

# Analysis of Hemodialysis-Associated Hypoglycemia in Patients with Type 2 Diabetes Using a Continuous Glucose Monitoring System

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## Abstract

**Background:** Adequate glycemic control is important for patients with end-stage renal disease on maintenance hemodialysis (HD). Continuous glucose monitoring (CGM) systems are reported as a useful method for glucose monitoring in patients under maintenance HD. The object of this study was to describe glucose profiles and hypoglycemia associated with HD in diabetes patients using a CGM system.

**Methods:** We recruited nine medically stable patients with type 2 diabetes under maintenance HD. CGMS<sup>®</sup> System Gold<sup>™</sup> (Medtronic MiniMed, Northridge, CA) was applied to the subjects for 144 h. During the period, HD using glucose-containing dialysate was performed every other day. Various glucose profiles were calculated from the CGM readings and compared between the day on and the day off dialysis.

**Results:** Mean  $\pm$  SD for age, duration of diabetes, and hemoglobin A1c were  $67 \pm 9$  years,  $24 \pm 9$  years, and  $8.6 \pm 1.2\%$ , respectively. Hemoglobin A1c was correlated with mean glucose ( $\rho = 0.780$ ,  $P < 0.05$ ) and with area under the curve for glucose above 180 mg/dL ( $\rho = 0.797$ ,  $P < 0.05$ ). Although there was no difference for mean amplitude of glycemic excursion between the day on and off HD, hypoglycemia occurred predominantly with day on HD. In the subjects who maintained antidiabetes agents with day on HD, glucose levels decreased with initiation of HD, causing significantly lower glucose levels compared to those during the equivalent time of the following day without HD.

**Conclusions:** According to the CGM system, glucose variability was not affected by HD. However, in spite of glucose-containing dialysate, HD seemed to increase the risk of hypoglycemia.

## Background

THE MOST COMMON CAUSE of end-stage renal disease (ESRD) is diabetes in the United States,<sup>1</sup> and so will it be in Asian countries, because of the sharp rise of diabetes in the region.<sup>2</sup> Therefore, those who have ESRD and are receiving maintenance hemodialysis (HD) are usually exposed to other complications of diabetes, too. Chronic diabetes complications result from hyperglycemia,<sup>3,4</sup> but glucose variability and hypoglycemia are additional components of diabetes morbidity.<sup>5,6</sup> Cardiac disease is the leading cause of mortality among patients undergoing HD.<sup>1</sup> Hyperglycemia was reported to be strongly associated with sudden cardiac death in

HD patients with type 2 diabetes, which accounted for increased cardiovascular events and mortality.<sup>7</sup> In the meantime, hypoglycemia is also fatal, especially in the presence of cardiovascular diseases.<sup>4</sup> Although there is no evidence-based guideline for the glycemic targets for hemodialysed patients with type 2 diabetes, adequate glycemic control in those population seems to be a predictor of survival<sup>8</sup> and should be in need of more attention than ever.

ESRD patients are not only insulin resistant but also prone to hypoglycemia because of impaired renal gluconeogenesis, malnutrition, altered pharmacokinetics of insulin, and hypoglycemic agents.<sup>9,10</sup> In addition, HD itself can induce hypoglycemia, the underlying mechanism of which has not been

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established.<sup>11</sup> Although the risk of hypoglycemia could be reduced by use of glucose-added dialysis fluid,<sup>12,13</sup> glycemic patterns are still hardly predictable, making it difficult to control blood glucose levels without a risk of hypoglycemia.

Continuous glucose monitoring (CGM) systems have been validated to be beneficial and are recommended in a subset of diabetes patients by the American Diabetes Association.<sup>14,15</sup> Recently, CGM was shown to provide glycemic information in patients with type 2 diabetes mellitus undergoing HD, too.<sup>16,17</sup> Therefore, if a CGM system can be effectively adapted, we might prevent both hypoglycemia and hyperglycemia causing high mortality in diabetes patients undergoing HD.

In this study, we described the glucose profiles, occurrence of hypoglycemia, and usefulness of a CGM device in maintenance-hemodialysed patients with type 2 diabetes. These results can suggest better antidiabetes regimens for patients under similar circumstances.

## Subjects and Methods

This study was approved by the Institutional Review Board of Seoul National University Hospital, Seoul, Republic of Korea, and written informed consent was obtained from all the subjects.

