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SHORT REPORT

Critical discrepancy in blood glucose control levels evaluated by glycated albumin and estimated hemoglobin A1c levels determined from a flash continuous glucose monitoring system in patients with type 2 diabetes on hemodialysis

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ABSTRACT

We aimed to investigate if estimated hemoglobin A1c (eHbA1c) levels determined using a flash continuous glucose monitoring system could be an indicator of glycemic control status in hemodialysis patients with diabetes. Hemodialysis patients with type 2 diabetes were recruited. eHbA1c levels were measured using the FreeStyle Libre Flash Glucose Monitoring System®. A total of 18 hemodialysis patients with diabetes were included in the study. The eHbA1c^{GA} – calculated based on glycated albumin level, and body mass index and serum hemoglobin concentration were also included in the formula – was higher than the eHbA1c in most patients. Furthermore, the eHbA1c^{GA} – eHbA1c values were >2% in all patients with body mass index <18.5 kg/m^2; the maximal value was 4.1%. This study shows that eHbA1c can be used as a reliable indicator for evaluating glycemic control and avoiding hypoglycemia in hemodialysis patients with diabetes, particularly those with decreased body mass index.

INTRODUCTION

As glycated albumin (GA) levels are unaffected by the shortened lifespan of red blood cells[1] and are associated with increased mortality in hemodialysis patients with diabetes[2], GA is considered a desirable indicator of glycemic control in diabetic hemodialysis patients[3,4]. However, discrepancies have been reported between GA levels and blood glucose or self-measurement of blood glucose levels in hemodialysis patients with diabetes[5,6,7,8]. This study aimed to investigate whether estimated hemoglobin A1c (eHbA1c) levels, determined using a flash glucose monitoring (FGM) system, could be an indicator of glycemic control status in hemodialysis patients with diabetes, particularly in those with decreased body mass index (BMI), who might show discrepant GA and blood glucose levels in clinical settings.

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METHODS

We randomly recruited hemodialysis patients with type 2 diabetes. All patients were receiving oral hypoglycemic agents, insulin or both. Patients received hemodialysis treatment at the outpatient dialysis units of Tojinkai Hospital in Kyoto, Japan. The inclusion criterion was stable glycemic control, as evidenced by two GA values within 5 percentage points of each other in 6 months before recruitment. Those using systemic corticosteroids or those with chronic liver disease, thyroid disorders, or malignant diseases were excluded. The study protocol was approved by the ethics committee of the Tojinkai Hospital (2019–05), and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Patients provided medical and demographic information. Blood was drawn from the dialyzer circuit before starting dialysis for analysis. Patients were provided with the FreeStyle

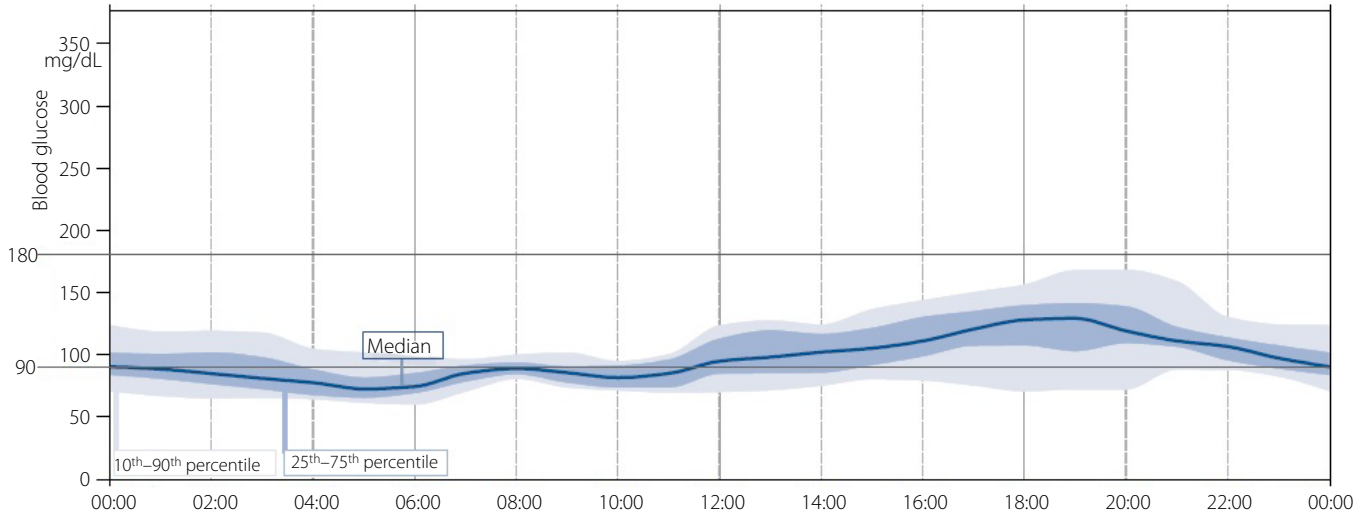

Figure 1 | The ambulatory glucose profiles uploaded from the FreeStyle Libre Flash Glucose Monitoring System®.

