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Evaluation of the relationship between hemodialysis-related glycemic variability and hormonal profiles in patients with type 2 diabetes on hemodialysis: a pilot study

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Abstract

Background: The number of dialysis patients with diabetes is currently increasing in Japan and a similar proportion worldwide. It was suggested that approximately 20% of these patients had hypoglycemia after dialysis session and most of these hypoglycemia were unconscious. Furthermore, it was suggested that glucose variabilities induced by hemodialysis may be related to insulin and insulin-counter hormones, such as glucagon, adrenocorticotropic hormone (ACTH), and cortisol and growth hormone, but conclusive evidence has not still been obtained.

Methods: We investigated in detail the glucose and hormonal profiles in 7 patients with type 2 diabetes on hemodialysis (all male, HbA1c $6.8 \pm 2.1\%$, glycosylated albumin $24.7 \pm 10.2\%$). All participants were attached continuous glucose monitoring (iPro2[®]). Blood glucose level, C-peptide immunoreactivity, plasma glucagon, ACTH, cortisol and growth hormone were measured by 7 points blood tests at before breakfast, after breakfast (predialysis), 2 h and 4 h after starting dialysis, after lunch and before/after dinner on the dialysis day and 6 points at before/after each meal on the non-dialysis day, and these relationship with blood glucose dynamics were examined. The meal contents were set to the indicated energy amount, and the same menu was served daily for breakfast, lunch, and dinner on dialysis and non-dialysis days of this study period. In addition, the start time of lunch on non-dialysis day was the same as the start time of lunch on the dialysis day.

Results: Serum C-peptide level was significantly increased by taking breakfast and lunch on the hemodialysis day, significantly decreased during hemodialysis, and was significantly lower before and after lunch on the hemodialysis day than on the non-hemodialysis day. Plasma glucagon level significantly decreased during hemodialysis and that before lunch on hemodialysis day was significantly lower than on non-hemodialysis day. ACTH, cortisol, and growth hormone did not show any changes related to hemodialysis.

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Conclusions: It was suggested that C-peptide and glucagon play an important role in hemodialysis-related glycemic variabilities in patients with type 2 diabetic hemodialysis.

Trial registration UMIN Clinical Trial Registry (Registration Number [UMIN000018707](https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&language=J&recptno=R000021647)). Registered 18 August 2015, <https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&language=J&recptno=R000021647>.

Keywords: Hypoglycemia, Glycemic variability, Hemodialysis-related hypoglycemia, C-peptide, Glucagon

Background

Chronic kidney disease and type 2 diabetes are long-term conditions that are recognized as major public health concern in not only Japan but also worldwide. Furthermore, diabetes is currently the leading cause of end-stage kidney disease (ESKD) accounting for over 40% of new dialysis cases in Japan and a similar proportion worldwide. On the other hand, advances in hemodialysis (HD) medical treatments, interventions, and equipment surrounding HD patients extend the average age of chronic HD patients and it may be seen occasionally that HD patients whose primary kidney disease is not diabetic nephropathy also newly develop glucose metabolism abnormalities after HD initiation. The mortality of patients with diabetes with ESKD is worse than non-complicated patients with diabetes [1]. Although previous studies showed that strict glycemic control improved survival of patients with diabetes with ESKD [2, 3], however, because due to strict glycemic control is also a risk of macroangiopathy and fatal arrhythmia, it is necessary to control glycemic profiles with an understanding of glycemic and hormonal dynamics in patients with ESKD [4]. Cardiovascular disease and cerebral arterial disease are reported not only in hyperglycemic condition, but postprandial hyperglycemia, glycemic fluctuation, and hypoglycemia also contribute to onset/progression of arteriosclerosis diseases and mortality [5–8]. There is a U-shaped relationship between HbA1c and mortality, suggesting that hypoglycemia may be a reason for higher mortality in those with HbA1c levels < 6.5% [9–12]. Thus in patients with diabetes undergoing HD, simply reducing average blood glucose is not enough, suggesting that it is mandatory to control blood glucose according to the individual's glycemic dynamics including reducing glycemic fluctuation and hypoglycemia avoidance. We reported the glycemic profiles using continuous glucose monitoring (CGM) in Japanese diabetic patients undergoing HD, and as a feature of glycemic dynamics, hypoglycemia after HD was approximately 20% and all of hypoglycemia were unconscious and that their glucose levels rise sharply due to dietary intake after HD. Furthermore, we reported that HbA1c and glycated albumin (GA) are reliable indicators for average glucose level and glycemic variability in type 2 diabetic patients

