Brief Communication

Flash Glucose Monitoring in Subjects with Diabetes on Hemodialysis: A Pilot Study

Rajesh S. Javherani, Vedavati B. Purandare[1], Anjali A. Bhatt[1], Suganthi S. Kumaran[1], Mehmood G. Sayyad[2], Ambika G. Unnikrishnan[1]

Departments of Clinical Nephrology and Critical Care, [1]Clinical Diabetology and Endocrinology and [2]Biostatistics, Chellaram Diabetes Institute, Pune, Maharashtra, India

Abstract

Background: In patients with diabetes related end-stage renal disease (ESRD) on hemodialysis, blood glucose management can be challenging due to the kinetics of glucose and insulin in addition to other factors. The glucose monitoring systems which measure glucose levels continuously may be useful to study the glucose profile of patients with diabetes undergoing hemodialysis. Our study is designed to use ambulatory glucose profile to study the glucose pattern – during, before, and after a session of hemodialysis. **Materials and Methods:** Ten patients with type 2 diabetes with ESRD undergoing hemodialysis were recruited. Forty-eight glucose readings were recorded in a 12-h period which included 4 h each prior, during, and after the dialysis session with a flash glucose monitor (FreeStyle Libre-pro). The same 12 h time frame was also monitored on a non-dialysis day. **Results:** On the day of dialysis, the mean glucose level was significantly lower ($P = 0.013$) compared to the day without dialysis (95 ± 12.7 mg/dl vs 194 ± 76.8 mg/dl). As compared to the pre-dialysis period, the mean blood glucose levels during dialysis were lower ($P = 0.004$). As compared to the dialysis period, the mean blood glucose levels in the post-dialysis period were higher but did not reach statistical significance. **Conclusion:** In our study, subjects with type 2 diabetes on hemodialysis had lower glucose levels on the day of dialysis compared to non-dialysis day. Glucose levels showed a fall during hemodialysis and then a rise to higher levels after dialysis.

Keywords: Ambulatory glucose profile, end-stage renal disease, glycemic variability, hypoglycemia

Introduction

Diabetic kidney disease is the leading cause of end-stage renal disease (ESRD). Published studies have reported the incidence of ESRD attributable to diabetes from 24% to 51%.[1] Tight blood glucose control is not recommended in subjects with diabetes and ESRD as they are at risk of hypoglycemia due to diminished renal gluconeogenesis, impaired renal insulin degradation, and poor intake.

Particularly, there is an increased risk of hypoglycemia in subjects with ESRD and diabetes who undergo hemodialysis. One of the reasons for hypoglycemia during hemodialysis is the loss of glucose across the dialyzer membrane. Continuous glucose monitoring (CGM), though not routinely recommended could be an excellent tool to assess glycemic patterns especially during the period of hemodialysis.

We report a study to document glycemic patterns in subjects with type 2 diabetes mellitus and ESRD undergoing hemodialysis.

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Research Design and Methods

The study was approved by the Institution's Ethics Committee and all patients provided written informed consent. In this pilot study, we recruited 10 patients with type 2 diabetes mellitus and ESRD undergoing maintenance hemodialysis in the Department of Nephrology and Critical Care. The glucose profile on the dialysis day was compared to the same time on the non-dialysis day with the aid of the Flash Glucose Monitoring system (FreeStyle Libre-pro).[2]

This is a retrospective type of glucose monitoring system which measures the interstitial glucose every 15 min. As the study was conducted in a masked manner, the glucose values were less likely to be modified by deliberate changes in diet, exercise, or

Address for correspondence: Dr. Ambika G. Unnikrishnan, Chellaram Diabetes Institute, Bavdhan Budruk, Pune, Maharashtra - 411 021, India.
E-mail: ceo@cdi.org.in

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medication adherence by the patients which can occur during real-time monitoring. Also, no changes in the management of glucose control were done during the study based on the CGM readings by the physician. The data are stored in the sensor and can be downloaded by flashing a reader over the sensor at a later date. The measurements are referred to as ambulatory glucose profile (AGP).

The glucose profile of the first dialysis day following the application of the sensor was compared with the glucose profile of the consecutive non-dialysis day. Typically, patients underwent dialysis in the morning time at around 10 AM and the duration of dialysis lasted for 4 h. On the day of the dialysis patients who were on insulin were asked to skip their pre-breakfast insulin dose. All the patients had a snack during dialysis as per the protocols by the dietician. The 12-h period, during which the glucose values were studied, included 4 h before and after dialysis and 4 h of dialysis time. The same 12 h time frame of the day was studied on the non-dialysis day, and a comparison was done using the statistical analysis. Patients received their usual dose of insulin and/or oral antidiabetic drug (OAD) on the non-dialysis day.

