.7±9.1</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (n men/women)</td>
<td>38/33</td>
<td>27/24</td>
<td>11/9</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index</td>
<td>22.3±2.5</td>
<td>22.0±2.3</td>
<td>23.1±2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of dialysis (months)</td>
<td>60.9±40.6</td>
<td>64.2±43.8</td>
<td>51.8±29.4</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.7±1.3</td>
<td>10.7±1.2</td>
<td>10.8±1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.1±0.4</td>
<td>3.2±0.4</td>
<td>3.0±0.5</td>
<td>0.038</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>117.5±26.0</td>
<td>111.5±17.7</td>
<td>135.9±37.5</td>
<td>0.022</td>
</tr>
<tr>
<td>GA (%)</td>
<td>13.7±2.8</td>
<td>12.9±1.6</td>
<td>16.4±4.0</td>
<td>0.004</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.8±0.5</td>
<td>4.7±0.3</td>
<td>5.3±0.7</td>
<td>0.005</td>
</tr>
<tr>
<td>GA/HbA1c (%)</td>
<td>2.8±0.4</td>
<td>2.75±0.3</td>
<td>3.1±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Weekly ESA dose (IU/kg)</td>
<td>106.7±52.1</td>
<td>114.6±50.0</td>
<td>86.1±53.8</td>
<td>0.042</td>
</tr>
<tr>
<td>Daily urine volume (mL)</td>
<td>479.9±551.6</td>
<td>443.3±531.2</td>
<td>577.9±607.0</td>
<td>NS</td>
</tr>
<tr>
<td>Weekly Ccr (L/1.73 m²)</td>
<td>55.7±27.9</td>
<td>51.1±21.9</td>
<td>68.6±38.1</td>
<td>NS</td>
</tr>
<tr>
<td>Daily protein loss (g)</td>
<td>6.3±3.4</td>
<td>6.4±3.8</td>
<td>5.9±2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Daily nPCRb (g/kg)</td>
<td>0.8±0.2</td>
<td>0.8±0.2</td>
<td>0.8±0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

a Data are mean ± standard deviation.
b Borah equation.
DM = diabetes mellitus; NS = nonsignificant; GA = glycated albumin; HbA1c = glycated hemoglobin; ESA = erythropoiesis-stimulating agent; Ccr = creatinine clearance; nPCR = normalized protein catabolic rate.
correlations between values (GA, HbA1c, and clinical factors listed in Table I) were analyzed using the Pearson correlation coefficient. Multiple regression analyses were performed with GA or HbA1c as the dependent variable and with factors that had shown a significant correlation with GA or HbA1c in the simple correlations as independent variables. All values are expressed as mean ± standard deviation, and a p value less than 0.05 was considered significant. All statistical analyses were performed using the SPSS statistical software (version 19: IBM, Tokyo, Japan).

Results

Correlations of GA, HbA1c, and blood glucose
We observed significant positive correlations between GA and HbA1c in all patients \( (r = 0.77, p < 0.001; \text{Figure 1}) \) and also in the DM \( (r = 0.81, p < 0.001) \) and non-DM groups \( (r = 0.42, p < 0.004) \) individually. We also observed significant positive correlations between blood glucose and HbA1c in all patients \( [r = 0.47, p < 0.001; \text{Figure 2}(A)] \), but no correlations between blood glucose and GA \( [r = 0.18, p = 0.19; \text{Figure 2}(B)] \). In the non-DM group, we observed no correlation between blood glucose and HbA1c \( (r = 0.22, \text{nonsignificant}) \) or between blood glucose and GA \( (r = 0.05, \text{nonsignificant}) \). In the DM group, blood glucose and HbA1c were significantly positively correlated \( (r = 0.59, p = 0.035) \), but blood glucose and GA were not \( (r = 0.17, \text{nonsignificant}) \).

Correlations of HbA1c with other clinical variables
We observed significant correlations of HbA1c with glucose, BMI, dose of erythropoiesis-stimulating agents, weekly creatinine clearance (CCr), and urine volume (Table II). However, no correlations

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**FIGURE 1** Correlation between glycosylated albumin and glycosylated hemoglobin in peritoneal dialysis patients \( (r = 0.77, p < 0.001) \).