on HD, respectively [13]. However, with these glycemic markers, it was difficult to detect the presence of hypoglycemia after HD and glycemic excursion after them. In other words, there is still unclear about the factors affecting specific blood glucose profile in patients with diabetes on HD. Previous studies have suggested that blood glucose elevation after HD may be related to decreased insulin secretion and insulin-counter hormones such as glucagon and cortisol, but conclusive evidence has not still been obtained [14, 15].

For these reasons, the aim of this study was to accurately determine the glycemic profile of patients with diabetes on HD using with CGM and to identify the endocrine hormone profiles, such insulin, glucan, and other insulin-counter hormones, which contribute to glycemic profiles.

Methods

Study design and patients

This study was registered with the UMIN Clinical Trial Registry (Registration Number UMIN000018707) and this study's protocols were approved by Kitasato University Medical School Ethics Committee (B14-72), and informed consent was obtained from all participants. All study methods were performed in accordance with the relevant guidelines and regulations of Kitasato University Hospital as well as the *Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan* and under the Code of Ethics of the Helsinki Declaration. We performed power analysis based on the study data of glucagon measured by the new assay in participants with diabetes and normal glucose tolerance [16]. Since this power analysis was not appropriate for the other glucose-regulating hormone, we roughly estimated the sample size reviewing the previous studies of glucoregulatory peptide or gastrointestinal hormones [16–19] and using CGM [20, 21] in HD patients. Finally, for a pilot study, a minimum sample size of 7–10 cases was set based on previous studies. However, due to the small number of inpatients on HD and the termination of the CGM supplies and service used in this study, the study was terminated when 8 cases were recruited and one was excluded due to insufficient data. The participants were admitted type 2 diabetes mellitus patients, who received 4 h HD

thrice weekly, and were enrolled at Kitasato University Hospital. Type 2 diabetes was defined by the American Diabetes Association criteria. Participants were confirmed to be free from any of the following excluding criteria: any infectious diseases, any accompanying conditions affecting hemoglobin and albumin metabolism/turnover, such as malignancy, liver cirrhosis, hematological disease, thyroid dysfunction, and pregnancy. All HD participants underwent dialysis thrice weekly of the admission. All participants agreed to perform at least 72 h CGM using Medtronic iPro2[®] CGM (Medtronic Minimed, Northridge, CA, USA) with ENLiTE sensor[®] (Medtronic Minimed, Northridge, CA, USA). Self-monitoring of capillary blood glucose using Medisafe FIT[®] (Terumo Corporation, Tokyo, Japan), accuracy requirements met ISO 15197, was performed at least four times a day, and these values were used to calibrate the CGM data. The CGM was attached after the dialysis conditions were stabilized and glycemic control was clinically judged stabilization by intermittent blood glucose measurement, and the CGM was attached in the morning of the day before HD day and was desorbed after about 72 h. Hypoglycemia was defined as below 63 mg/dL (3.5 mmol/L) of sensor glucose level (SGL) of CGM in accordance with previous studies [22, 23] and a valid hypoglycemia episode as a period of SGL below threshold for over 20 min [24]. The meal contents were set to the indicated energy amount (30–35 kcal/ideal body weight (kg)/day). Since we avoided the second meal effect [25], the same menu was served daily for breakfast, lunch, and dinner on HD and non-HD days of this study period. In addition, the start time of lunch on non-HD day was the same as the start time of lunch on the HD day. Information on family history, medical history, smoking history, physical history, other blood test findings, and clinical findings was extracted by interviews or medical records.

