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ORIGINAL RESEARCH

Effects of DPP-4 Inhibitors on Blood Glucose Variability in Japanese Patients with Type 2 Diabetes on Maintenance Hemodialysis: A Prospective Observational Exploratory Study

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ABSTRACT

Introduction: The precise blood glucose (BG) profile of hemodialysis patients is unclear, as is the effectiveness of dipeptidyl peptidase-4 (DPP-4) inhibitors in hemodialysis patients with type 2 diabetes. Here, we used continuous glucose monitoring (CGM) to evaluate BG variability in these patients and to assess the efficacy of DPP-4 inhibitors, particularly during hemodialysis sessions and at nighttime (UMIN000012638).

Methods: We examined BG profiles using CGM in 31 maintenance hemodialysis patients with type 2 diabetes. Differences between patients with and without DPP-4 inhibitors (n = 15 and 16, respectively) were analyzed using a linear mixed-effects model to assess changes in glucose levels in 5-min intervals.

Results: The model revealed that DPP-4 inhibitor use was significantly associated with suppression of a rapid drop in glucose levels, both with and without adjustment for BG levels at the start of hemodialysis. Moreover, the model revealed that the two groups differed significantly in the pattern of changes in BG levels from 0:00 to 6:55 am. DPP-4 inhibitors

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suppressed the tendency for subsequent nocturnal hypoglycemia.
Conclusions: This prospective observational exploratory study showed that DPP-4 inhibitors could suppress BG variability during hemodialysis sessions as well as subsequent nocturnal changes in patients with type 2 diabetes.
Trial Registration: ClinicalTrials.gov identifier, UMIN000012638.

Keywords: Blood glucose variability; Continuous glucose monitoring; DPP-4 inhibitors; Hemodialysis; Hypoglycemia

Key Summary Points

Why carry out this study?

The precise blood glucose profile is unclear in patients with type 2 diabetes on maintenance hemodialysis, who are often reported to have asymptomatic hypoglycemia.

Few studies have examined in detail the effects of DPP-4 inhibitors in these patients.

Using continuous glucose monitoring (CGM), we investigated blood glucose variability and the efficacy of DPP-4 inhibitors in these patients.

What was learned from the study?

DPP-4 inhibitors can suppress blood glucose variability during hemodialysis sessions as well as subsequent nocturnal changes, and can prevent hypoglycemia in patients with type 2 diabetes.

A linear mixed-effects model is likely to be particularly useful for analyzing CGM data over time, such as during hemodialysis treatment or at nighttime.

Glycemic control with DPP-4 inhibitors may improve the prognosis of patients with diabetes on maintenance hemodialysis, and further studies are warranted to examine this hypothesis.

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INTRODUCTION

The number of maintenance hemodialysis patients with diabetes has recently increased worldwide [1]. Previous studies revealed that poor glycemic control causes high cardiovascular morbidity and mortality in these patients, but also that intensive diabetes therapy has long-term beneficial effects on the risk of cardiovascular disease and all-cause death [2–5]. However, since the ACCORD study showed that severe hypoglycemia could increase the risk of cardiovascular death in participants with high underlying cardiovascular disease risk [6], hypoglycemia has become one of the most important considerations in diabetes treatment. Sun et al. found that 54 of 102 type 2 diabetes patients on hemodialysis had symptomatic hypoglycemia during a 3-month follow-up period [7]. However, asymptomatic hemodialysis-associated hypoglycemia might also be important in these patients. Patients with end-stage renal disease are at high risk of asymptomatic hypoglycemia [8], and asymptomatic hemodialysis-associated hypoglycemia has been reported in patients with type 2 diabetes [9–11].

Furthermore, high blood glucose (BG) variability in chronic glycemic control [standard deviation (SD) of glycated hemoglobin (HbA1c)] is associated with a high risk of hypoglycemia-related hospitalization [12]. BG fluctuations activate oxidative stress and have been associated with arteriosclerosis [13, 14]. The mean amplitude of glycemic exclusion (MAGE) is also used as an index of BG variability and has been reported to be associated with the presence and severity of coronary artery disease in patients with type 2 diabetes [15–17]. Hypoglycemia can also lead to vascular injury and is associated with an adverse prognosis in patients with diabetes and chronic kidney disease [18–21]. However, the precise BG profile and its variability in type 2 diabetes patients undergoing maintenance hemodialysis are unclear.

Continuous glucose monitoring (CGM) is useful for elucidating BG variability in diabetes patients by analyzing the amplitude and timing of glucose fluctuations [22]. CGM is now commonly used for monitoring BG levels in patients undergoing maintenance hemodialysis [9, 10, 23–32]. Nonetheless, there are only a few detailed reports on BG variability during hemodialysis therapy. Even though these studies showed a decrease in BG during hemodialysis [9, 29, 31, 32], BG variability in these patients was complex, and its details are still unknown. Thus, further study involving CGM is needed to understand BG variability in diabetes patients undergoing maintenance hemodialysis.

Dipeptidyl peptidase-4 (DPP-4) inhibitors enhance the therapeutic effects of glucagon-like peptide-1 (GLP-1) by blocking its rapid degradation. Therefore, by increasing the circulating levels of biologically active GLP-1, DPP-4 inhibitors can elevate insulin levels. Furthermore, GLP-1 reduces meal-stimulated glucagon levels and improves BG control in diabetic patients [33–36]. Some reports have suggested that DPP-4 inhibitors can potentially suppress BG variability in patients with type 2 diabetes [37, 38]. Moreover, DPP-4 inhibitors can be safely used even in type 2 diabetes patients undergoing maintenance hemodialysis, in conjunction with appropriate dose regulation [39, 40]. However, the effects of DPP-4 inhibitors on BG variability during hemodialysis and at nighttime in hemodialysis patients are unclear.

