Original Article

Targeting Predialysis Glucose up to 180 mg/dl Reduces Glycemic Variability in End Stage Diabetic Nephropathy

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Abstract

Context: Glycemic variability plays a major role in the development as well as the progression of cardiovascular disease in diabetes. **Aims:** We compared the mean plasma glucose and glycemic variability (GV) parameters on and off hemodialysis (HD) in patients with End-Stage Diabetic Nephropathy (ESDN) and End-Stage Renal Disease (ESRD). **Settings and Design:** Cross-sectional study. **Methods and Material:** We included 23 ESDN and 6 ESRD patients who underwent continuous glucose monitoring (CGM) (iPro2) for 6 days and a glucose-free dialysate for 4 hours thrice weekly. EasyGV software was used to calculate the variability parameters {mean glucose, Time in range (TIR), Time above and below range (TAR/TBR), CV (Coefficient of Variation) and MAGE}. **Statistical Analysis Used:** The quantitative data variables were expressed by using mean and SD. Unpaired *t*-test was used to compare the two groups. *P* value <0.05 was considered significant. **Results:** In the ESDN group, TIR was significantly lower whereas TAR and TBR were significantly higher on HD day. MAGE (101.88 ± 40.5 v/s 89.46 ± 30.0, $P < 0.007$) and CV (29.41% v/s 21.67%) were higher on HD day. Subjects with pre-HD glucose values ≥180 mg/dl (Group B, n = 24) had a rapid drop with a delayed higher rise in glucose values than those with pre-HD glucose values <180 mg/dl (Group A, n = 27). Ten patients had 13 episodes of hypoglycemia. The CGM parameters were not different in the ESRD group. **Conclusions:** Targeting a pre- HD glucose value <180 mg/dl could be a good strategy to prevent larger fluctuation during and post HD.

Keywords: Continuous glucose monitoring system, end stage diabetic nephropathy, glycemic variability, hemodialysis, mean amplitude of glycemic excursion (MAGE), type 2 diabetes mellitus

Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the leading causes of end-stage renal disease (ESRD) accounting for nearly 50% of patients on hemodialysis (HD).[1-3] Glucose metabolism in patients with ESRD on HD is affected by a number of factors like insulin secretion and degradation, worsening of insulin resistance, change in drug metabolism, increase in inflammatory markers, protein catabolism, counter-regulatory hormonal surge, glucose-free/low glucose dialysate, glucose loss during dialysis, and decreased renal gluconeogenesis.[4] All these factors affect Glycemic variability (GV) also which is defined by both the frequency and amplitude of blood glucose oscillations around a mean value. Oxidative bursts as a result of high glycemic variability can cause widespread endothelial dysfunction and play a major role in the development as well as the progression of cardiovascular disease in diabetes.[5-8]

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.ijem_157_22

Both hyper and hypoglycemia are associated with higher mortality.[5,9] Currently, there is no consensus regarding optimum glycemic management on the day of hemodialysis. Many centers avoid or reduce the dose of insulin on the day of HD to minimize the risk of hypoglycemia. Patients may have intra-dialysis hypoglycemia followed by post-dialysis hyperglycemia which leads to an unpredictable pattern and a

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Submitted: 19-Apr-2022 **Revised:** 15-Jul-2022
Accepted: 26-Aug-2022 **Published:** 22-Nov-2022

How to cite this article: Shah N, Gada JV, Billa VS, Kothari JP, Bichu SD, Usulumarty DH, *et al.* Targeting predialysis glucose up to 180 mg/dl reduces glycemic variability in end stage diabetic nephropathy. Indian J Endocr Metab 2022;26:439-45.

huge patient-to-patient variation. Also, it is unknown whether pre-HD glucose values have any bearing on these fluctuations.

Although the Continuous Glucose Monitoring System (CGMS) is a valid tool to assess GV, its experience in patients with HD is limited.[10-12] Hence, we decided to study the glycemic patterns and variability in patients with T2DM with ESRD undergoing HD using CGMS which would provide us with useful insights for better glycemic management in these patients.