### Participants and laboratory analysis

Nine subjects with type 2 diabetes and ESRD who were clinically stable and were undergoing maintenance HD for more than 2 months were recruited. Some of them were using insulin. Their blood glucose levels were monitored regularly, but a CGM system had not been applied (Table 1). HD was performed for 3 h three times per week, and the dialytic solution contained 100–200 mg/dL glucose. A history of cardiovascular disease, including ischemic heart disease, cerebrovascular disease, or peripheral vascular disease, and retinopathy due to diabetes mellitus were established through history taking and medical records. Fasting blood samples were taken for measurement of hemoglobin A1c (HbA1c) using Diabetes Control and Complications Trial-aligned high-performance liquid chromatography (Variant® II Turbo,

Bio-Rad, Hercules, CA) (normal values, 4.0–6.4%), hemoglobin (Sysmex XE-2100 autoanalyzer, Sysmex, Kobe, Japan), and blood chemistry (Hitachi 7600 autoanalyzer, Hitachi, Tokyo, Japan).

### CGM and diaries

A 72-h CGM system (CGMS® System Gold™, Medtronic MiniMed, Northridge, CA) was used in this study. This system has been described in detail elsewhere.<sup>18,19</sup> In brief, it is a Holter-type device with a sensor having a glucose oxidase-based platinum electrode. The sensor is inserted into the subcutaneous tissue of the anterior abdominal wall, where the glucose oxidase catalyzes the oxidation of glucose in the interstitial fluid, which generates an electrical current. The current is carried to a pager-sized monitor that analyzes the data every 10 s and stores a smoothed average over 5 min. The range of interstitial glucose range is 40–400 mg/dL, and each sensor is used continuously for up to 72 h. In various studies on the device accuracy compared with reference serum/blood glucose levels in subjects with diabetes, the correlation coefficient range was 0.8–0.9, and mean absolute differences were 11–16%.<sup>20–23</sup> The subjects were educated to calibrate the system using capillary blood glucose tests four times a day and to record the time and amounts of meals, snacks, medications, exercise, and episodes of hypoglycemia during the study period. After the device was applied to each patient twice in succession for 144 consecutive h by a trained nurse, the data were downloaded using MiniMed Solutions Software version 2.0b.

### Calculation of glucose profiles

We defined the first 24 h from the start of HD as day on dialysis (HD-on) and the next 24 h as day off dialysis (HD-off). The following variables were calculated from CGM readings in each subject day on and off dialysis, respectively:

- *Mean glucose.* CGM measures at 5-min intervals were averaged for 24 h.
- *Mean postmeal maximum glucose (MPMG).* Highest CGM measures in the postprandial 4 h were averaged during the study period.
- *Area under the curve above 180 mg/dL (AUC180).* The area under the curve for CGM measures above 180 mg/dL was calculated.
- *Mean amplitude of glucose excursions (MAGE).* The means and SDs of glucose for HD-on and HD-off were calculated. The peak was defined as CGM measures increased and then decreased more than 1 SD, and the nadir was CGM measures decreased and then increased more than 1 SD, respectively. MAGE was the mean of absolute difference of peak-to-nadir or nadir-to-peak direction. The details for calculation of MAGE have been described previously.<sup>24</sup>
- *Hypoglycemia.* Hypoglycemia was defined as a CGM reading <80 mg/dL for ≥20 min. Frequency and duration of hypoglycemia were counted.

### Analysis of food diaries

Food diaries were analyzed by a registered dietitian. Total calorie intake and carbohydrate intake were calculated using CAN-Pro software version 3.0 (The Korean Nutrition Society, Seoul, Republic of Korea).<sup>25</sup>

TABLE 1. BASELINE CHARACTERISTICS OF PARTICIPANTS

Characteristic	Value
Age (years)	67 ± 9
Sex ratio (male:female)	1:2
BMI (kg/m <sup>2</sup> )	23.3 ± 3.5
Waist circumference (cm)	85.9 ± 7.8
DM duration (years)	24 ± 9
HD duration (years)	5 ± 5
BUN (mg/dL)	45 ± 15
Hb (g/dL)	11.3 ± 1.3
HbA1c (%)	8.6 ± 1.2
CVD (numbers)	4
DM retinopathy (none:NPDR:PDR)	1:1:7
Medication (insulin:OAD:combined)	5:2:2

Data are mean ± SD values.