Accordingly, this study aimed to evaluate BG variability in type 2 diabetes patients undergoing maintenance hemodialysis by using CGM to assess the effectiveness of DPP-4 inhibitors, particularly during hemodialysis sessions and the subsequent nocturnal period.

METHODS

Participants and Study Design

The primary outcome in this multicenter prospective observational exploratory study was BG variability in type 2 diabetes patients undergoing maintenance hemodialysis with or without a DPP-4 inhibitor [DPP-4 inhibitor (+) and DPP-4 inhibitor (−), respectively]. This variability was evaluated using the SD, MAGE, and a linear mixed-effects model. The frequency of hypoglycemia and the mean BG level were also evaluated. Participants were enrolled from November 2012 to March 2014 by T.I., M.H., and E.K. at Niigata University, Itoigawa General Hospital and Nagaoka Chuo Hospital, Niigata, Japan. The inclusion criteria were (1) age $\geq$ 20 years, (2) diagnosis of type 2 diabetes mellitus, (3) maintenance hemodialysis, and (4) the ability to provide informed consent. The exclusion criteria were (1) severe heart disease (New York Heart Association III or IV), (2) severe hepatic insufficiency, (3) apparent signs of current systemic infection or sepsis requiring active use of intravenous antibiotics, (4) perioperative status, (5) insulin therapy, (6) fasting, and (7) allergy to DPP-4 inhibitors. The reasons for hospitalization were shunt occlusions, pneumonia, and urinary tract infections. All participants were able to consume the prescribed meal, which had restricted calories, salt, and protein according to body weight, at 8:00 am, 12:00 pm, and 6:00 pm on the non-hemodialysis day and at 8:00 am, 2:00–3:00 pm after dialysis, and 6:00 pm on the day of hemodialysis.

This study was approved by the institutional review boards of Niigata University, Itoigawa General Hospital, and Nagaoka Chuo Hospital,

and was performed in accordance with the principles embodied in the Declaration of Helsinki. All participants provided written informed consent. The Ethics Committee of the Niigata University School of Medicine approved the study (approval numbers: 2015-1476 and 2015-2119). The study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000012638).

Measurement of Glucose Profiles

Glucose levels were measured by CGM for 48–168 h. A CGM System Gold (Medtronic MiniMed, Northridge, CA, USA) was used for 7 patients and a CGM System iPro2 (Medtronic MiniMed) was used for 38 patients. Patients underwent 3–5 h of hemodialysis 3 days per week; the dialysate glucose concentration was 100 mg/dL or 150 mg/dL. The CGM system was calibrated by nurses four times a day by comparison with the capillary BG value using the Medisafe-Mini (Terumo, Tokyo, Japan), a self-monitoring BG device. CGM was used to evaluate glucose levels from 7:00 am on the day of hemodialysis for 24 h. Hypoglycemia was defined as a CGM reading of < 70 mg/dL. The CGM test was performed for at least 2 weeks after DPP-4 inhibitor therapy was started. Pre-hemodialysis venous blood samples were obtained at the beginning of the week, and routine biochemical parameters, including HbA1c, were measured.

Statistical Analysis

For continuous variables, we used an unpaired *t* test for parametric variables and the Mann–Whitney *U* test for nonparametric variables. Differences in proportions were evaluated using Fisher's exact test. Relationships between two continuous variables were evaluated using Spearman's rank correlation coefficient. Mean SD and MAGE were calculated to evaluate BG variability. We calculated MAGE as the average of the variability above 1 SD of the 24 h wave of BG variability from 7:00 am to the next morning on the hemodialysis and non-hemodialysis days. A linear mixed-effects model was used to evaluate the between-group and within-group differences in the slope of the BG levels. The slope represents the estimated coefficient for changes in BG levels per unit time calculated using the linear mixed-effects model. The model included the time since initiation of hemodialysis and the time at night, the DPP-4 inhibitor (+) and (−) groups, and the interaction between time and treatment. The approximate inference regarding fixed or covariate effects in linear mixed-effects models was determined using the Kenward–Roger approximation method for degrees of freedom. Given that the study was exploratory in nature, the sample size was calculated to detect a difference in slope of 0.1 mg/dL per minute during a hemodialysis session with 70% power at the 5% level of significance in the analysis using the linear mixed-effects model. From this calculation, the number of cases required in each group was 14. All tests were two-sided and *P* values of less than 0.05 were considered statistically significant. The statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and IBM SPSS Statistics 25 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical Characteristics

The recruitment process for participants is outlined in Fig. 1. Forty-five patients undergoing dialysis during the daytime were eligible for this study; 18 patients were treated with a DPP-4 inhibitor and 27 patients were not. Three patients were subsequently excluded from the DPP-4 inhibitor (+) group: 1 due to mitochondrial encephalomyopathy, 1 due to parenteral alimentation, and 1 because he was receiving insulin therapy. Eleven patients were also excluded from the DPP-4 inhibitor (−) group: 1 due to parenteral alimentation and 10 because they were receiving insulin therapy. Finally, we examined BG profiles using CGM in 31 patients with type 2 diabetes on maintenance hemodialysis.