Our primary objective was to study and compare the mean plasma glucose and GV parameters in patients of ESRD on maintenance HD with type 2 DM on the day of HD and the day off HD. Our secondary objective was to study and compare the mean plasma glucose and GV parameters in patients of ESRD on HD with T2DM and those without T2DM as well as to study glycemic trends depending upon the pre-HD glucose values </>180 mg/dl.

Material and Methods

This was a cross-sectional study conducted by the Endocrinology services of a tertiary care center after the Institutional Ethics Committee approval (Ethics Committee for Academic Research Projects, PG academic Committee) (No. ECARP/2018/99). This study was also approved by the Ethics Committee of the dialysis center (LET/DM/EC/01). The study was conducted according to the World Medical Association Declaration of Helsinki.

Study population

The study recruited 35 patients (29 with T2DM and 6 without T2DM) from a single dialysis center from August 2018 to April 2019 after written informed consent. We recruited patients aged more than 18 years with/without diabetes and on regular HD for at least 3 months. We excluded patients with Type 1 diabetes, intercurrent acute illness, liver disease, pregnancy, and changes to medication regimen during the study period. Twenty-three patients in End Stage Diabetic Nephropathy (ESDN) group and 5 patients in End Stage Renal Disease (ESRD) group completed the study and were analyzed [Figure 1].

Hemodialysis

Each patient underwent HD for 4 hours alternate day (3/week) in 3 different shifts: morning, afternoon and evening. During HD, the blood flow rate was 300 ml/min and a dialysate flow rate of 500 mL/min. HD was carried out with 17 M middle flux dialyzers using polysulphone membranes (NIPRO). The glucose free dialysate contained 138 mM Na, 2.20 mM K, 1.5 mMCa, 0.5mM Mg, 109 mM Cl, 4.5 mM CH_3OO and 35 mM HCO_3.

CGM procedures and glycemic variability measurement

Continuous glucose monitoring with the iPro2 CGM (Model REF-MMT 7102 W, Medtronic MiniMed, USA)

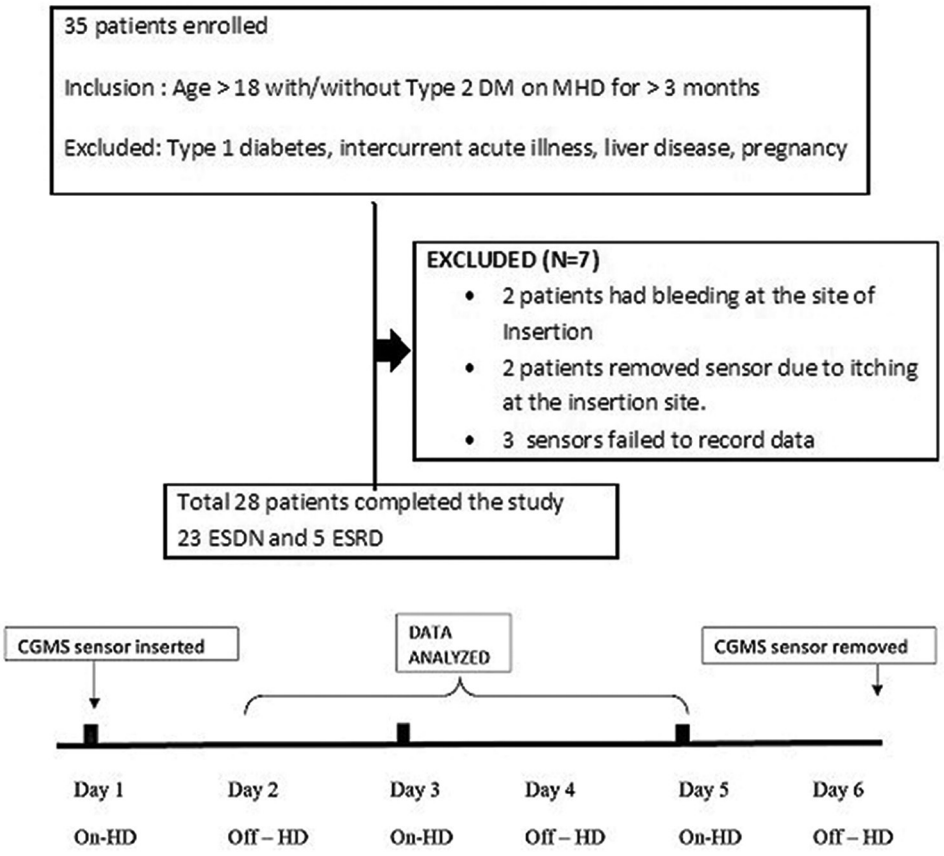

Figure 1: Methodology and chronology of blood glucose monitoring using a CGMS in this study

