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Glycated albumin is a better indicator of the glucose excursion than predialysis glucose and hemoglobin A1c in hemodialysis patients

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Abstract

Background: Glycated albumin (GA) has been reported to be a better indicator of glycemic control than hemoglobin A1c (HbA1c) in diabetic hemodialysis (HD) patients.

Methods: We performed a cross-sectional study to evaluate associations between daily glucose profiles based on blood glucose measurements at seven different times a day and their GA, HbA1c, and pre-dialysis glucose levels in 90 HD patients with ($n = 46$) and without ($n = 44$) diabetes.

Results: The results of a univariate analysis showed that the GA, HbA1c, and pre-dialaysis glucose levels were significantly correlated with the daily glucose profiles. In a multivariate analysis, the GA levels were found to be independently correlated with maximum glucose levels ($F = 9.448$, $P = 0.0028$) and mean amplitude of glucose excursion (MAGE, $F = 5.169$, $P = 0.0255$), but no significant correlation was found between the HbA1c levels and daily glucose profiles. The pre-dialysis glucose levels were independently correlated with minimum glucose levels ($F = 8.336$, $P = 0.0049$). In a stratified analysis, the identical trend was seen in the diabetic HD patients, but an independent correlation was found only between HbA1c values and mean glucose levels in nondiabetic HD patients.

Conclusions: GA levels may be a better indicator of glycemic control than HbA1c and pre-dialysis glucose levels, especially as a means of evaluating the glucose excursions in diabetic HD patients.

Keywords: Glycated albumin, Hemoglobin A1c, Hemodialysis, Glucose profiles

Background

Diabetes mellitus is the leading cause of chronic kidney disease and of being started on hemodialysis (HD) [1], and it is associated with cardiovascular disease that represents a common risk of morbidity and mortality in HD patients [2]. Hyperglycemia causes micro- and macroangiopathy in diabetic patients, and better glycemic control prevents diabetic complications [3, 4]. However, observational studies that have evaluated the relationship between glycemic control and the survival of HD patients with diabetes have yielded conflicting results [5–7]. Using serum glycated hemoglobin (HbA1c) to assess glycemic control in HD patients may result in underestimation of the level of glycemic control, because the life span of the red blood cells of HD patients is shorter, because the percentage of immature red blood cells is increased by erythropoiesis-stimulating agent therapy, and because blood loss may occur during HD therapy [8]. Previous studies have shown that glycated albumin (GA), whose levels are unaffected by the life-span of red blood cells, may be a better indicator of glycemic control in HD patients than HbA1c [9, 10]. The Japanese Society for Dialysis Therapy recommends pre-dialysis glucose levels and GA levels as better indicators of glycemic control than HbA1c in diabetic HD patients [11]. However, these studies used only casual blood glucose levels as the gold standard for comparison with HbA1c and GA levels.

The glucose excursions have been shown to increase the risk of diabetic macroangiopathy [4, 12]. GA levels

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have been reported to be more useful indicator of glycemic control, especially as a means of evaluating postprandial glycemic excursion than HbA1c in diabetic patients without nephropathy [13]. The aim of this study was to investigate associations between the pre-dialysis glucose, HbA1c, GA levels of HD patients, and their daily glucose profiles.

Methods

Subjects

We performed a cross-sectional study of 90 HD patients who had been admitted to Shinjuku Ishikawa Hospital. Patients who had inflammatory disease, gastrointestinal hemorrhage, or malignant disease were excluded. Patients capable of an oral diet were included in this study, and they were mostly admitted because of vascular access trouble and social problem. The glucose-lowering therapy of the subjects had been unchanged for at least 3 months prior to enroll into this study.

After a full explanation of this study, written informed consent was obtained from each patient. The study was performed in accordance with the Declaration of Helsinki and the Principles of Good Clinical Practice, and the Institutional Research Ethics Committee approved the study protocol.

Biochemical measurements

All blood samples for biochemical measurements were collected before the first HD session after hospital admission. HbA1c, GA, and the other parameters were measured at reference laboratories (SRL Inc., Tokyo, Japan). The daily glucose profile was based on measurements made by medical staff before and 2 h after each meal and at bedtime, and the data was used to calculate the mean, minimum (Min), maximum (Max) glucose levels, and the mean amplitude of glucose excursion (MAGE) [14].

Statistical analysis

Continuous variables are reported as the mean ± SD, and categorical variables are reported as percentages unless otherwise stated. The relationships among continuous variables were analyzed by the Pearson correlation test. A multiple linear regression analysis was performed to evaluate the relationships among glycated protein levels and various parameters of the daily glucose profile. *P* values less than 0.05 were considered to indicate statistical significance. All analyses were performed with the JMP for Windows software program (SAS Institute, Cary, NC, USA).