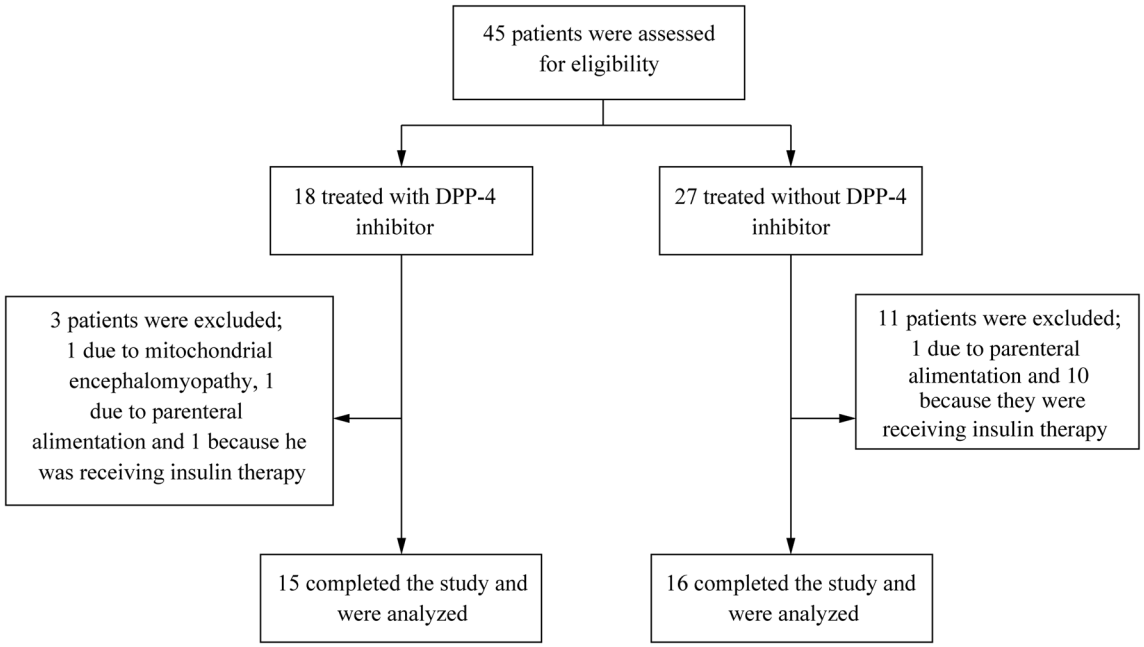

Fig. 1 Flow chart of patient enrollment

The clinical and biological characteristics of the participants are summarized in Table 1. There were no significant differences in age, sex, duration on hemodialysis, and duration of diabetes mellitus between the two groups. Fifteen patients were receiving a DPP-4 inhibitor: sitagliptin (12.5 mg daily), 1; vildagliptin (50 mg daily), 1; vildagliptin (100 mg daily), 2; alogliptin (6.25 mg daily), 4; linagliptin (5 mg daily), 4; teneligliptin (20 mg daily), 2; and teneligliptin (40 mg daily), 1. Moreover, 2 patients were receiving mitiglinide, and 1 patient was taking miglitol with a DPP-4 inhibitor. The patients in the DPP-4 inhibitor (−) group ($n = 16$) were not receiving any oral hypoglycemic agents or insulin therapy.

BG Variability on Hemodialysis and Nonhemodialysis Days

The average concentration and the SD of BG were not significantly different between hemodialysis and nonhemodialysis days [average BG concentration: 128.5 ± 19.0 mg/dL vs. 130.6 ± 18.7 mg/dL, respectively ($P = 0.77$); SD of BG: 29.9 ± 14.5 mg/dL vs. 24.0 ± 12.3 mg/dL, respectively ($P = 0.05$)]. However, MAGE was significantly higher on the hemodialysis day than on the nonhemodialysis day (76.7 ± 37.0 mg/dL vs. 60.5 ± 30.5 mg/dL, $P = 0.04$). No patient had symptomatic hypoglycemia.

Effects of DPP-4 Inhibitors on BG Variability and Hypoglycemia

Next, we evaluated the efficacy of the DPP-4 inhibitors. There was no significant difference in mean glucose concentration between the DPP-4 inhibitor (+) and (−) groups, as shown in Figs. 1 and 2 [hemodialysis day: 128.7 ± 17.5 mg/dL vs. 128.4 ± 20.7 mg/dL, respectively ($P = 0.96$); nonhemodialysis day: 128.9 ± 20.5 mg/dL vs. 132.2 ± 17.6 mg/dL, respectively ($P = 0.64$)]. However, the magnitudes of the SD for BG and MAGE were markedly lower in the DPP-4 inhibitor (+) group than in the DPP-4 inhibitor (−) group [SD of BG: hemodialysis day, 24.3 ± 12.7 mg/dL vs. 35.1 ± 14.4 mg/dL ($P = 0.04$); nonhemodialysis day, 19.6 ± 12.2 mg/dL vs. 27.8 ± 11.5 mg/dL ($P = 0.07$); MAGE: hemodialysis day, 62.3 ± 32.1 mg/dL vs. 90.3 ± 37.1 mg/dL ($P = 0.03$); nonhemodialysis day, 48.6 ± 27.7 mg/dL vs. 70.9 ± 29.8 mg/dL ($P = 0.04$)] (Fig. 2).