was initiated for 6 days. A glucose sensor was inserted subcutaneously over the abdomen at least 1 hour prior to the HD and stayed for 6 days and including all the HD sessions during that period. We defined the first 24 hours from the start of HD as 'Day on HD' and the next 24 hours as "Day off HD." The 24 hours following the first hemodialysis were excluded [Figure 1] The instrument was calibrated by four capillary glucose values obtained on a glucometer (Freestyle OptiumXceed) prior to three major meals and at bedtime. Blood glucose meters and test strips were provided to the patients. Patients were instructed to be consistent with their meal timings, pattern, and to maintain a food diary which was analyzed by a registered dietician. Total calorie intake was calculated and compared for on and off HD days. As per the dialysis center protocol, patients on insulin skipped their pre-HD dose and continued the other doses of the day. No changes in any medications were made during the study period.

CGM data was downloaded with the CareLink Ipro1 software (MMT-7340) (Medtronic, Minneapolis, MN, USA) and this data was used to calculate the variability parameters by an automated Software EasyGV version 9.0. R2. Glycemic variability was defined as intraday glycemic excursions, including episodes of hyperglycemia and hypoglycemia. The following variables were calculated from CGM readings for each patient: Time In Range (TIR), Time Above Range (TAR) and Time Below Range (TBR), Mean glucose, Standard deviation (SD), Coefficient of Variation (CV), Mean Amplitude of Glycemic excursion (MAGE).[13-15]

Sample size and statistical analysis

The sample size of our study was calculated based on the study by Y Jin *et al.*[15] by comparison of mean and SD method for the paired data (on and off HD days) at 80% power and 95% confidence interval with 5% alpha error. The minimum sample size was 5 patients per group.

The data analysis was done by using SPSS (Statistical Package for Social Sciences) version 25:0. The qualitative data variables were expressed by using frequency and percentage (%). The quantitative data variables were expressed by using mean and SD. Unpaired *t*-test was used to compare the two groups. *P* value <0.05 was considered as significant.

Results

Baseline characteristics

A total of 23 patients in ESDN group and 5 patients in ESRD group completed the study. The patients had an average age of 63.17 ± 10.24 years in ESDN group and 61.6 ± 9.94 years in the ESRD group. The average duration of diabetes in the ESDN group was 17.4 ± 6.1 years and the mean HbA1c was 7.39 ± 1.64%. The average duration of patient on HD was 3.68 ± 3.39 years in ESDN group and 4.5 ± 6.44 years in the ESRD group. Five out of 23 in the ESDN group required treatment for diabetes (3 patients were on insulin and 2 were on Linagliptin. The total energy intake, determined from the patient's diaries, for each patient was similar on HD and Off HD days (1610 ± 218 kCal in the HD vs. 1692 ± 225 kCal in the day off, $P = 0.171$). Some patients had a late removal of the CGM sensor, a total of 61 HD days (51 ESDN + 10 ESRD) and 69 off HD days (58 ESDN + 11 ESRD) were analyzed.

Comparison of CGM parameters on HD day and off HD day

In the ESDN group, TIR was significantly lower (41.30 v/s 66.1, $P = 0.002$) whereas TAR (>180) {38.10 v/s 26.7, $P = 0.039$} and TBR (<70) {1.2 v/s 0.00, $P = 0.02$} were significantly higher on HD day as compared to off HD day [Table 1]. Although, the mean glucose was similar (Group mean, 180.54 ± 53.1 vs. 181.08 ± 39.24, $P = 0.9$), the MAGE and CV were higher on HD day compared to off HD day. (Group MAGE = 101.88 ± 40.5 v/s 89.46 ± 30.0 with $P < 0.007$, CV = 29.41% v/s 21.67%, Table 1, Figure 2a and b). Our data suggests that patients in the ESDN group had larger glycemic variability on HD days.