BMI, body mass index; BUN, blood urea nitrogen; CVD, cardiovascular disease; DM, diabetes mellitus; Hb, hemoglobin; HbA1c, hemoglobin A1c; HD, hemodialysis; NPDR, nonproliferative diabetic retinopathy; OAD, oral antidiabetes drug; PDR, proliferative diabetic retinopathy.

Statistical analysis

All data are expressed as mean ± SD values and were analyzed using SPSS software version 11.0 (SPSS Inc., Chicago, IL). For comparisons between HD-on and HD-off, Wilcoxon signed ranks test and repeated-measures analysis of variance were applied. For correlation analysis, Spearman's ρ was calculated. The level of significance was defined as  $P < 0.05$ .

Results

Baseline characteristics of participants (Table 1)

Most of the nine subjects with type 2 diabetes who were undergoing maintenance HD had diabetes complications other than nephropathy, and blood glucose control was not adequate (HbA1c,  $8.6 \pm 1.2\%$ ). To prevent hypoglycemia, five of the nine patients reduced doses of insulin or oral anti-diabetes drugs before HD (dose reduction by  $36 \pm 13\%/day$ , Table 2).

Associations between HbA1c and CGM measurements in hemodialysed patients

Results of correlation analysis between HbA1c and mean glucose levels were statistically significant. Indices of postprandial hyperglycemia such as AUC180 and MPMG were

TABLE 2. DETAILS OF MEDICATIONS

Patient number	Day off HD	Dose reduction for day on HD (%)	Hypoglycemia
1	Nateglinide 45 mg tid; glimepiride 2 mg qd	0	Yes
2	NPH 27 units/day	22	Yes
3	Nateglinide 120 mg tid; NPH 6 units/day	33	No
4	MSII 28 units/day	29	Yes
5	RI 8 units/day	50	No
6	NPH 16 units/day	0	No
7	Gliclazide 80 mg bid	50	Yes
8	MSII 55 units/day	0	Yes
9	Acarbose 50 mg bid; NPH 18 units/day	0	No

bid, two times a day; HD, hemodialysis; MSII, multiple subcutaneous insulin injections; NPH, neutral protamine Hagedorn; qd, once a day; RI, regular insulin; tid, three times a day.

also related with HbA1c (Fig. 1A). In contrast, MAGE, an index of glucose variability, was not correlated with either HbA1c or other CGM calculations (Fig. 1B).