Table 1 Patient demographics, clinical characteristics, and laboratory findings at baseline

	DPP-4 inhibitor (+) (*n* = 15)	DPP-4 inhibitor (−) (*n* = 16)	*P* value
Age (years)	58.3 ± 12.9	62.8 ± 11.9	0.323[¶]
Sex (male: female)	11:4	8:8	0.273[‡]
Height (cm)	166.7 ± 11.8	161.2 ± 10.4	0.175[¶]
Dry weight (kg)	64.8 ± 16.4	60.3 ± 9.8	0.360[¶]
Ideal body weight (kg)	61.4 ± 8.6	57.4 ± 7.3	0.165[¶]
Body mass index (kg/m^2)	23.2 ± 4.5	23.2 ± 2.8	0.999[¶]
HD duration (months)	32.0 (14.0, 132.0)	13.0 (2.9, 68.4)	0.281[§]
Diabetes duration (years)	24.0 (5.5, 30.8)	9.0 (7.0, 24.0)	0.270[§]
Energy (kcal/kg/day)	30.1 ± 2.4	29.3 ± 4.3	0.520[¶]
HD time (3 h:4 h)	1:14	2:14	1.000[‡]
Pre-HD body weight (kg)	66.3 ± 17.0	61.8 ± 10.1	0.385[¶]
Post-HD body weight (kg)	64.7 ± 16.4	60.3 ± 9.7	0.382[¶]
Water removal (kg)	1.6 ± 1.1	1.5 ± 1.0	0.756[¶]
Glucose concentration (100 mg/dL:150 mg/dL)	13:2	14:2	1.000[‡]
Blood flow rate (mL/min)	194.0 ± 30.9	185.6 ± 31.0	0.457[¶]
Dialyzer membrane area (m^2)	1.6 (1.5, 1.8)	1.6 (1.3, 1.8)	0.800[§]
HbA1c (%)	6.2 ± 0.9	5.8 ± 0.7	0.172[¶]
Hb (g/dL)	10.3 ± 1.3	10.4 ± 1.4	0.864[¶]
BUN (mg/dL)	50.4 ± 23.0	51.0 ± 16.3	0.936[¶]
Cr (mg/dL)	8.9 ± 2.8	8.0 ± 3.0	0.377[¶]
Alb (g/dL)	3.5 ± 0.5	3.2 ± 0.6	0.086[¶]
CRP (mg/dL)	0.19 (0.11, 0.32)	0.25 (0.05, 0.72)	0.274[¶]

Normally distributed data are presented as the mean ± SD; non-normally distributed data are presented as medians and interquartile ranges

Alb albumin, *BUN* blood urea nitrogen, *Cr* creatinine, *CRP* C-reactive protein, *Hb* hemoglobin, *HbA1c* glycated hemoglobin, *HD* hemodialysis

[¶] *P* value calculated using the unpaired *t* test

[§] *P* value calculated using the Mann–Whitney *U* test

[‡] *P* value calculated using Fisher's exact test. *Ideal body weight* was calculated as height × height × 22, *Energy* amount of energy in the prescribed hospital meals, *Water removal* water removal during dialysis, *Glucose concentration* glucose concentration in dialysate

Next, we analyzed hypoglycemic events. Although no patients had symptomatic hypoglycemia, some patients showed nocturnal hypoglycemia on CGM, especially on the day of hemodialysis. There were no significant differences in the proportions of nocturnal hypoglycemic events from 0:00 am to 6:55 am between the DPP-4 inhibitor (+) and (−) groups [0 of 15 (0%) vs. 4 of 16 (25%), $P = 0.058$] (Table 2). The rates were similar on hemodialysis and nonhemodialysis days (data not shown).

BG Variability During Hemodialysis Sessions and at Nighttime in Analysis Using the Linear Mixed-Effects Model

During hemodialysis (from time 0 to 235 min), the slope of the BG levels in the DPP-4 inhibitor (+) group was − 0.2 ± 0.01 mg/dL/min,