Biochemical measurement

Blood glucose level, C-peptide immunoreactivity (CPR), plasma glucagon, adrenocorticotrophic hormone (ACTH), cortisol, growth hormone (GH) were measured by 7 points blood tests at before breakfast, after breakfast (predialysis), 2 h after starting HD, 4 h after starting HD (end of HD and before lunch), after lunch and before/after dinner on the HD day and 6 points at before/after each meal on the non-HD day, and these relationships with blood glucose dynamics were examined. Blood tests were performed in advance by placing a catheter for blood sampling on the contralateral upper extremity of the vascular access. CPR was measured with chemiluminescent enzyme immunoassay (CLEIA) method (Presto II, FUJIREBIO INC, Tokyo, Japan). Plasma glucagon was measured by glucagon enzyme-linked

immunosorbent assay (ELISA) kit (Mercodia AB, Uppsala, Sweden). ACTH and cortisol were measured by eclusys ACTH Electro-chemiluminescence immunoassay (ECLIA) method (Roche Diagnostics K.K., Tokyo, Japan) and eclusys cortisol II ECLIA method (Roche Diagnostics K.K., Tokyo, Japan) with Cobas8000 (Roche Diagnostics K.K., Tokyo, Japan). GH was measured by ECLIA method (Roche Diagnostics K.K., Tokyo, Japan) with Cobas8000 (Roche Diagnostics K.K., Tokyo, Japan). GA was measured by enzymatic synthesis using automated system Lucica[™] glycosylated albumin-L assay kit (Asahi Kasei Pharma, Japan, total analytic error [TAE] of intra-assay < 0.51).

Statistical analysis

Statistical analyses were carried out with GraphPad Prism 5.02 software (GraphPad Software Inc., San Diego, CA, USA) and JMP ver. 14 (SAS Institute, Cary, NC, USA). Data are presented as the mean \pm standard deviation (SD) or median (minimum–maximum), unless otherwise indicated. The Wilcoxon signed-rank test was used to evaluate differences in ordinal data between 2 groups. $p < 0.05$ was considered to show statistical significance.

Results

Demography of the participants and clinical data

The demography of the participants is shown in Table 1. All participants were males. Average age was 62 ± 13 years, dry weight 69.6 ± 17.8 kg, duration of diabetes 23 ± 10 years, duration of HD 1.0 (0.5–30.0) months, HbA1c $6.8 \pm 2.1\%$, and GA $24.7 \pm 10.2\%$. Five patients took insulin therapy with or without oral hypoglycemic agents. Dipeptidyl peptidase-4 (DPP-4) inhibitor was prescribed in 3 patients (2 linagliptin and 1 teneligliptin) and glucagon-like peptide-1 (GLP-1) analog in 1 patients (dulaglutide). The dialysis mode for all participants is HD. The dialysate glucose concentration was 150 mg/dL in 2 and 125 mg/dL in 5 participants. Blood flow was 200 mL/min in 5, 230 mL/min in 1, and 250 mL/min in 1, dialysis fluid flow was 400 mL/min in 6 and 500 mL/min in 1, and dialysis membrane area was 1.8 m² in 2, 1.9 m² in 1, and 2.1 m² in 4 participants.

The average sensor glucose level (SGL) and SD of SGL in 48 h CGM data, including HD day and non-HD day, were 156.1 ± 28.6 mg/dL and 41.9 ± 11.2 mg/dL, respectively. The average SGL and SD of SGL were 153.8 ± 27.1 mg/dL and 35.5 ± 13.4 mg/dL in HD day, respectively, and 158.4 ± 32.7 mg/dL and 48.2 ± 20.8 mg/dL in non-HD day, respectively. Two of them had hypoglycemic episodes in 48 h CGM data, and only 1 patient had hypoglycemic episode in the period from the end of HD to the next dietary intake (SGL < 40 mg/dL).