In the ESRD group, TIR, Mean glucose and CV were similar on and off HD day. MAGE was higher (43.11 ± 13.44 vs. 39.61 ± 12.40*$P = 0.680$) on the day of HD as compared to off HD day but did not reach statistical significance.

Table 1: CGM parameters of ESDN & ESRD group

	ESDN Group			ESRD Group		
	On HD	Off HD	*P*	On HD	Off HD	*P*
TBR (%) < 54 mg/dl	0.07	0.00	0.317	0.00	0.00	_
TBR (%) < 70 mg/dl	1.20	0.00	0.02*	0.00	0.00	_
TIR TARGET (%) 71-180 mg/dl	41.30	66.12	0.002*	99.44	97.93	0.880
TAR (%) > 180 mg/dl	38.10	26.70	0.039*	0.56	2.07	0.881
TAR (%) > 250 mg/dl	19.77	6.74	0.118	0.00	0.00	_
MEAN mg/dl	180.54±53.1	181.08±39.24	0.9	117.59±10.73	123.05±8.95	0.408
SD mg/dl	50.22±21.06	46.98±17.64	0.98	18.9±3.96	18.36±3.42	0.813
CV %	29.41	21.67	_	9.12	7.27	_
MAGE	101.88±40.5	89.46±30.0	0.007*	43.11±13.44	39.61±12.40	0.680

ESRD=End-Stage Renal Disease, GV=Glycemic Variability, ESDN=End Stage Diabetic Nephropathy, CGM=Continuous Glucose Monitoring System, TIR=Time in Range, TAR=Time above Range, TBR=Time Below Range, MAGE=Mean Amplitude of Glycemic Excursion, SD=Standard deviation, CV=Coefficient of Variation. **P* significant

The glycemic pattern on HD and off HD in the ESDN group and ESRD group

The 12-hour glucose pattern (4 hours pre-post and during HD) of 23 diabetes patients on HD days and off HD days is shown in Figure 3a. The mean glucose of all the patients showed a decreasing trend after the start of HD followed by a rising trend post HD when compared to the time matched value off HD day. Of interest, the mean glucose level reached a nadir of 152 mg/dl at 145 minutes after the start of HD and a peak of 224 mg/dl was seen at 475 minutes.

ESRD group also showed a reducing trend of glucose since the start of HD followed by a post HD rise but to a lesser degree of fluctuation as compared to the ESDN group.

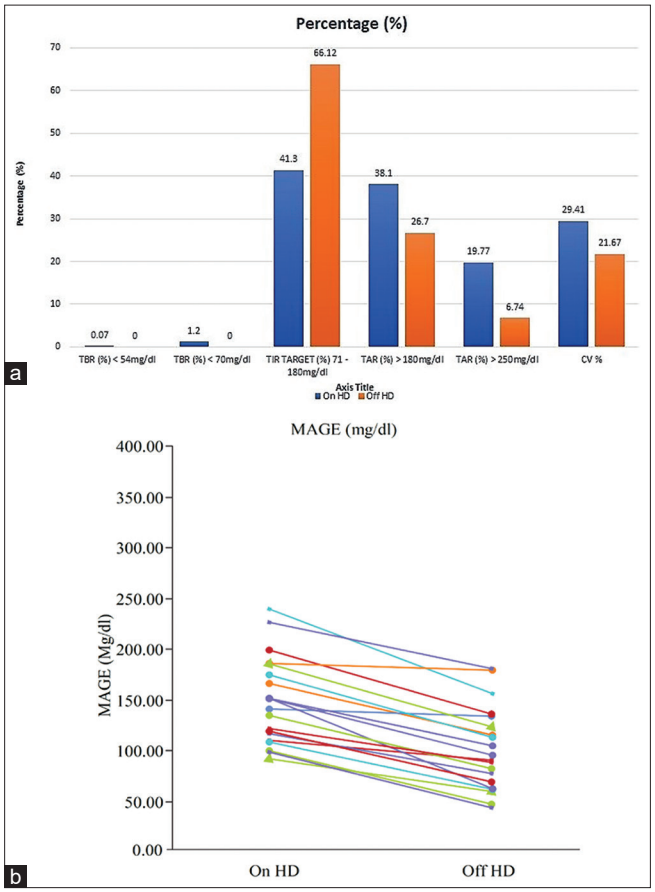

Figure 2: (a) Mean glucose of each patient on HD and off HD day (Group mean, 180.54 ± 53.1 vs. 181.08 ± 39.24*P = 0.9). (b) Mage of each patient on HD and off HD day (Group MAGE, 101.88 ± 40.5 and 89.46 ± 30.0, respectively, with $P < 0.007$*)