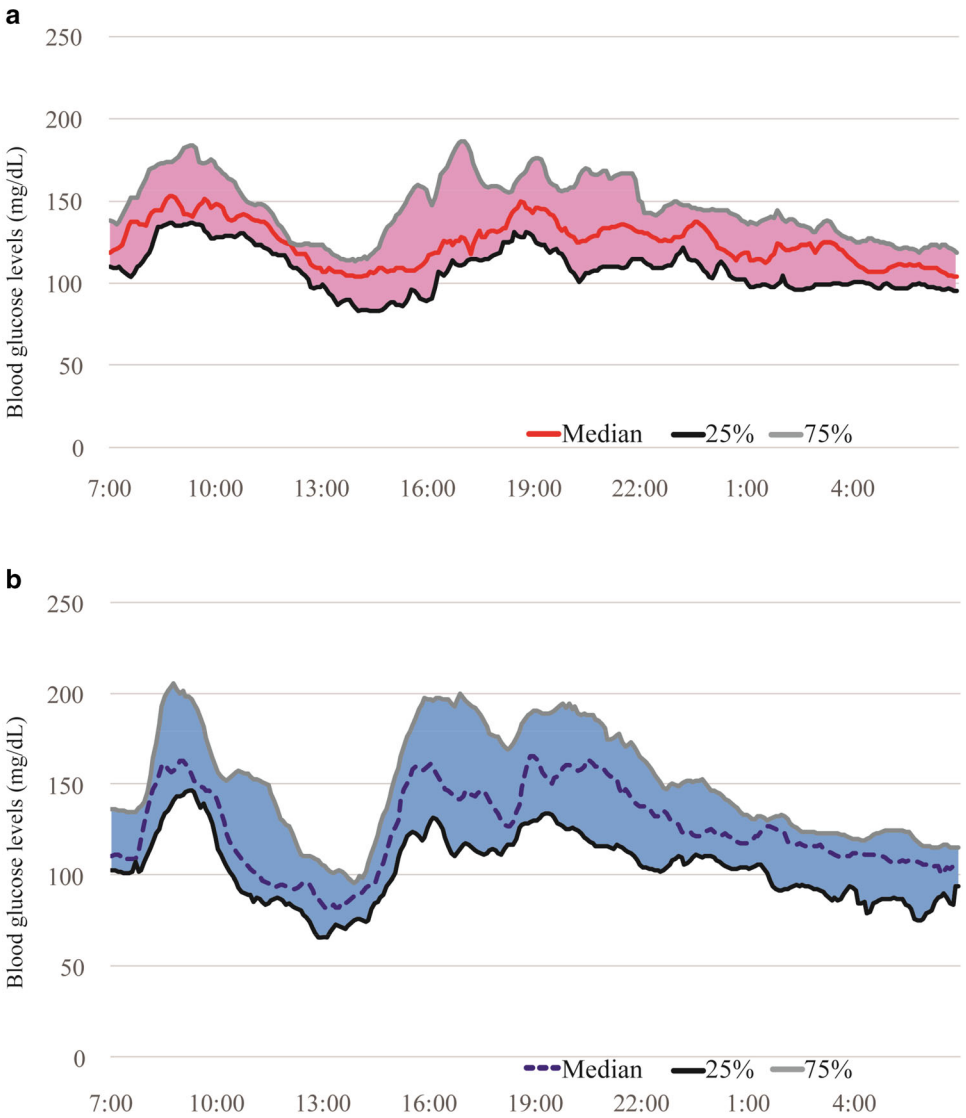

Fig. 2 Glucose levels on the day of hemodialysis in patients with or without a DPP-4 inhibitor. 24 h continuous glucose monitoring data on the day of hemodialysis are shown for patients **a** with or **b** without a DPP-4 inhibitor (n = 15 and n = 16, respectively). The *curves* show the median and 25th–75th percentiles

whereas that in the DPP-4 inhibitor (−) group was − 0.3 ± 0.01 mg/dL/min. The absolute between-group difference in mean rate of change in BG levels during hemodialysis was 0.1 ± 0.01 mg/dL/min. Therefore, there was a significant difference in the slope of the BG levels between the two groups ($P < 0.001$, linear mixed-effects model; Table 3; Figs. 2, 3).

During the night (from 0:00 am to 6:55 am), the slope of the BG levels of the DPP-4 inhibitor (+) group was − 0.05 ± 0.002 mg/dL/min, whereas that of the DPP-4 inhibitor (−) group was − 0.1 ± 0.004 mg/dL/min. The absolute between-group difference in mean rate of change in BG levels during hemodialysis was 0.05 ± 0.004 mg/dL. There was thus a significant difference between the two groups in the slope of the BG levels ($P < 0.001$, linear mixed-effects model) (Table 4; Figs. 2, 4).

Table 2 Analysis of the contingency table for the effect of DPP-4 inhibitors and nocturnal glucose levels from 0:00 am to 6:55 am

	DPP-4 inhibitor		Total
	(+)	(−)	
BG < 70 mg/dL	0	4	4
BG ≥ 70 mg/dL	15	12	27
Total	15	16	31

P value calculated using Fisher's exact test was 0.058
BG blood glucose

DISCUSSION

There is little information on BG variability in maintenance hemodialysis patients. Our study shows that maintenance hemodialysis patients with type 2 diabetes have high BG variability, as evidenced by the higher SD of BG, MAGE, and linear mixed-effects model coefficients. Also, our data from the linear mixed-effects model showed a rapid BG drop during hemodialysis and a tendency for hypoglycemia in the subsequent nighttime period in maintenance hemodialysis patients with type 2 diabetes. Although DPP-4 inhibitors have been shown to improve BG variability in patients with type 2 diabetes in many randomized controlled trials (RCTs) [41–49] (see the table in the Electronic supplementary material), few studies have reported the same effect in maintenance hemodialysis patients [50]. Our study illustrates the usefulness of DPP-4 inhibitors in these patients. Moreover, we showed that DPP-4 inhibitors ameliorated not only the 24 h BG variability but also the BG drop during hemodialysis and the tendency for nocturnal hypoglycemia in particular.