Table 1 Characteristics of enrolled patients

Male (%)	7 (100)
Age (years)	62.1 ± 13.3
Dry weight (kg)	69.6 ± 17.8
Duration of diabetes (years)*	19 (12–40)
HD duration (months)*	1 (0.5–30)
Glucose level of dialysate, 125/150 mg/dL	5/2
Red blood cell (/ μ L)	355.3 ± 72.3
Hemoglobin concentration (g/dL)	10.3 ± 1.8
Hematocrit (%)	32.6 ± 4.9
Albumin concentration (g/dL)	3.8 ± 1.0
HbA1c (%)	6.8 ± 2.1
Glycated albumin (%)	24.7 ± 10.2
Fasting glucose level (mg/dL)	123.6 ± 80.4
Fasting C-peptide (ng/mL)*	3.70 (0.14–10.80)
Dietary treatment (kcal/IBWkg)	30.9 ± 2.4
ESA dosage (U/week)*	8000 (0–12,000)
Diabetic treatment, N	
Insulin + OHA/Insulin + GLP-1A/OHA alone	4/1/2
Diabetic neuropathy, –/ +	0/7
Diabetic retinopathy, None/SDR/pre-PDR/PDR	2/0/0/5

Data are mean ± SD, unless otherwise indicated

HD hemodialysis, IBW ideal body weight, ESA erythropoiesis stimulating agents (200 U of epoetin = 1 μ g of novel erythropoiesis stimulating protein), OHA oral hypoglycemic agent, GLP-1A glucagon-like peptide-1 analog, SDR simple diabetic retinopathy, pre-PDR pre-proliferative diabetic retinopathy, PDR proliferative diabetic retinopathy

*Median (minimum–maximum)

Glucose profile and various hormone profiles in HD day and non-HD day

Plasma glucose profile and various hormone profiles in each HD day and non-HD day are shown in Fig. 1. On comparing plasma glucose on HD day, we observed postprandial glucose excursions at breakfast (from 100.9 ± 8.5 to 173.9 ± 21.8 mg/dL [mean ± SE], $p = 0.0223$) and lunch (from 142.4 ± 13.7 mg/dL to 196.7 ± 18.5 mg/dL [mean ± SE], $p = 0.0156$) but not at dinner (from 179.0 ± 19.6 to 178.0 ± 23.9 mg/dL [mean ± SE]). There is no significant glucose change during HD time, but glucose level tended to decrease. On non-HD day, plasma glucose level after breakfast was significantly higher than before breakfast (219.1 ± 40.5 mg/dL, 110.9 ± 22.0 mg/dL [mean ± SE], $p = 0.0313$) and plasma glucose level before lunch was significant lower than after breakfast and after lunch ($p = 0.0313$ and $p = 0.0313$). Furthermore, on comparing between on HD day and non-HD day there is no significant difference at each time point (Fig. 1A). On comparing CPR level, postprandial CPR level increased by taking breakfast (from 4.50 ± 1.31 ng/mL to 7.92 ± 1.80 ng/dL [mean ± SE], $p = 0.0156$) and lunch (from 3.09 ± 0.80 to 5.07 ± 1.24 ng/mL [mean ± SE], $p = 0.0156$) but not by taking dinner (from