Results

A total of 90 HD patients were enrolled in this study. Their baseline characteristics, including laboratory data, are shown in Table 1. The mean age of the subjects was 68.8 ± 12.1 years, and their mean HD vintage was 115.8 ± 166.1 months. The patients who were started on HD therapy because of diabetic nephropathy accounted for 43.3 %, and patients diagnosed with type 2 diabetes accounted for 51.1 %. The baseline characteristics of the diabetic and nondiabetic HD patients are also shown in Table 1. Whereas the serum creatinine levels were significantly lower in the diabetic HD patients, the BMI and blood urea nitrogen levels tended to be higher but did not reach statistical significance. Oral hypoglycemic agents were being used to treat 28.3 % of the diabetic HD patients, and 26 % were on insulin therapy. Their glycemic parameters, including the Min, mean, Max glucose levels, Max-Min glucose levels, and MAGE values are shown in Table 2. All parameters, particularly the

Table 1 Baseline demographic data and clinical characteristics of the enrolled hemodialysis patients

	All patients ($n = 90$)	Diabetic patients ($n = 46$)	Nondiabetic patients ($n = 44$)	*P* value[a]
Age (years)	68.8 ± 12.1	66.3 ± 11.4	71.3 ± 12.5	0.0536
Gender (male)	66.6	73.9	59.1	0.135
Hemodialysis vintage (months)	115.8 ± 166.1	102.4 ± 194.9	129.4 ± 131.2	0.447
Body mass index (kg/m^2)	21.2 ± 3.9	22.0 ± 4.4	20.4 ± 3.1	0.0596
Hemoglobin (g/dl)	9.9 ± 1.4	10.2 ± 1.4	9.6 ± 1.5	0.062
Albumin (g/dl)	3.3 ± 0.4	3.3 ± 0.4	3.3 ± 0.4	0.7119
Blood urea nitrogen (mg/dl)	60.1 ± 17.8	62.1 ± 18.7	58.0 ± 16.8	0.2767
Creatinine (mg/dl)	9.7 ± 3.1	9.1 ± 3.0	10.4 ± 3.2	0.0480
Diabetes (%)	51.1	100	0	<0.0001
Oral hypoglycemic agent (%)	14.4	28.3	0	<0.0001
Insulin (%)	13.3	26.1	0	<0.0001
Erythropoiesis-stimulating agents (IU/week)	5270.8 ± 4186.5	5225.5 ± 4428.9	5318.2 ± 3968.0	0.9171

Variables are presented as mean ± SD
[a]Diabetic patients vs nondiabetic patients

Table 2 Glycemic control parameters among the enrolled hemodialysis patients

	All patients ($n = 90$)	Diabetic patients ($n = 46$)	Nondiabetic patients ($n = 44$)	P value[a]
Min glucose (mg/dl)	109.1 ± 31.3	120.5 ± 34.7	97.2 ± 22.0	<0.001
Mean glucose (mg/dl)	152.3 ± 38.6	175.5 ± 38.6	128.0 ± 18.2	<0.001
Max glucose (mg/dl)	203.4 ± 62.0	241.9 ± 61.2	163.2 ± 28.3	<0.001
Max-Min glucose (mg/dl)	100.3 ± 58.9	130.6 ± 64.9	68.7 ± 27.8	<0.001
MAGE	66.8 ± 38.3	85.4 ± 42.1	47.4 ± 20.7	<0.001
Pre-dialysis glucose (mg/dl)	144.6 ± 49.6	165.2 ± 56.3	123.2 ± 29.1	<0.001
HbA1c (%)	5.4 ± 0.9	5.8 ± 1.1	4.9 ± 0.5	<0.001
GA (%)	19.1 ± 4.7	21.9 ± 4.7	16.1 ± 2.4	<0.001

Variables are presented as mean ± SD
Min minimum, *Max* maximum, *MAGE* mean amplitude of glucose excursion, *HbA1c* hemoglobin A1c, *GA* glycated albumin
[a]Diabetic patients vs nondiabetic patients

Max glucose levels and MAGE values, were higher in the diabetic HD patients. The pre-dialysis glucose levels were close with the mean glucose levels.

Glycated albumin, HbA1c, and pre-dialysis glucose levels in all patients

The GA values, HbA1c values, and pre-dialysis glucose levels of the subjects as a whole were correlated with their daily glucose profiles (Table 3).