The statistical analysis included the mean glucose ± SD level across all values on the day with dialysis compared to the day off dialysis, and the area under the curve (AUC) of glucose across the 12 h on the day with dialysis compared to the day without dialysis.

Analysis and Results

The patients had an average age of 60.4 ± 10.5 years and 7 out of 10 were males. All subjects had long-standing diabetes, the average duration being 16.6 ± 4.8 years. Only 50% patients were on medications for treatment of type 2 diabetes mellitus. The mean HbA1C was 6.6 ± 0.7%.

Table 1 shows the comparison of AGP data according to the day with or without dialysis session. A total of 96 glucose readings were analyzed for each patient. During the dialysis the mean glucose level was lower at 95 ± 12.7 mg/dl, which is statistically significant in comparison to the same period on non-dialysis day (194.1 ± 76.8 mg/dl) $P < 0.05$. Even the mean value of glucose levels during the 4 h before the start of dialysis was lower (127.8 ± 50.8 mg/dl) on the dialysis day in comparison to the same time frame on non-dialysis day (165.5 ± 61.9 mg/dl). This was statistically significant. (P value = 0.05).

The mean glucose levels in the immediate post-dialysis period rose significantly ($P < 0.05$) from a mean of 95 mg/dl during the dialysis to 151.8 ± 52.1 mg/dl. But, this value is not significantly different from the value of 186.1 ± 77.8 mg/dl during the same time period on non-dialysis day (P value = 0.226).

On the dialysis day, 9 out of 10 subjects had recorded at least one value of glucose reading ≤70 mg/dl and 4 out of 10 subjects recorded <55 mg/dl. However, none of these patients had symptoms of hypoglycemia. On non-dialysis day, one subject had at least one glucose reading <70 mg/dl.

Similar to mean glucose values, the AUC of glucose values during dialysis indicated statistically significant fall in comparison to non-dialysis days ($P = 0.001$). The AUC glucose 4 h before dialysis when compared with the same time period on the non-dialysis day did not indicate significant difference ($P = 0.166$). A detailed comparison of mean glucose values and AUCs during the specified time frame on dialysis and non-dialysis day is shown in Table 1. Overall, the mean glucose and the entire 12-h glucose measurements (measured as AUC) were lower on the dialysis day compared to the off dialysis day [$P < 0.05$; Table 1].

On the day of dialysis, the glucose levels fell from a pre-dialysis mean value of 125.7 ± 44.5 mg/dl to an intra-dialysis mean value of 96.2 ± 26.8 mg/dl within 30 min and remained fairly constant throughout the dialysis only to rise later to a post-dialysis mean value of 151.8 ± 52.1 mg/dl.

The time-matched values, when compared between the days on and off dialysis showed uniformly lower glucose values on dialysis days [Table 2 and Figures 1 and 2].

Discussion

To our knowledge, this pilot study is the first AGP-based evaluation on subjects with diabetes and kidney disease undergoing chronic hemodialysis.

Glucose, as a molecule, weighs around 180 Da, and does not bind to plasma proteins. It can readily cross the dialysis filter and could lead to positive or negative glucose balance depending on concentration gradient across the membrane. Presently, dialysate solutions do not contain glucose and thereby cause loss of blood glucose in the dialysis effluent.[3]

In view of other coexisting factors such as poor food intake, reduced renal gluconeogenesis, and reduced insulin excretion,

Table 1: Comparison of data in type 2 diabetes patients on chronic hemodialysis according to the day with or without dialysis session

Parameter	Day with dialysis session ($n=10$)		Day without dialysis session ($n=10$)		P
	Mean	SD	Mean	SD	
Glucose readings (mg/dl)					
4-h before	127.8	50.8	165.5	61.9	0.050*
During dialysis	95.0	12.7	194.1	76.8	0.004**
4-h after	151.8§§	52.1	186.1	77.8	0.226NS
Whole 12 h	115.7	25.6	179.5	69.9	0.013*
AUC glucose (mg/dl × 12 h)					
4-h before	2049.9	840.5	2642.7	990.3	0.166NS
During dialysis	1505.6	211.6	3110.9	1235.6	0.001***
4-h after	2453.1§	851.0	2972.3	1248.2	0.291NS
Whole 12 h	6008.6	1507.4	8725.9	3046.5	0.021*

$P \leq 0.05$ is considered to be statistically significant. *$P<0.05$, **$P<0.01$, ***$P<0.001$, NS:Statistically non-significant. AUC:Area under the curve, §Intra-day P (during dialysis vs. after dialysis) (§$P<0.05$, §§$P<0.01$)