Comparison of glycemic pattern as per pre-HD glucose values in ESDN Group

We analyzed the glycemic patterns in the ESDN group depending on the pre-HD glucose values on the HD day. Fifty-one HD sessions in ESDN group were categorized into 2 groups based on the pre-HD glucose values: Group A (<180 mg/dl) (n = 27) and Group B (≥180 mg/dl) (n = 24). The mean pre-HD values in groups A and B were 151.5 and 226.1 mg/dl, respectively. These values were taken as time point "0." We calculated the delta/difference of this pre-HD mean glucose values on HD days with the values available every 5 minutes for 12 hours from the CGM to get a trend analysis.

The group A which started at a mean value of 151.5mg/dl had a nadir value of 123.6 mg/dl (Delta = −27.9 mg/dl) at 160 minutes followed by a peak value of 192.3 mg/dl (Delta = +40.8 mg/dl) at 380 minutes. The group B which started at a mean value of 226.1 mg/dl had a nadir value of 131.2 (Delta = −94.9mg/dl) at 115 minutes followed by the peak value of 274.4 mg/dl (Delta = +46 mg/dl) at 575 minutes. This suggests that group B had a rapid drop in glucose with a later and higher rise compared to group A [Figure 3b]. Seven of the total 13 hypoglycemic episodes occurred in Group A and the remaining six episodes occurred in group B.

Hypoglycemia

A total of 13 episodes of hypoglycemia were recorded in 10 patients [Table 2]. All episodes occurred on the HD day. Seven out of total 13 episodes occurred during four hours of HD and the remaining six episodes occurred post HD. All except one episode were asymptomatic. During the 6-day study period, 10 patients (43%) in the ESDN group had at least one value of glucose ≤70mg/dl but more than 54 mg/dl. Three patients had episodes of hypoglycemia twice. Two patients had one episode each of glucose value ≤54 mg/dl defined as clinically important hypoglycemia. Figure 4 shows

Table 2: Duration and severity of no. of episodes hypoglycemia of 10 patients

Patient no	No. of episodes	Time duration (mins)	Lowest glucose value	≤70 mg/dl (43%)	≤54 mg/dl (9%)	≤40 mg/dl (3%)
Patient 1	2	15 and 20	67/65	2	0	0
Patient 2	2	35 and 30	67/65	2	0	0
Patient 3	1	5	65	1	0	0
Patient 4	1	55	55	1	0	0
Patient 5	1	30	65	1	0	0
Patient 6	1	25	61	1	0	0
Patient 7	1	35	59	1	0	0
Patient 8	2	45 and 20	58/67	2	0	0
Patient 9	1	140	40	0	0	1
Patient 10	1	25	52	0	1	0
Total	13			11	1	1

the duration (width) and the severity (height) of hypoglycemia episodes of these 10 patients [Figure 4].

Discussion

There is a direct relationship between glycemic control and mortality in ESRD patients on HD.[16] The recommended Hba1c goal for patients with ESDN is 7–8%.[17] However, glycemic variability with the highs and lows in plasma glucose plays an important role in morbidity and mortality irrespective of Hba1c control.[5] We included 23 patients with ESDN with a mean HbA1cof 7.39 ± 1.64% and observed that the mean glucose value was similar but the MAGE was significantly higher on the HD day than the off HD day. The findings of higher MAGE were consistent with other studies in the literature,[15,18] but the results of mean glucose were discrepant. There were some studies[15,19,20] that found higher mean glucose during off HD days while a study done by Mirani *et al.*[18] found a higher mean on HD days. However, some researchers[20] also found no difference in the mean glucose on and off HD days which was similar to our findings. This disparity could be due to the differences in the number of days the sensor was used, type of sensor and dialysis related factors.