7.68 ± 2.16 to 8.67 ± 2.38 ng/dL [mean ± SE]). During HD, CPR level at 2 h and 4 h after starting HD was significantly lower than at predialysis (from 7.92 ± 1.80 ng/mL to 4.53 ± 1.09 ng/dL [mean ± SE], $p = 0.0156$, to 3.09 ± 0.80 ng/dL [mean ± SE], $p = 0.0156$) and CPR level at 4 h after starting HD was significantly lower than at 2 h after starting HD ($p = 0.0156$). On non-HD day, serum CPR level significantly increased from before breakfast to after breakfast (from 3.47 ± 0.81 to 8.03 ± 2.26 ng/dL [mean ± SE], $p = 0.0313$) and from after lunch to before dinner (from 8.39 ± 2.31 to 12.97 ± 4.54 ng/dL [mean ± SE], $p = 0.0313$). On comparing between on HD day and non-HD day, CPR level before and after lunch on HD day was significantly lower than that on non-HD day ($p = 0.0156$, $p = 0.0156$, respectively) (Fig. 1B). In plasma glucagon profile, on HD day plasma glucagon levels at 2 h and 4 h after starting HD were significantly lower than at predialysis (from 19.09 ± 3.53 pg/mL to 10.06 ± 1.61 pg/dL [mean ± SE], $p = 0.0313$, to 11.71 ± 1.71 pg/dL [mean ± SE], $p = 0.0469$), but there was no difference between 2 h and 4 h after starting HD. Furthermore, there was no difference between before and after each meal (Fig. 1C). Plasma glucagon level before lunch on HD day was significantly lower than on non-HD day (11.71 ± 1.71 pg/dL vs 18.33 ± 3.27 pg/dL, $p = 0.0223$) (Fig. 1C). ACTH, cortisol, and GH profiles are shown in Fig. 1D, E, respectively. ACTH level before dinner was lower than after lunch ($p = 0.0469$) on before dinner non-HD day. ACTH level before dinner on HD day was higher than on non-HD day ($p = 0.0469$). Cortisol level at 2 h after starting HD significantly decreased than at predialysis ($p = 0.0469$). ACTH level after dinner on HD day was higher than after dinner on non-HD day ($p = 0.0156$). GH level before lunch on HD day was lower than before lunch on non-HD day ($p = 0.0469$).

Discussion

This is the first study in which a newly constructed and currently most accurate plasma glucagon assay system was used to clarify the hormonal profiles affected the blood glucose dynamics in HD patients, as well as to elucidate the relationship between HD-related hypoglycemia and the hormone kinetics by detailed blood glucose monitoring using CGM. In this study, we evaluated some endocrinological hormonal profiles contributing to the glucose dynamics in patients with type 2 diabetes undergoing HD. Although the number of patients with diabetes on HD has increased worldwide, HD-related glycemic variability and hormonal profiles in them remain unappreciated. This present study has revealed that HD-related glycemic disarrays are suggested not to depend on ACTH, cortisol, and GH but on endogenous insulin and glucagon.