**FIGURE 2** (A) Correlation between blood glucose and glycosylated hemoglobin in peritoneal dialysis patients \( (r = 0.47, p < 0.001) \). (B) Correlation between blood glucose and glycosylated albumin (GA) in peritoneal dialysis patients \( (r = 0.18, p = 0.19) \).
were observed between HbA1c and hemoglobin. A multiple regression analysis showed that the independent variables glucose, weekly CCr, and BMI were significantly associated with HbA1c ($R^2 = 0.47$, $p < 0.001$).

To further examine factors that might influence the correlation between blood glucose and HbA1c, we grouped the patients by median hemoglobin (<10.6 g/dL and ≥10.6 g/dL). In both groups, we observed significant correlations between blood glucose and HbA1c (Figure 3(A,B)); hemoglobin concentration therefore did not markedly influence the close relationship between blood glucose and HbA1c.

Similarly, we grouped patients by median weekly dose of erythropoiesis-stimulating agent (<108 IU/kg and ≥108 IU/kg body weight). In both groups, we observed significant correlations between blood glucose and HbA1c (Figure 3(C,D)), indicating that the dose of erythropoiesis-stimulating agent did not markedly influence the relationship between blood glucose and HbA1c.

**Correlations of GA with other clinical variables**

We observed significant simple correlations of GA with the presence or absence of DM, urine volume, weekly CCr, and normalized protein catabolic rate (Table III). However, correlations of GA with blood glucose, serum albumin, and protein losses in urine and dialysate were not observed. Multiple regression analysis showed that the presence or absence of DM was the only significant independent variable associated with GA ($R^2 = 0.43$, $p < 0.001$).

**TABLE II** Simple correlation between glycated hemoglobin (HbA1c) and other clinical variables and multiple regression analysis (HbA1c as the dependent variable)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Simple correlation</th>
<th>Multiple regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$</td>
<td>$p$ Value</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.31</td>
<td>0.015</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.007</td>
<td>NS</td>
</tr>
<tr>
<td>ESA dose</td>
<td>-0.28</td>
<td>0.031</td>
</tr>
<tr>
<td>Weekly CCr</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine volume</td>
<td>0.32</td>
<td>0.014</td>
</tr>
</tbody>
</table>

$R^2 = 0.47; p < 0.001$

ESA = erythropoiesis stimulating agent; NS = nonsignificant; CCr = creatinine clearance.

To further examine the factors affecting the correlation between blood glucose and GA, we grouped the patients by median serum albumin. The correlation between blood glucose and GA was significant only in patients with a high serum albumin concentration ($\geq 3.2$ g/dL: $r = 0.32$, $p = 0.047$; Figure 4(B)). However, we observed no differences in GA between the high and low serum albumin groups (data not shown). Similarly, we grouped patients by daily median urinary and peritoneal protein losses (<5.9 g and ≥5.9 g). In patients with low daily protein losses, the correlation between blood glucose and GA was significant ($r = 0.37$, $p = 0.041$; Figure 4(C)). We observed no differences in GA in between the high and low protein loss groups (data not shown). Albumin metabolism therefore substantially influenced the relationship between blood glucose and GA.

**Discussion**

Our study demonstrated that HbA1c is better than GA as a glycemic indicator in PD patients because hypoalbuminemia and transperitoneal and urinary losses of protein strongly affect GA values. Patients with DM on dialysis are at especially high risk of various complications: In the United States, more than 23% of these patients experience cardiovascular and infectious complications during their first year of renal replacement therapy, and only 31% are expected to survive for 5 years (9). Glycemic control improves survival in patients on hemodialysis (10,11), and poor glycemic control is associated with higher mortality in PD patients (2,12). Mild hyperglycemia in non-DM dialysis patients has been associated with reduced survival (13). Accurate assessment of glycemic control in the dialysis population is therefore critical to improve outcomes and survival.