The current CGM recommendations[13] for the high-risk group suggests target of >50% for TIR, <10% for TAR >250 mg/dl, and <1% for TBR. The TIR was significantly lower while the TAR was significantly higher on the HD day than off HD day. These results signify poor glycemic control on the HD day compared to the off HD day.

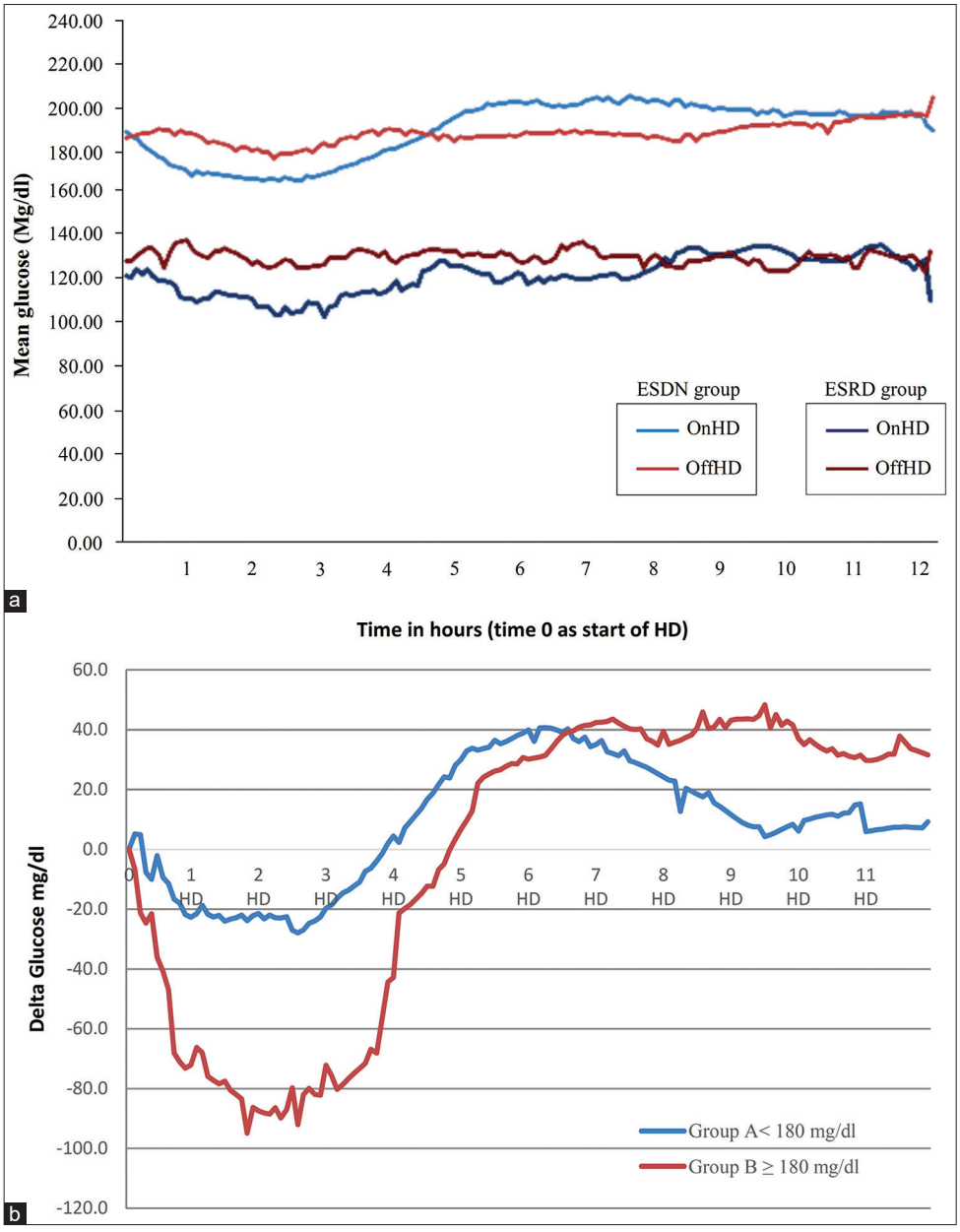

Figure 3: (a) The12 hour glucose pattern (4 hours pre, 4 hours post and during HD) in ESDN and ESRD group. (b) Comparison of Glycemic Pattern on HD between Group A and Group B