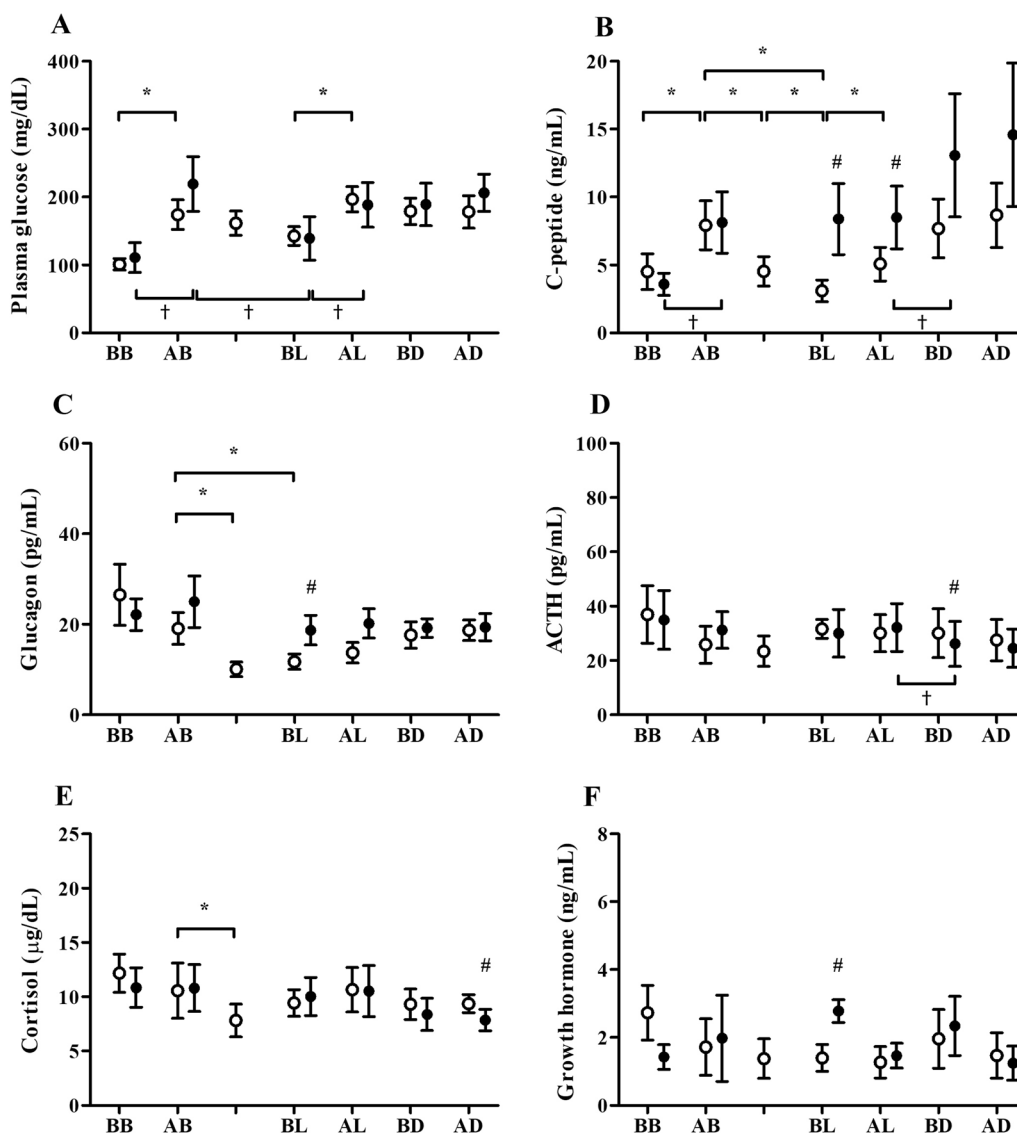


Fig. 1 The daily profiles of plasma glucose (A), serum C-peptide (B), plasma glucagon (C), ACTH (D), cortisol (E) and growth hormone (F) in 7 patients with type 2 diabetes undergoing hemodialysis on hemodialysis day (open circle) and non-hemodialysis day (filled circle). * $p < 0.05$ on hemodialysis day by Wilcoxon signed-rank test; † $p < 0.05$ on non-hemodialysis day by Wilcoxon signed-rank test; # $p < 0.05$ derived from the comparison between hemodialysis day and non-hemodialysis day

Previous studies showed that HD-related hypoglycemia was caused by glucose-free dialysate [26, 27]. Presence of dialysate glucose, containing 100–150 mg/dL glucose, is believed to prevent intradialytic hypoglycemia [28]. Theoretically, plasma glucose level during HD is determined from the concentration gradient on the blood side and the dialysate side, and never lower than the glucose concentration added to the dialysate. However, in clinical situation, plasma glucose levels fall below the dialysate glucose levels during and after HD session, and some patients complain

of hypoglycemic symptoms. Our previous study in diabetic patients undergoing HD showed that about 20% of them presented with hypoglycemia after HD and all of them revealed asymptomatic [29, 30]. The cause of this HD-related hypoglycemia has suggested abnormal response of insulin secretion and the reaction disorder of insulin-counter hormones such as glucagon, ACTH, and cortisol, but there was not sufficient evidence. In addition, until recently, it has been difficult to construct an accurate measurement system, especially for plasma glucagon, and it was difficult to determine how truly