Libre™ of the first generation, a sensor-based FGM system (FSL FGM; Abbott, Diabetes Care, Witney, UK). The system consists of a glucose oxidase-based electrochemical sensor that measures glucose levels every 15 min, placed subcutaneously, and a receiver that transmits and stores interstitial glucose measurements wirelessly. Patients were instructed to use the device for 14 days. The results from the FGM were downloaded to a research computer in the outpatient clinic. The eHbA1c level based on the average glucose levels from the FGM data was calculated using the following equation: eHbA1c (%) = (average glucose [mg/dL] + 46.7) × 28.7^{-1}.[9]

The GA levels were measured within 1 week before or after FGM use by an enzymatic method involving ketoamine oxidase, albumin-specific proteinase and serum albumin assay reagent (Lucica® GA-L Kit; Asahi Kasei Pharma Co., Tokyo, Japan)[10]. The eHbA1c level based on the GA level ($eHbA1c^{GA}$) was calculated using the following equation:[11] $eHbA1c^{GA}$ − 1 (%) = GA × (4.688 − 18.833 × GA^{-1} − 0.015 × BMI − 0.037 × Hb)$^{-1}$. BMI and serum Hb concentration, which were included in the equation, were significantly lower in the end-stage renal disease group than in the normal renal function group, and showed significant negative correlations with the GA/HbA1c ratio[11].

Regression models were used to evaluate the effects of factors, such as BMI and hemoglobin, on the difference between $eHbA1c^{GA}$ and eHbA1c, and on the ratio of $eHbA1c^{GA}$ to eHbA1c. The mean values were compared using the unpaired Student's *t*-test. The χ^2–test was used to compare categorical variables between patients with BMI <18.5 kg/m^2 and ≥18.5 kg/m^2[12,13]. The SPSS statistical package, version 19.0J (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. All tests were two-sided, and *P*-values < 0.05 were considered statistically significant.

RESULTS

A total of 18 hemodialysis patients with type 2 diabetes were included in the study (Table 1). The $eHbA1c^{GA}$ was greater than the eHbA1c. $eHbA1c^{GA}$ – eHbA1c values were >2% in all patients with BMI <18.5 kg/m^2, and its maximal value was 4.1%. The $eHbA1c^{GA}$ – eHbA1c value and $eHbA1c^{GA}$/eHbA1c ratio were significantly high in patients with BMI <18.5 kg/m^2 (Table 2). On multivariate analyses, BMI was significantly associated with the $eHbA1c^{GA}$ – eHbA1c value (β = –0.123, *P* = 0.045) and $eHbA1c^{GA}$/eHbA1c ratio (β = –0.025, *P* = 0.023), and hemoglobin was significantly associated with the $eHbA1c^{GA}$ – eHbA1c value (β = –0.426, *P* = 0.040) and $eHbA1c^{GA}$/eHbA1c ratio (β = –0.075, *P* = 0.043). Figure 1 shows the ambulatory glucose profile of a 74-year-old female patient with an 8-year history of dialysis, GA level of 24.6% and $eHbA1c^{GA}$ level of 8.3%. A stable, flat glucose trend was observed with glucose in the target range. Similar findings were observed in all other patients.

DISCUSSION

Strict glycemic control is important for reducing microvascular and macrovascular complications[14], and reducing the risk of mortality in hemodialysis patients with diabetes[15]. In contrast, an increased frequency of hypoglycemia is associated with a high risk of mortality in patients with diabetic kidney disease[16].

Consensus guidelines for managing diabetes patients have identified GA levels and pre-dialysis casual plasma glucose levels as indicators of glycemic control in hemodialysis patients with diabetes[17]. However, there is no reliable indicator in patients with discordant GA levels and blood glucose levels or self-measurement of blood glucose levels. In the present study, the critical discrepancy between blood glucose control levels evaluated by GA and estimated hemoglobin A1c levels