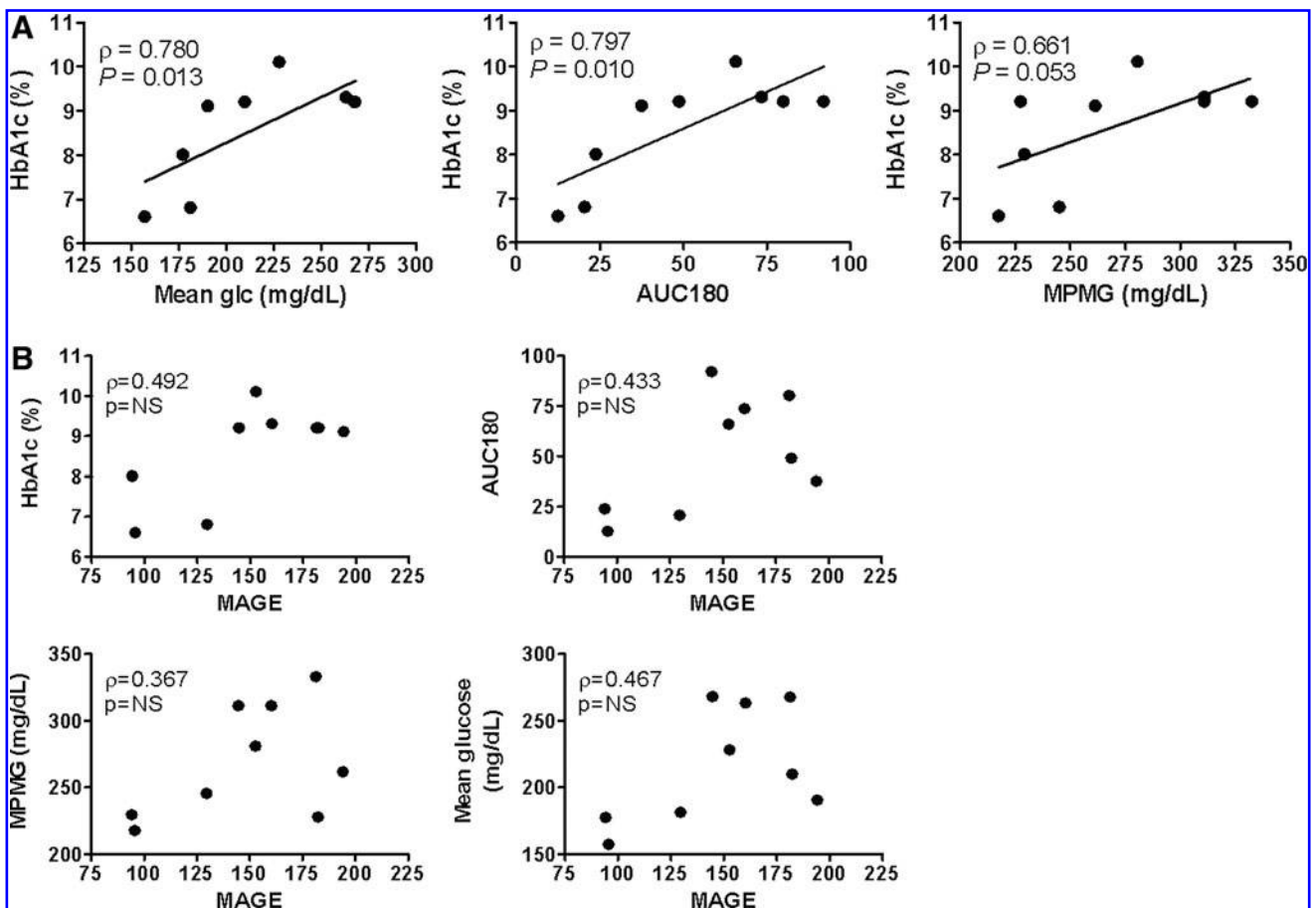
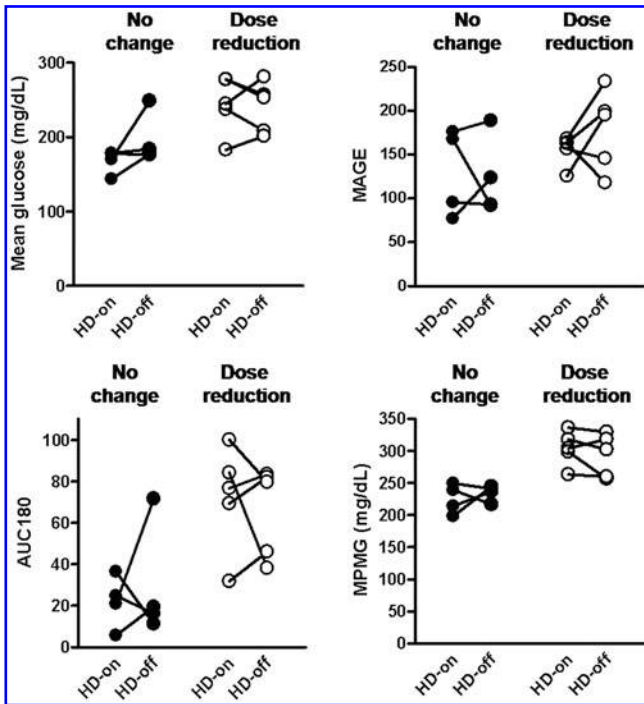


FIG. 1. (A) Correlation analysis between glucose profiles from continuous glucose monitoring readings and hemoglobin A1c (HbA1c). (B) Correlation analysis between mean amplitude of glucose excursions (MAGE) and other glucose profiles. The subjects were medically stable patients with type 2 diabetes mellitus undergoing chronic hemodialysis. AUC180, area under the curve above 180 mg/dL; glc, glucose; MPMG, mean postmeal maximum glucose; NS, not significant.



**FIG. 2.** No changes in glucose profiles between days on and off hemodialysis (HD-on and HD-off, respectively): mean glucose, mean amplitude of glucose excursions (MAGE), area under the curve above 180 mg/dL (AUC180), and mean postmeal maximum glucose (MPMG).