In DM patients on hemodialysis, GA has been reported to more accurately reflect glycemic control than HbA1c does, because GA is not affected by renal anemia (5–7). Albumin synthesis and catabolism rates influence GA. In patients with diabetic nephropathy presenting with marked proteinuria, GA values are lower relative to plasma glucose levels because of the increased turnover of albumin (3,14).

In patients on PD, losses of albumin into urine and across the peritoneal membrane contribute to hypoalbuminemia. However, in PD patients, albumin synthesis can increase to compensate for albumin loss as long as inflammation and malnutrition...
are not suppressing that synthesis (14). As already described, GA values can potentially be lower than plasma glucose values in patients on PD (4).

Only a few reports have directly compared HbA1c with GA in PD patients. Our study showed that the serum albumin is not correlated with GA, and we observed no correlations between blood glucose and GA in our patient groups with low serum albumin and high daily protein losses. Conversely, we observed significant correlations between blood glucose and GA in the patient groups with high serum albumin and low daily protein losses. In PD patients, GA is affected by albumin metabolism, especially losses into urine and dialysate. As a result, GA cannot be used as a glycemic
HbA1c and GA in Peritoneal Dialysis

Glycated albumin can reflect glycemic control during the preceding 2–4 weeks, and HbA1c reflects glycemic control during the preceding 1–3 months (15,16). In the present study, casual blood glucose levels were obtained on 3 occasions during the month before the determination of serum GA and HbA1c. Despite the shorter observational period, HbA1c was more accurate than GA in indicating blood glucose levels. Multiple regression analyses showed that GA and HbA1c were both significantly correlated with factors other than blood glucose: the independent variables of weekly CCr and BMI were significantly associated with HbA1c. In the DM group, we observed a trend toward higher BMI, shorter dialysis intervals, and preservation of residual renal function that reflected better weekly CCr. HbA1c might therefore be associated with weekly CCr and also with BMI.

The independent variable of urine volume was significantly associated with GA. In the DM group, the duration of dialysis tended to be shorter, and the volume of urine produced was greater, although the differences were not statistically significant. Glycated albumin might therefore be associated with urine volume, and preservation of residual renal function might be related to glucose and protein metabolism. The precise mechanisms of these correlations are unknown, and further study is needed.

The present report has several important limitations. First, this cross-sectional observational study examined correlations of single GA and HbA1c measurements with an average blood glucose level determined from measurements taken on 3 different occasions. The timing of sample collection during the study period might therefore have influenced the results. Recently, continuous glucose monitoring has been adopted for clinical use, providing more accurate information regarding variations in blood glucose. In light of that change, correlations of blood glucose measured using continuous glucose monitoring with GA or HbA1c in PD patients should be studied in the near future.

Second, even among the DM patients eligible for this study, blood glucose was relatively well controlled. The mean casual blood glucose level was 135.9 ± 37.5 mg/dL, HbA1c was less than 6.2%, and GA was less than 17%. Whether similar results would be obtained in a population with higher blood glucose levels is unknown and deserves further study.

In the present study, serum albumin was lower than the reference value in the DM and non-DM groups alike. Because albumin synthesis might increase and GA might decline, no correlation between blood glucose and GA could be detected.

Conclusions
In PD patients, HbA1c is better than GA as a glycemic indicator. Glycated albumin can be used as a glycemic indicator in PD patients with normal serum albumin and low daily protein losses in urine and dialysate. For a definitive conclusion, further studies are needed in a larger group of PD patients, especially patients with higher blood glucose levels.

Disclosures
The authors declare that they have no conflicts of interest with respect to this study.

References
4. Chujo K, Shima K, Tada H, Ooshashi T, Minakuchi J, Kawashima S. Indicators for blood glucose control in...

**Figure 4** Correlation between blood glucose and glycated albumin (GA) in (A) the lower albumin (Alb) group (<3.2 g/dL: \( r = 0.03, p = 0.446 \)); (B) the higher Alb group (≥3.2 g/dL: \( r = 0.32, p = 0.047 \)); (C) the group experiencing lower daily protein losses (<5.9 g: \( r = 0.37, p = 0.041 \)); (D) the group experiencing higher daily protein losses (≥5.9 g: \( r = 0.02, p = 0.453 \)).


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