The ability of DPP-4 inhibitors to suppress BG variability in patients with type 2 diabetes has been shown in studies using CGM [51, 52]. Furthermore, several RCTs using CGM found that BG variability is suppressed more effectively by DPP-4 inhibitors than by other agents such as sulfonylureas [41, 42] and sodium glucose cotransporter 2 inhibitors [43–45] or by combination with insulin therapy [46–49]. The patients in these RCTs who showed suppressed BG variability with DPP-4 inhibitors had a mean age of less than 60 years [42–44, 46, 48, 49], had HbA1c > 7% [41–44, 46–49], were drug naïve [41, 49], or had used metformin only [41–43, 46]. There have also been some reports on the usefulness of DPP-4 inhibitors in patients on hemodialysis [50], but none has shown obvious suppression of BG variability. In this prospective observational exploratory study, analysis using a linear mixed-effects model showed that DPP-4 inhibitors could suppress BG variability in patients with type 2 diabetes. However, it is not known whether DPP-4 inhibitors are more effective at suppressing BG variability than any other drugs, even in patients on hemodialysis. This is an issue to be resolved in the future. Several reports have examined the efficacy of DPP-4 inhibitors for

Table 3 Linear mixed-effects model with glucose level (measured every 5 min from the start of HD to 235 min) as the dependent variable and DPP-4 inhibitor use and time as independent variables

Source	Estimated coefficient	SE of coefficient	*T* value	*P* value
DPP-4 inhibitor	12.2	8.4	1.5	0.155
Time	− 0.3	0.0	− 36.0	< 0.001
DPP-4 inhibitor × time	0.1	0.0	6.0	< 0.001
Constant	− 15.0	5.8	− 2.6	0.015

Time effect of time elapsed from the start of HD to 235 min, *DPP-4 inhibitor* × *time* interaction between DPP-4 inhibitor and time. The variables were coded as follows: time (in min): 0, 5, 10, …, 235. DPP-4 inhibitor group: 0, not receiving a DPP-4 inhibitor; 1, receiving a DPP-4 inhibitor
HD hemodialysis, *SE* standard error

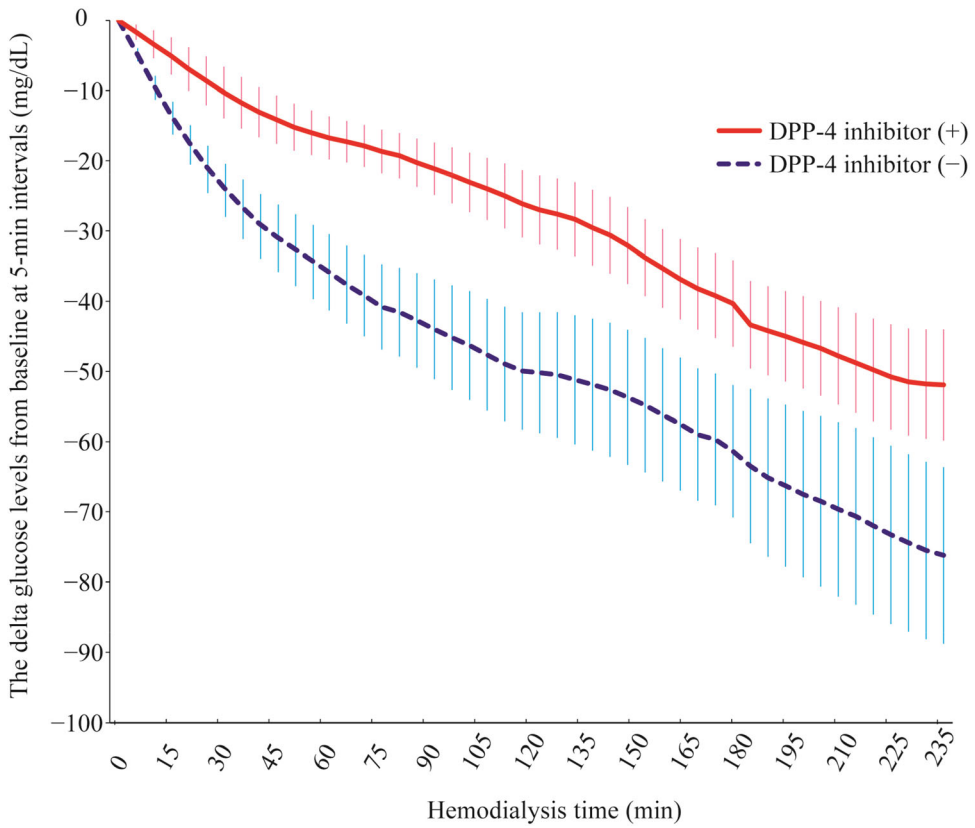

Fig. 3 Differences in blood glucose levels from baseline in 5-min intervals during each hemodialysis session in the DPP-4 inhibitor (+) and (−) groups. Error bars indicate 1 × standard error. Number of patients at risk: 31 (15 with a DPP-4 inhibitor and 16 without a DPP-4 inhibitor) between 0 and 175 min and 28 (14 with a DPP-4 inhibitor and 14 without a DPP-4 inhibitor) between 180 and 235 min

suppressing BG variability not only during the day and after a meal but also at night [53, 54]. However, until now, there has been no clear evidence that DPP-4 has a nocturnal effect. Using a linear mixed-effects model, we have shown that DPP-4 inhibitors could potentially suppress BG variability during hemodialysis sessions as well as subsequent nocturnal changes. Whether this effect is a feature of DPP-4 inhibitors in general or specific to patients on dialysis needs further investigation.