*Comparison of glycemic profiles from CGM measurements between HD-on and HD-off*

For each subject, we could collect at least 2 days of CGM readings HD-on and HD-off, respectively. When the averaged values were compared, glycemic patterns in each subject were not statistically different between HD-on and HD-off. Whether antidiabetes drugs for day on HD were reduced or not,

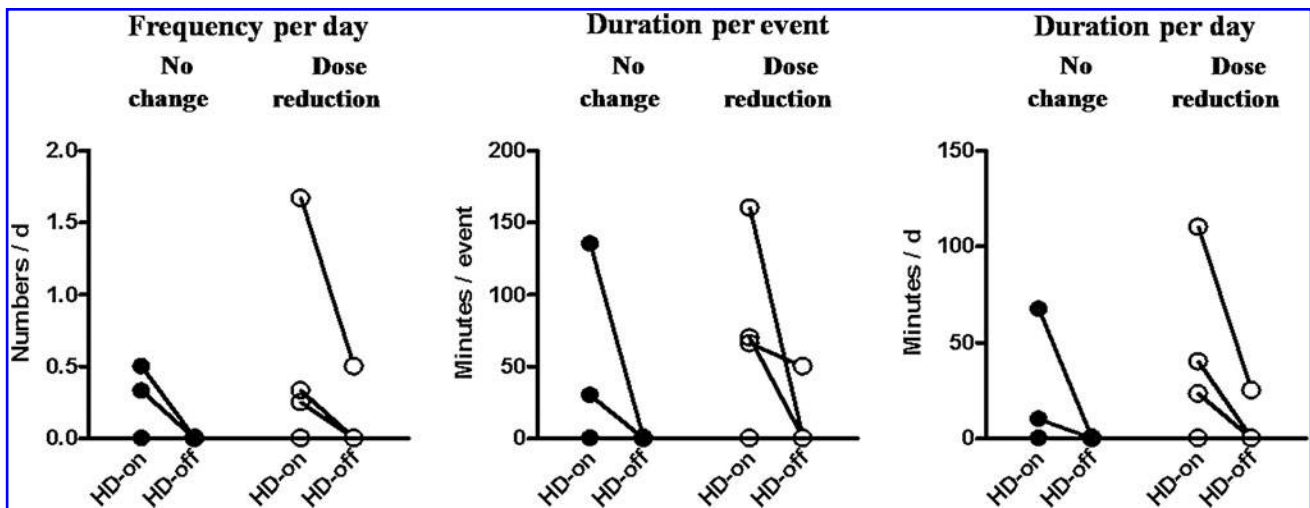
there were no differences in mean glucose levels, MAGE, AUC180, and MPMG between HD-on and HD-off (Fig. 2).

*Occurrence of hypoglycemia*

During the study period, 10 hypoglycemia episodes defined as a CGM reading <80 mg/dL  $\geq$ 20 min happened in five subjects, and 80% occurred in the day on HD. The lowest readings in each episode were 71, 70, 40, 77, 40, 40, 61, 68, 56, and 54 mg/dL. However, because the reading range of the CGM device was 40–400 mg/dL, the values could be overestimated. Among these episodes, only three were associated with hypoglycemic symptoms and confirmed by capillary blood glucose tests. The other episodes were not associated with any symptoms, and the CGM device does not give real-time glucose values to the wearer; simultaneous capillary blood glucose tests were not performed. Regardless of medication reduction, frequency and duration of hypoglycemia were apparently predominant in the day on HD (Fig. 3). To examine if there is “a hot spot” of hypoglycemia, we determined duration and severity of hypoglycemia (Fig. 4A [width and height of each rectangle, respectively]) in the subjects who experienced hypoglycemia with day on dialysis. We found that major events usually occurred during the first 12 h of the day on HD. When the CGM readings of subjects were averaged, we also observed that glucose levels started to decrease with HD in the subjects whose medications were maintained ( $F = 8.88, P < 0.05$  of the enlarged graph in Fig. 4B), which caused a significant difference during the first 6 h between HD-on and HD-off ( $F = 11.9, P < 0.05$  in Fig. 4B). However, such results were not observed in the subjects who had reduced medications for the day on dialysis (Fig. 4C).

*Dietary analysis*

A food diary was completed by eight subjects. A difference of carbohydrate intake between HD-on and HD-off was observed with marginal significance (HD-on,  $261.7 \pm 69.4$  g/day; HD-off,  $235.2 \pm 37.3$  g/day;  $P = 0.05$ ), which mainly resulted from the increased intake in the dose-reduction group



**FIG. 3.** Frequency and duration of hypoglycemia according to days on and off hemodialysis (HD-on and HD-off, respectively).