The GA levels, HbA1c levels, and pre-dialysis glucose levels of the subjects as a whole were correlated with their daily glucose profiles (Table 3). In univariate analysis, the HbA1c values were strongly correlated with the mean glucose levels as a whole. The pre-dialysis glucose levels were also significantly correlated with the Min and mean glucose levels. The GA values, on the other hand, were strongly correlated with the Max glucose levels as well as with the mean glucose levels.

Accordingly to the multivariate analysis, the GA values were independently correlated with the Max glucose levels and MAGE values, and the strongest correlation was found between the GA values and Max glucose levels, but a significant correlation was not found between the HbA1c values and daily glucose profiles. The pre-dialysis glucose levels were independently correlated with the Min glucose levels.

Table 3 Association between the indicators of glycemic control and parameters of daily glucose profiles in hemodialysis patients with and without diabetes

		All patients ($n = 90$)				Diabetic patients ($n = 46$)				Non diabetic patients ($n = 44$)			
Factors	Parameters	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
		R2	P	F	P	R2	P	F	P	R2	P	F	P
GA (%)	Min glucose (mg/dl)	0.216	<0.0001	0.917	0.341	0.174	0.004	1.167	0.2863	0.000	0.941	0.459	0.502
	Mean glucose (mg/dl)	0.532	<0.0001	2.665	0.1063	0.385	<0.0001	1.334	0.2548	0.098	0.0383	0.848	0.3627
	Max glucose (mg/dl)	0.511	<0.0001	9.448	0.0028	0.329	<0.0001	7.906	0.0075	0.122	0.0201	0.012	0.9152
	MAGE	0.286	<0.0001	5.169	0.0255	0.111	0.0235	6.349	0.0157	0.114	0.0253	0.821	0.3705
	Max-Min glucose (mg/dl)	0.323	<0.0001			0.136	0.0118			0.124	0.0192		
HbA1c (%)	Min glucose (mg/dl)	0.363	<0.0001	2.726	0.1024	0.385	<0.0001	1.849	0.1814	0.027	0.2861	0.0018	0.9664
	Mean glucose (mg/dl)	0.501	<0.0001	3.751	0.0561	0.363	<0.0001	0.636	0.4299	0.274	0.0003	8.259	0.0066
	Max glucose (mg/dl)	0.393	<0.0001	2.957	0.0892	0.226	0.0008	2.995	0.0910	0.181	0.0040	1.898	0.1761
	MAGE	0.171	<0.0001	2.817	0.0970	0.038	0.1918	2.959	0.0930	0.122	0.0200	2.889	0.0972
	Max-Min glucose (mg/dl)	0.169	<0.0001			0.032	0.2334			0.118	0.0223		
Pre-dialysis glucose (mg/dl)	Min glucose (mg/dl)	0.363	<0.0001	8.336	0.0049	0.435	<0.0001	9.730	0.0033	0.014	0.4449	0.043	0.8366
	Mean glucose (mg/dl)	0.376	<0.0001	0.950	0.3324	0.262	0.0003	0.012	0.9150	0.168	0.0058	1.198	0.2804
	Max glucose (mg/dl)	0.312	<0.0001	0.802	0.3729	0.167	0.0049	0.139	0.7114	0.182	0.0039	0.001	0.9724
	MAGE	0.147	0.0002	0.259	0.6124	0.034	0.2190	0.009	0.9266	0.127	0.0174	0.531	0.4705
	Max-Min glucose (mg/dl)	0.142	0.0003			0.027	0.2773			0.132	0.0153		

Pearson correlation test was performed for univariate analysis. Multiple linear regression analysis was performed for multivariate analysis
GA glycated albumin, *HbA1c* hemoglobin A1c, *MAGE* mean amplitude of glucose excursion

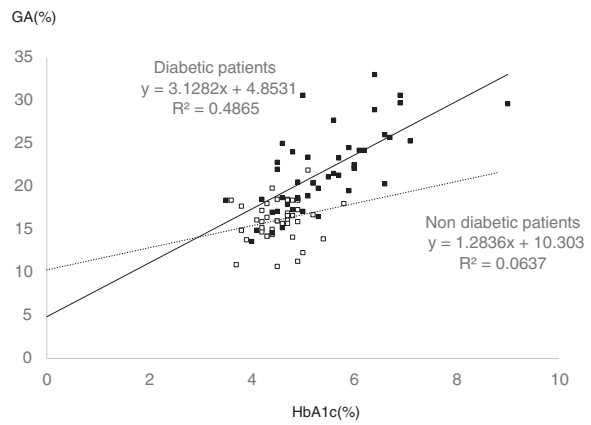

Fig. 1 Correlation between the glycated albumin (GA) and hemoglobin A1c (HbA1c) levels of diabetic (*black squares*) and nondiabetic (*white squares*) hemodialysis patients

Diabetic patients and nondiabetic patients

As shown in Fig. 1, the GA values of the diabetic HD patients were correlated with their HbA1c values ($r = 0.697$, $P < 0.0001$), but not of the nondiabetic HD patients ($r = 0.252$, $P = 0.0984$). The GA/HbA1c ratio was 3.1 in the diabetic HD patients.