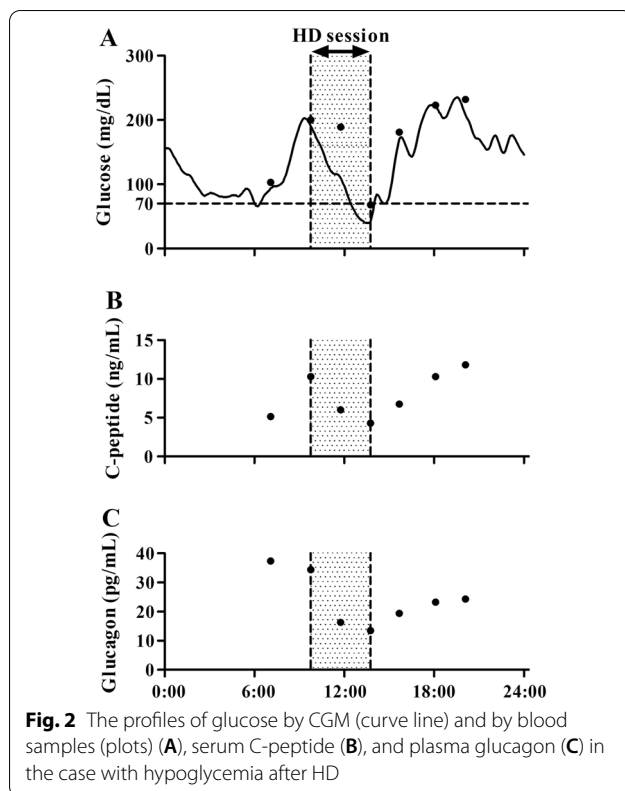
plasma glucagon affects the blood glucose profile in diabetic patients on HD.

During HD, CPR level and accurate measuring plasma glucagon level decrease but ACTH, cortisol, and GH levels did not change. As some previous studies showed [31–33], the lack of reciprocal elevation in plasma glucagon level relative to changes in plasma glucose and endogenous insulin concentration may suggest failing of the feedback system, related to the chronic low responsibility of insulin-counter hormones including plasma glucagon. In the glucose profiles in these patients, there was no significant glycemic daily variability in non-HD day, but there was a significant glycemic excursion before and after breakfast and before and after lunch (Fig. 1A). In addition, as reported in previous studies [29], blood glucose levels during HD gradually decreased from pre- to intermediate- and post-HD, although there was no significant difference in this study. Serum CPR reflected with insulin kinetics on HD day was significantly elevated from before to after breakfast and significantly decreased from pre- to intermediate-HD and from intermediate- to post-HD and significantly decreased before and after HD (Fig. 1B). This C-peptide kinetics suggests the removal of insulin and C-peptide by HD and a decrease in endogenous insulin secretion, negative feedback, due to the aforementioned hypoglycemia during HD. It may be able to be distinguished by conducting a glucagon load test and measuring CPR in dialysate [34]. However, glucagon kinetics tended to decrease from pre- to intermediate-HD and significantly decreased before and after HD. This is because, as mentioned above, under conditions where blood glucose tends to fall during HD, it was not the suppression of endogenous glucagon secretion but the removal of plasma glucagon by the dialysis membrane. In the daily variation of plasma glucagon on the HD day (Fig. 1C), it decreased significantly during HD. Furthermore, comparing the HD day and the non-HD day, plasma glucagon concentration before lunch, this point on HD day was after HD, was significantly lower on the HD day than the non-HD day. However, there are no fluctuations related to HD session or obvious differences between HD and non-HD days in the levels of ACTH, cortisol, and GH. Therefore, it was suggested that the dynamics of insulin/CPR and glucagon induced to the onset of HD-related hypoglycemia. That is, the blood glucose level tended to decrease during HD, insulin and CPR are removed and decreased during HD, and endogenous insulin secretion is also suppressed. On the other hand, it was suggested that plasma glucagon is also removed and decreases during HD, but it shows a low value after the end of HD, and plasma glucagon does not respond well to hypoglycemia, which causes blood glucose to further decrease in some cases. And although