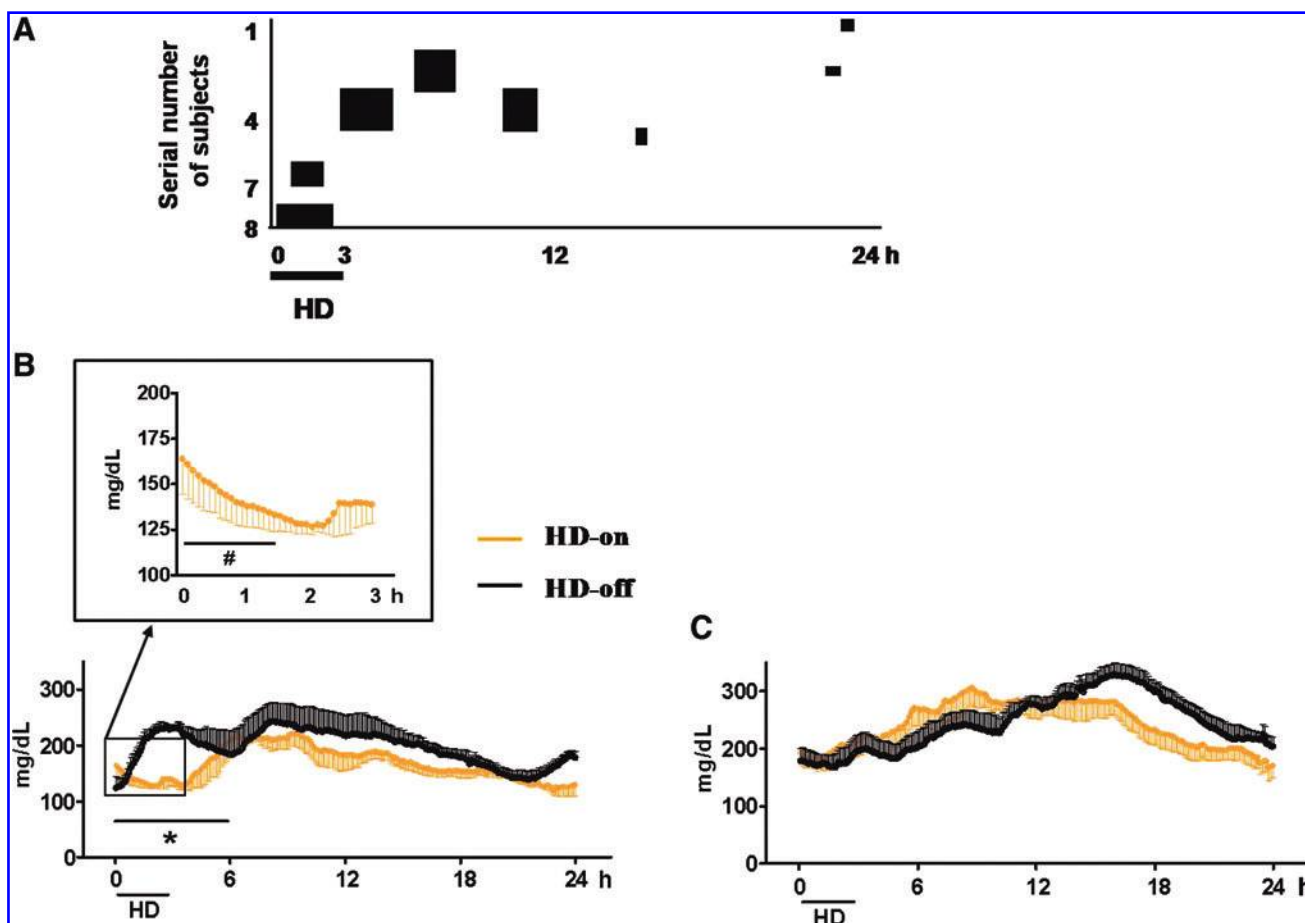


FIG. 4. (A) Duration (width) and severity (height) of hypoglycemia (each rectangle) for day on hemodialysis (HD). (B and C) Averaged continuous glucose monitoring readings of the no-change group and the dose-reduction group, respectively. \* $P < 0.05$  between HD-on and HD-off; # $P < 0.05$  within the day on HD. Color image available online at [www.liebertonline.com/dia](http://www.liebertonline.com/dia).

for the days on HD (HD-on,  $299.7 \pm 84.3$  g/day; HD-off,  $252.3 \pm 47.7$  g/day;  $P = 0.068$ ).