The relationship of each indicator of glucose control and the Min, mean, Max glucose levels, and MAGE values of diabetic and nondiabetic HD patients is also shown in Table 3. The GA values, HbA1c values, and pre-dialysis glucose levels were correlated with the daily glucose profile in diabetic patients similar in all subjects. The identical trend was seen in multivariate analysis that the independently correlation was found in the GA values with Max glucose levels and MAGE values, which show the glucose excursion, and pre-dialysis glucose levels with the Min glucose levels. In contrast, the correlation of daily glucose profiles and GA values was weaker than the correlation between the HbA1c values and pre-dialysis glucose levels in nondiabetic HD patients. The results of the multivariate analysis did not show any independent correlation between the GA values, pre-dialysis glucose levels, and their daily glucose profiles in nondiabetic HD patients. On the other hand, the HbA1c values were independently correlated with the mean glucose levels in nondiabetic HD patients.

Discussion

The results of this study showed significant correlations between the pre-dialysis glucose, HbA1c values, and GA values and their daily glucose profiles in HD patients. They also showed that only the GA levels were independently correlated with the glucose excursions.

Since the lifespan of erythrocytes is approximately 120 days, serum HbA1c levels reflect blood glucose levels over the preceding several months. GA levels are used as an indicator of short-term glycemic control, because metabolic albumin turnover is faster than hemoglobin turnover; albumin has a lifespan of approximately 17 to 23 days. Furthermore, large blood glucose fluctuation could enhance the glycation and oxidation reaction of albumin, followed by increases in GA levels. Moreover, hyperglycemia has been reported to reduce erythrocyte survival [15]. Since diabetic HD patients have many factors that affect their serum HbA1c levels, their GA levels were better indicator of glycemic control, especially of the glucose excursions than HbA1c in HD patients who have a large glucose fluctuation. We did not find a correlation between hemoglobin, ESA use and HbA1c, serum albumin and GA that have been reported by previous studies [9, 10]. However, the GA/HbA1c ratio in the present study was higher than reported in a previous study [13].

A large cohort study of 1484 HD patients reported finding that poor glycemic control of maintenance HD patients was not associated with their mortality [7]. This study used casual glucose and HbA1c levels as the indicator of glycemic control, and this cohort included nondiabetic HD patients, and their HbA1c levels were generally low. The GA, HbA1c, and pre-dialysis glucose levels in our study were not correlated with their glucose excursions of nondiabetic HD patients. One of the potential reasons for this finding is that the glucose levels in nondiabetic HD patients fluctuated within a narrow range. The results of other studies that investigated the impact of HbA1c on the survival of HD patients showed only extremely high or low HbA1c levels were associated with longer survival [5, 6]. Thus, the optimal target glycemic control to improve the survival of diabetic HD patients is still unknown [16]. It is well known that postprandial hyperglycemia in diabetic patients is associated with the progression of diabetic macroangiopathy [17, 18]. Our data showed that GA levels were a better indicator of the glucose fluctuations. A few recent studies have reported finding that high GA levels were associated with increased mortality in diabetic HD patients [19, 20].

Our study had several limitations. First, only hospitalized patients were enrolled as subjects. The hospital diet provided 30–35 kcal/kg/day, and since it may have differed from the subjects' usual diet, the difference may have affected their daily glycemic profiles. Second, the daily glucose profiles were based on a seven-point blood glucose measurement a day, and a continuous glucose-monitoring system, which provides continuous detailed records of glucose levels, may have provided more accurate information.

Conclusions

HbA1c and pre-dialysis glucose levels were affected by the daily glucose profiles in diabetic HD patients. The

GA levels could be a better indicator of glycemic control than HbA1c and pre-dialysis glucose levels, because serum GA levels may reflect the glucose excursion. These results warrant further trials to assess the usefulness of GA levels as an indicator of diabetic complications and mortality in diabetic HD patients.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
YT planned the study, searched the literature, assessed the studies, extracted the data, analyzed the data, and prepared the article. KK searched the literature, assessed the studies, and assisted in the article preparation. AI and YE assisted in the data analysis. TO searched the literature and assisted in the article preparation. KN planned the study, analyzed the data, and assisted in the article preparation. All authors read and approved the final manuscript.

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