insulin was secreted by dietary intake after HD, glucagon was also secreted, which is considered to be the cause of a glucose excursion due to dietary intake after HD. On the other hand, it has been reported that patients with diabetes on HD are prone to glycemic excursion, HD-related hyperglycemia, due to food intake after dialysis and that HD-associated hyperglycemia may be associated with an increase in glucagon levels in response to HD-induced hypoglycemia [35]. HD-associated hyperglycemia was not found in the present study, but this may be because the patients were treated with incretin modulators. The number of cases was reduced, but when the two groups were divided into two groups by whether incretin modulators were used ($N=4$) or not ($N=3$), the group treated with incretin modulators had a smaller decrease in blood glucose before and after HD, 14.0 ± 23.8 mg/dL [mean \pm SE], than the group not treated with incretin modulators, 54.7 ± 27.5 mg/dL [mean \pm SE], and a smaller glucose excursion by meal after HD (52.3 ± 40.3 mg/dL [mean \pm SE] vs 57.0 ± 15.1 mg/dL [mean \pm SE]). In addition, the changes in CPR and glucagon by meal after HD were 8.84 ± 2.53 ng/mL [mean \pm SE] and 0.73 ± 1.99 pg/mL [mean \pm SE], respectively, in the group treated with incretin modulators and 6.69 ± 2.92 ng/mL [mean \pm SE] and 3.77 ± 2.29 pg/mL [mean \pm SE], respectively, in the group without incretin modulators, and it was suggested that insulin secretion by food intake after HD may be stimulated and glucagon secretion may be suppressed in the group treated with incretin modulators.

In this study, hypoglycemia after HD was observed by CGM in 1 of 7 cases. In this case with hypoglycemia after HD, the glucose level at the end of HD was 68 mg/dL and SGL by CGM at the same time was 42 mg/dL (the lowest glucose level during HD was 40 mg/dL, which is lower limit of measurement) (Fig. 2A). CPR level gradually decreased during HD and increased by lunch intake after HD, but the increase in CPR level was not enough compared to the degree of increase in blood glucose (Fig. 2B). Glucagon level also decreased during HD, slightly increased after lunch after HD, and continued to increase (Fig. 2C). It is suggested that such fluctuations in insulin/C-peptide and glucagon contribute to HD-related hypoglycemia and glucose excursion due to dietary intake after HD. Previous several studies showed that incretin modulators, such as DPP-4 inhibitors and GLP-1 analogs, improve the HD-related hypoglycemia and glycemic variability in patients with diabetes undergoing HD [36–38]. Our result could prove that the efficacy of using incretin modulators which intervene in the glucagon secretion response may be expected to improve the specific hemodynamics of diabetic patients on HD.

The limitations of the present study are that the sample size was small and some patients were in the



introduction phase of HD. As previous studies suggest [39], glucose tolerance and insulin sensitivity may differ between patients on dialysis induction and those on chronic HD. Furthermore, this is an observation study using a univariate analysis without adjusting confounders and it may limit generalizability. Additionally, because this study included participants who had a short dialysis duration and had residual renal function, and it has been reported that plasma CPR was cleared by HD [40], their plasma CPR levels, measured as insulin secretion capacity, may be lower than those of anuric patients. In addition, we examined C-peptide, glucagon, ACTH, cortisol, and GH in this study, but other hormones involved in glucose hemodynamics, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), have not been investigated. A further investigation involving a larger sample size including GIP and GLP-1 should be taken to establish the overall effectiveness in the incretin modulators for type 2 diabetes patients on HD.

Conclusion

In patients with type 2 diabetes on HD, it was suggested that ACTH, cortisol, and GH were not involved in HD-related glycemic fluctuations, including HD-related

hypoglycemia, but that C-peptide and glucagon were involved.

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Author contributions

AH and MS designed this study. AH, KM, YO, NS, AS, SF, and MS collected the clinical information and blood sampling. AH, KT, and MS analyzed the data and drafted the manuscript. All authors revised the paper, and all authors approved the final version of the manuscript.

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

This study was registered with the UMIN Clinical Trial Registry (Registration Number UMIN000018707) and this study's protocols were approved by Kitasato University Medical School Ethics Committee (B14-72), and informed consent was obtained from all participants. All study methods were performed in accordance with the relevant guidelines and regulations of Kitasato University Hospital as well as the *Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan* and under the Code of Ethics of the Helsinki Declaration.

Consent for publication

Not applicable.

Competing interests

A.H. reports speaker honoraria from Medtronic, Abbott, Terumo, Roche; research grants from Abbott and Roche outside of the submitted work. N.S. reports speaker honoraria from Medtronic. The authors report no other potential conflicts of interest relevant to this article.

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