## Discussion

HbA1c has been known to be a poor marker for mean glucose in patients with ESRD undergoing HD.<sup>26–28</sup> However, when Rivelin et al.<sup>16</sup> examined it using a CGM system, HbA1c was significantly associated with mean glucose, although the power was weaker than that in those without nephropathy. In the current study, we reproduced the value of HbA1c in type 2 diabetes mellitus patients undergoing chronic HD. HbA1c was significantly correlated with mean glucose and MPMG measured by the CGM system for 144 h. In terms of glucose variability, MAGE was not related with mean glucose, HbA1c, and postmeal glucose levels in the subjects, in agreement with a study performed in well-controlled type 2 diabetes patients with normal renal function.<sup>29</sup> According to a recent report, glycemic variability correlated with postprandial  $\beta$ -cell dysfunction.<sup>30</sup>

Kazempour-Ardebili et al.<sup>31</sup> reported that mean glucose levels from a CGM system were lower on the day on dialysis than on the day off dialysis. In that study, antidiabetes regimens and calorie intake had not been different according to

HD. However, when we analyzed glucose profiles between HD-on and HD-off, there was no difference. This result could be come from the small sample size for statistical significance because there was a tendency to decrease for mean glucose levels of the day on HD in the no-change group as seen in Figure 2. Therefore, if more patients had been recruited in that group, we could have observed a statistically significant reduction for glucose levels of the day on HD.

The Working Group of the American Diabetes Association defined hypoglycemia as plasma glucose levels  $\leq 70$  mg/dL<sup>32</sup> because the glycemic threshold for activation of glucagon and epinephrine secretion as glucose levels decline was 65–70 mg/dL<sup>33,34</sup> and because antecedent plasma glucose levels  $\leq 70$  mg/dL reduced sympathoadrenal responses to subsequent hypoglycemia.<sup>35</sup> However, the threshold for neuroglycopenia seems to be above 70 mg/dL.<sup>36</sup> In addition, renal dysfunction and HD are risk factors for hypoglycemia,<sup>9,11,37</sup> and mild hypoglycemic episodes frequently precede severe hypoglycemia.<sup>38</sup> Therefore, in this study, we determined hypoglycemia as a CGM reading  $< 80$  mg/dL for  $\geq 20$  min to prevent severe hypoglycemia in the fragile subjects. Despite there being no differences in mean glucose levels and glucose variability between HD-on and HD-off, hypoglycemia usually occurred with day on HD both in the

no-change and the dose-reduction groups (Fig. 3). Calorie and carbohydrate intakes of the day on HD were larger than those of the day off HD, which reflects the occurrence of more hypoglycemic episodes for day on HD. According to Loipl et al.,<sup>39</sup> hypoglycemic events in insulin-treated type 2 diabetes mellitus assessed by a patient questionnaire occurred at any time during the day on HD, but 33% of all episodes occurred during or within 3 h after HD. Using a CGM system, we could observe that most mild hypoglycemia events also occurred during similar periods (Fig. 4A).

There was a significant decrease in glucose levels along with HD in the no-change group (Fig. 4B) as in the study by Riveline et al.,<sup>16</sup> which was not definite in the dose-reduction group. This result suggests that there can be more risk for hypoglycemia during HD if antidiabetes medication is adjusted for days off HD and is not modified for days on HD. In fact, it was not clear if dose reduction affected the glucose reduction during HD or not, which necessitates evaluation in the same subjects. However, we can speculate that antidiabetes medication would be decreased or not be required just before HD, that hypoglycemia should be monitored more closely during and within some hours after HD, and that glucose levels of the day off HD can be controlled more intensively with lower risk of hypoglycemia because of the need for adequate glycemic control for a better survival rate in diabetes patients with ESRD.<sup>4,7,8</sup> For this purpose, we can make use of a CGM system and many kinds of antidiabetes preparations with various action times and biologic half-lives.

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#### Author Disclosure Statement

No competing financial interests exist.

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