One of the essential endpoints of our study was the slope of the BG levels measured in mg/dL/min throughout hemodialysis and at night. This slope was calculated using CGM data obtained at baseline and every 5 min during the treatment phase. The difference in slope between the DPP-4 inhibitor (+) and (−) groups was evaluated with a linear mixed-effects model. CGM data usually show a periodic waveform. However, the changes between time points can be approximated using the slope of a linear mixed-effects model. Linear mixed-effects methods are used to fit the model to repeated-measures data such as those of CGM [55], in which measurements are obtained repeatedly over time or under different conditions. The model comprises repeated effects, fixed or covariate effects, and random effects, and the interactions among combinations of these as predictor variables. In general, many study designs generate longitudinal or repeated-measures data sets. These designs are applied in a variety of settings throughout the medical, biological, and physical sciences. Repeated-measures data obtained using such a design

Table 4 Linear mixed-effects model with glucose levels (measured every 5 min from 0:00 am to 6:55 am) as the dependent variable and DPP-4 inhibitor use and time as independent variables

Source	Estimated coefficient	SE of coefficient	*T* value	*P* value
DPP-4 inhibitor	− 50.0	9.2	− 5.5	< 0.001
Time	− 0.1	0.0	− 26.7	< 0.001
DPP-4 inhibitor × time	0.0	0.0	11.2	< 0.001
Constant	80.3	6.4	12.6	< 0.001

Time effect of time elapsed from 0:00 am to 6:55 am, *DPP-4 inhibitor* × *time* interaction between DPP-4 inhibitor and time. The variables were coded as follows: time (in minutes): 0, 5, 10, …, 235. DPP-4 inhibitor group: 0, not receiving a DPP-4 inhibitor; 1: receiving a DPP-4 inhibitor
HD hemodialysis, *SE* standard error

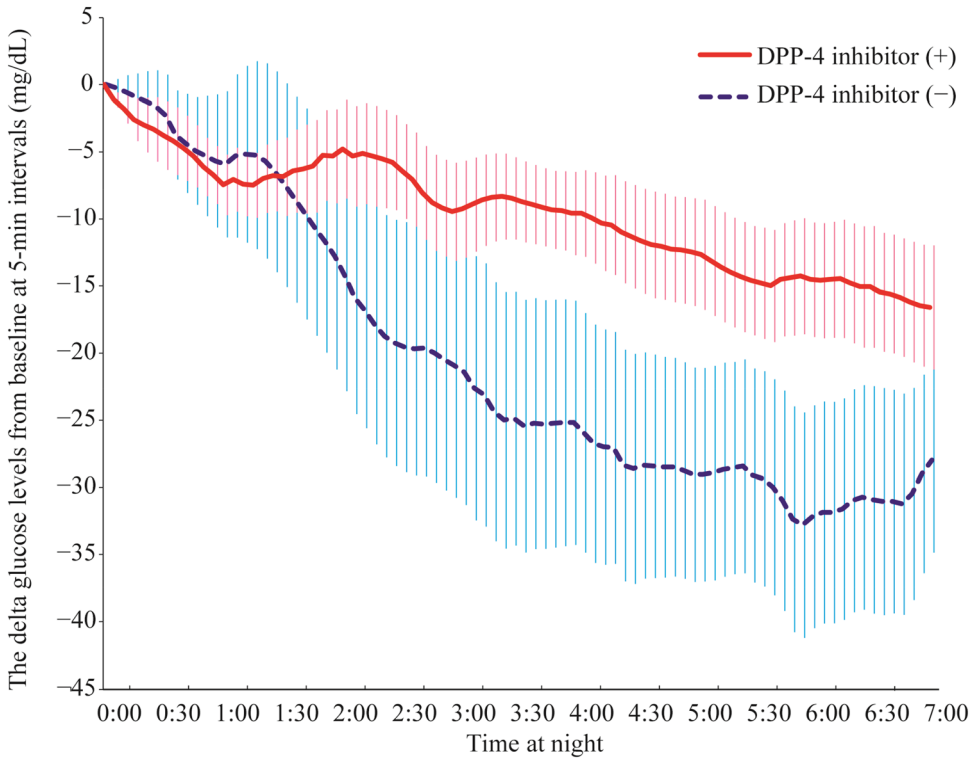

Fig. 4 Differences in blood glucose levels from 0:00 am in 5 min intervals in the DPP-4 inhibitor (+) and (−) groups (0:00–6:55 am). Error bars indicate 1 × standard error. Number of patients at risk: 31 (15 with a DPP-4 inhibitor and 16 without a DPP-4 inhibitor)

often involve missing values, but the linear mixed-effects model can nonetheless estimate the parameters without ad hoc imputation of the missing values. Therefore, linear mixed-effects models provide researchers with powerful and flexible analytic tools for these types of data. They are considered especially useful for analysis of CGM data over time, such as during hemodialysis or at nighttime.

A comparison of our maintenance hemodialysis patients treated with and without DPP-4 inhibitors revealed that the average BG

was similar but that the SD of BG and MAGE were significantly lower in the DPP-4 inhibitor (+) group. Some studies have shown that DPP-4 inhibitors, which can increase insulin secretion but reduce prandial glucagon, improve the BG wave [51, 56]. The reduction in prandial glucagon is believed to be the most important mechanism through which DPP-4 inhibitors improve the BG wave [35]. The present study showed that DPP-4 inhibitors are as effective in dialysis patients as in type 2 diabetes patients not undergoing hemodialysis [41, 44, 48]. The mechanisms are unclear, and more detailed studies are needed, including those that analyze the fluctuation in glucagon.