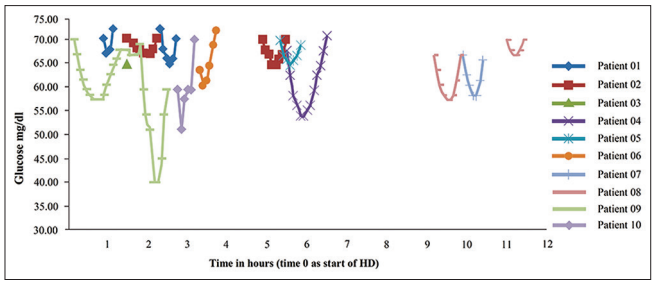

Figure 4: Duration (width) and severity (height) of hypoglycemia episodes of 10 patients

The ESRD group also has had similar mean glucose on and off HD days with a higher but non-significant CV and MAGE indicating a lesser fluctuation despite a similar trend of glucose values compared to the ESDN group.

We also found a clear trend of hemodialysis induced drop in the glucose levels followed by post dialysis rise in glucose on the day of HD as compared to the day off HD in both the ESDN and ESRD groups. This has been previously reported in the literature.[21] Hemodialysis induced hypoglycemia is due to diffusion of plasma glucose across the concentration gradient from the blood to the dialysate due to its low molecular weight and possibly because of diffusion of plasma glucose into erythrocytes with changes in the cytoplasmic pH of erythrocytes due to accelerated anaerobic metabolism and increased glucose consumption.[4] The routine practice across India is to use glucose free dialysate due to the cost, storage considerations, and convenience. This may be associated with an increased likelihood of hemodialysis-induced hypoglycemia. Post HD hyperglycemia is due to the counter regulatory hormone response, the postprandial state, and a decrease in plasma insulin level due to reduced endogenous insulin secretion in response to the decrease in plasma glucose level together with adsorption of insulin by the dialyzer.[4]

The pre-HD glycemic trends of Group B (≥180 mg/dl) as compared to Group A (<180 mg/dl) showed a rapid and a greater intradialytic decrease in the blood glucose level followed by a later and a higher glucose surge in the immediate post HD period [Figure 3b]. This indicates that poor control at the start of HD may have a role in the larger fluctuations in glucose levels on the day of HD. Thus, in Group B, optimizing the pre-HD treatment to get the glucose levels <180 mg/dl range could to be a useful strategy in preventing the huge fluctuations in glucose values.

Our study showed that on the dialysis day in the ESDN group, 43% of patients recorded glucose values <70 mg/dl and 9% recorded <54 mg/dl. Many of the episodes were asymptomatic making them difficult to detect unless monitored intensively. Frequent recurrence of hypoglycemia episodes, despite their asymptomatic nature, might increase the risk of progressive cognitive impairment in patients with diabetes.[22-24] Other studies have shown varying incidences of hypoglycemia ranging from 2% to 16%.[15,20,25] This is due to the differences in definitions of hypoglycemia in terms of value and time[20] sensor type[25] dialysate fluid glucose and diabetes medications are used. Our results suggest that all hypoglycemia episodes were on HD day. However, a study by Chantrel *et al.*[25] showed hypoglycemia on both HD and off HD days with a higher incidence on HD days. This difference probably could be attributed to the fewer patients on insulin in our study compared to their study.

Conclusion

CGMS could be a very useful tool in understanding and managing diabetes in this high-risk group with CKD. The mean glucose decreases after the start of HD followed by a rising trend post HD in patients of ESDN. Targeting a pre-HD glucose value of less than 180 mg/dl could be a good strategy to prevent larger fluctuation during and post HD.

Key messages

The mean glucose decreases after the start of HD followed by a rising trend post HD in patients of End Stage Diabetic Nephropathy (ESDN). Targeting pre-HD glucose of <180 mg/dl at the start of HD could prevent larger peri-HD fluctuations and reduce the glycemic variability.

Financial support and sponsorship

Endocrinology Department Development Fund.

Conflicts of interest

There are no conflicts of interest.

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