Table 1 | Characteristics of the study participants

	Age (years)	Sex	Duration of diabetes (years)	Duration of dialysis (years)	Medications	BMI (kg/m^2)	Serum albumin (g/dL)	Blood glucose (mg/dL)	Hb (g/dL)	GA (%)	$eHbA1c^{GA}$ (%)	eHbA1c (%)	$eHbA1c^{GA}$ − eHbA1c (%)	$eHbA1c^{GA}$/ eHbA1c (%)
1	76	Female	11	7	OHA	16	3.8	130	11.4	19.0	7.3	4.9	2.4	1.5
2	63	Female	4	4	IT	22	4.4	143	10.4	24.0	8.5	5.4	3.1	1.6
3	50	Female	30	10	IT	28	4	101	11.4	19.6	7.8	6.1	1.7	1.3
4	67	Female	30	5	OHA/IT	32	3.3	131	10.7	22.7	8.6	7.2	1.4	1.2
5	74	Female	24	8	OHA/IT	15	3.4	132	8.7	24.6	8.3	5.0	3.3	1.7
6	46	Male	26	22	IT	16	3.4	181	9.4	36.0	11.1	7.3	3.8	1.5
7	60	Female	33	20	OHA/IT	21	3.9	156	10.5	22.0	8.0	7.4	0.6	1.1
8	60	Male	37	2	OHA/IT	23	3.7	196	11.1	23.0	8.4	6.3	2.1	1.3
9	73	Female	44	11	OHA	17	3.7	147	7.5	25.2	8.4	5.0	3.4	1.7
10	57	Female	11	11	OHA/IT	16	4.3	137	9.9	28.3	9.3	5.2	4.1	1.8
11	70	Female	33	18	OHA/IT	22	3.7	96	11.2	20.5	7.8	5.3	2.5	1.5
12	57	Male	23	4	IT	24	3.8	96	9.1	19.0	7.3	6.1	1.2	1.2
13	67	Female	39	9	IT	22	3.7	146	11	23.3	8.4	7.0	1.4	1.2
14	55	Male	26	4	IT	24	3.7	111	9.7	16.5	6.8	5.5	1.3	1.2
15	72	Male	21	21	OHA	18	3.7	174	9.3	23.5	8.2	5.4	2.8	1.5
16	56	Male	36	5	OHA/IT	25	4	122	13	17.7	7.4	8.6	−1.2	0.9
17	61	Male	46	13	OHA/IT	20	3.2	132	8.2	24.6	8.4	5.2	3.2	1.6
18	61	Male	26	9	OHA/IT	25	3.8	102	9.9	17.0	7.0	5.0	2.0	1.4

eHbA1c, estimated hemoglobin A1c based on the average glucose levels from FreeStyle Libre Flash Glucose Monitoring System®; $eHbA1c^{GA}$, estimated hemoglobin A1c based on the glycated albumin level; GA, glycated albumin; Hb, hemoglobin; IT, insulin therapy; OHA, oral hypoglycemic agent.

Table 2 | Clinical characteristics of study patients

	Body mass index		*P*
	<18.5	≥18.5	
Sex (male/female)	2/4	6/6	0.638
Age (years)	66.3 ± 12.1	60.6 ± 5.7	0.310
Duration of diabetes (years)	25.2 ± 12.0	30.3 ± 10.4	0.772
Duration of dialysis (years)	13.3 ± 6.5	8.6 ± 5.8	0.136
Serum albumin (g/dL)	3.7 ± 0.3	3.8 ± 0.3	0.758
Hemoglobin (g/dL)	9.4 ± 1.3	10.5 ± 1.2	0.083
$eHbA1c^{GA}$	7.8 ± 1.3	6.9 ± 0.6	0.068
eHbA1c	5.5 ± 0.9	6.3 ± 1.1	0.148
$eHbA1c^{GA}$ − eHbA1c	3.3 ± 0.6	1.6 ± 1.2	0.005
$eHbA1c^{GA}$/eHbA1c	1.6 ± 0.1	1.3 ± 0.2	0.004

Data are means ± standard deviation or number. $eHbA1c^{GA}$, estimated hemoglobin A1c based on the glycated albumin level; eHbA1c, estimated hemoglobin A1c based on the average glucose levels from FreeStyle Libre Flash Glucose Monitoring System®.

determined using a flash continuous glucose monitoring system was observed in hemodialysis patients with type 2 diabetes, particularly those with decreased BMI. This was probably due to elongation of the albumin lifespan, which leads to more increased GA than actual, in those patients associated with common complications experienced by end-stage renal disease patients, including hypothyroidism and decreased BMI[18].

GA showed short-term (~2–4 weeks) glycemic control status, and HbA1c showed long-term (~3 months) glycemic control status. We added the blood glucose of the enrolled population in short-term and long-term periods as confounding factors in multivariate analyses. The result was almost the same (data not shown).

Furthermore, eHbA1c level based on the casual blood glucose was calculated[9]. The difference between eHbA1c and eHbA1c based on casual blood glucose was significantly lower than the difference between $eHbA1c^{GA}$ and eHbA1c based on casual blood glucose ($P < 0.001$).

The readings from the FGM data for the first 2 days are known to be not entirely precise. We have provided a sensitivity analysis excluding the first 2 days, and the result did not change (data not shown).

There were some limitations of this study. First, FGM might be underestimated when blood glucose levels are low, which could lead to the estimated HbA1c also being lower. However, Yajima *et al.*[19] reported that FGM might be clinically acceptable. Second, the GA levels were measured within 1 week before or after FGM. Deviations in measurement timing could be a source of bias; however, they do not contribute significantly to the results, as GA levels showed approximately 2–4 weeks of glycemic control status. In conclusion, the current study shows that eHbA1c might be used as a reliable indicator for evaluating glycemic control and for avoiding hypoglycemia in hemodialysis patients with diabetes, particularly those with decreased BMI. Prospective studies are required to establish that the use of eHbA1c as an index of glycemic control will improve microvascular and macrovascular complications, and will result in low mortality rates.

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DISCLOSURE

The authors declare no conflict of interest.

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