The average BG, MAGE, and SD of BG were not significantly different between non-hemodialysis and hemodialysis days. However, a significant BG drop was seen during hemodialysis on the hemodialysis day. Asymptomatic hypoglycemia has been reported in hemodialysis patients during hemodialysis [25, 57, 58]. It has long been thought that the diffusion of glucose from blood to dialysate causes this hypoglycemia, and that the use of glucose-containing dialysate can prevent such hypoglycemia [11, 57, 59]. On the other hand, some patients experience a lower BG than the dialysate glucose concentration [58], and hypoglycemia is not completely preventable by glucose-containing dialysate [59]. In addition to chronic undernutrition [60, 61], a delay in lunchtime due to hemodialysis extends the fasting time, causing a loss of glycogen in maintenance hemodialysis patients and increasing the likelihood of developing hypoglycemia. Other mechanisms for hypoglycemia in maintenance hemodialysis patients have been reported. Takahashi et al. stated that excessive consumption of glucose is the result of an accelerated anaerobic metabolism, and causes hypoglycemia during hemodialysis in these patients [62].

Additionally, diabetic patients have less protection against a rapid fall in BG. Counter-regulation of the autonomic nervous system and the hormonal response to hypoglycemia are impaired by diabetic complications in patients with long-term diabetes [11, 63, 64]. These conditions may impair the body's ability to control BG and cause a loss of response to increasing BG in the hypoglycemic state. In the present CGM study, there were only a few cases of hypoglycemia during or after hemodialysis, but almost all patients experienced a rapid fall in BG during hemodialysis. Compared with the DPP-4 inhibitor (−) group, the rate of decrease in BG during hemodialysis was reduced in the DPP-4 inhibitor (+) group. Our study thus suggests that DPP-4 inhibitors can prevent a rapid BG drop during hemodialysis. The mechanisms are unclear, but DPP-4 inhibitors may be able to improve the fluctuation in BG during hemodialysis in a similar manner to their ability to ameliorate the circadian variation of BG [51, 56, 65]. In terms of other factors, glucagon is probably associated with an improvement in BG fluctuation during hemodialysis in the same way as during nocturnal BG control. A previous study revealed that vildagliptin, a DPP-4 inhibitor, reduces postprandial glucagon levels and improves hyperglycemia in patients with type 2 diabetes [35]. Also, DPP-4 inhibitors improve the ability of both β-cells and α-cells to sense and appropriately respond to hypoglycemia [66]. Thus, DPP-4 inhibitors may be able to improve the response to hypoglycemia and prevent a rapid BG drop during hemodialysis in diabetic hemodialysis patients.

In our study, patients in the DPP-4 inhibitor (+) group seldom had BG < 70 mg/dL during the night. Diabetic patients frequently experience hypoglycemia due to a reduced autonomic nerve response, hormonal antagonism [63], and glucagon secretion in response to hypoglycemia [64]. Previous work also showed the potential ability of DPP-4 inhibitors to improve not only hyperglycemia but also hypoglycemia [37, 38]. Excessive glucagon secretion was seen in diabetes patients as well as a lack of glucagon responsiveness to hypoglycemia. When constant oversecretion of glucagon is inhibited by DPP-4 inhibitors [35], glucagon shows its normal response to a BG fall and may be able to prevent hypoglycemia [66]. Hypoglycemia in hemodialysis patients can occur even when they have never been diagnosed with diabetes or have not been exposed to hypoglycemic agents [25, 67]. Chronic kidney disease or hemodialysis can probably cause hypoglycemia

per se [7, 8, 11, 18, 62]. Glycogenesis is as vital in the kidney as it is in the liver [68], especially under hypoglycemic conditions or during fasting [68–74]. When BG falls, glucagon and catecholamine secretion boosts glycogenesis in the kidney and increases BG levels in healthy people [75]. This mechanism is lost in maintenance hemodialysis patients, which is why they easily develop hypoglycemia under nocturnal fasting conditions.

Moreover, maintenance hemodialysis patients can often be undernourished due to protein loss during hemodialysis, and they often consume much smaller meals than recommended. Thus, not only are chronic malnutrition and lack of kidney glycogenesis important reasons for hypoglycemia in maintenance hemodialysis patients [61], but energy loss during hemodialysis and reduced energy storage can also explain nocturnal hypoglycemia on hemodialysis days [76]. Previous work showed that DPP-4 inhibitors improve hyperglycemia without inducing hypoglycemia during Ramadan, which has a long fasting time [77]. This efficacy of DPP-4 inhibitors during Ramadan may be somewhat similar to their efficacy during nocturnal fasting in maintenance hemodialysis patients.

There are some limitations to this study. Firstly, this study had a small number of patients. Moreover, the subjects were hospitalized patients, who are evidently in a different setting from outpatients. Secondly, this was not a RCT, so there could be confounding. Thirdly, in this study, five types of DPP-4 inhibitors were prescribed for 15 patients. However, Craddy et al. [78] recently reported that DPP-4 inhibitors have equivalent effects across the entire class in terms of essential efficacy and safety outcomes. Fourthly, although we surmise that glucagon plays a key role in hypoglycemia episodes and the prevention of hypoglycemia by DPP-4 inhibitors, we did not measure glucagon. This should be the next step. In the future, the use of only one type of DPP-4 inhibitor in a larger RCT is warranted.

CONCLUSION

In summary, this study used a linear mixed-effects model to show that DPP-4 inhibitors can suppress BG variability during hemodialysis sessions and subsequent nocturnal changes in patients with type 2 diabetes. DPP-4 inhibitors may be able to ameliorate the BG fluctuation and prevent hypoglycemia, thereby improving the prognosis of maintenance hemodialysis patients with diabetes. Further detailed examinations are needed in the future.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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