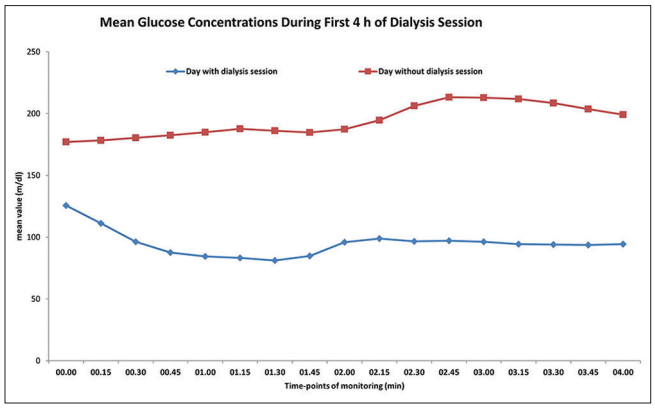

Figure 1: The time-matched values, when compared between the days on and off dialysis showed uniformly lower glucose values on dialysis days

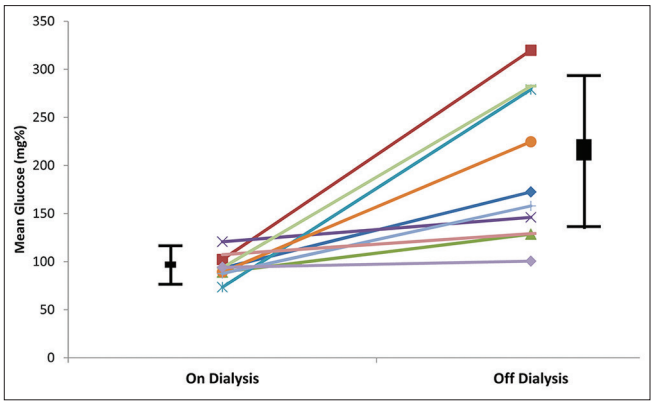

Figure 2: Shows the individual mean glucose on dialysis days vs the mean glucose on the non-dialysis days. Each subject had a total of 96 readings. The result indicates that 9 of the 10 subjects had a rise in both the mean glucose as well as mean area under the curve of glucose on the off dialysis days, based on the total number of readings (n = 960)

Table 2: Comparison of mean glucose concentrations in the 4 h of dialysis session with corresponding time of the consecutive day without dialysis

Time-points of monitoring	Glucose values (mg/dl)				*P*
	Day with dialysis (n=10)		Day without dialysis (n=10)		
Time (min)	Mean	SD	Mean	SD	
00	125.7	44.5	177.0	70.8	0.011*
15	111.2	34.7	178.3	69.7	0.003**
30	96.2	26.8	180.3	66.4	0.001***
45	87.6	22.1	182.5	64.7	0.001***
60	84.4	21.2	184.9	68.9	0.002**
75	83.3	25.8	187.7	69.2	0.003**
90	81.2	23.4	186.2	70.0	0.003**
105	84.8	26.8	184.8	75.2	0.006**
120	96.0	33.7	187.3	82.9	0.018*
135	98.9	29.2	194.6	88.7	0.018*
150	96.7	23.7	206.3	92.6	0.010**
165	97.1	25.9	213.2	96.5	0.009**
180	96.2	28.5	212.8	97.3	0.011*
195	94.3	29.3	211.8	93.9	0.009**
210	94.0	32.3	208.5	91.3	0.010**
225	93.7	36.2	203.7	91.7	0.013*
240	94.3	40.2	199.1	89.7	0.016*

$P \leq 0.05$ is considered to be statistically significant, *P<0.05, **P<0.01, ***P<0.001

these patients are at an additional risk of hypoglycemia. Our study showed that on the dialysis day 9 out of 10 subjects recorded at least one glucose reading ≤70 mg/dl and 4 out of 10 subjects recorded values <55 mg/dl. All hypoglycemic episodes were asymptomatic making them more dangerous and difficult to detect unless monitored intensively. It is well known that hypoglycemia is a risk factor for cardiovascular events like stroke and that controlling hyperglycemia may protect from retinopathy and neuropathy even in subjects with diabetes related ESRD.

Interestingly, subjects on the morning of dialysis day had a lower fasting glucose, when compared with the day without dialysis. The reason could be that the patients may have travelled long distance without adequate calorie intake and may have been relatively more active during their visit to the hospital for dialysis. Low glucose on the day of dialysis may also have led to counter regulatory hormone release and a higher glucose values on the (subsequent) day off dialysis. This has been described in a previous study, which has shown that hypoglycemia on the dialysis day may even be followed by higher glucose levels later on.[3]

Also, insulin is said to be removed from blood and filtered during dialysis, especially when high flux dialyzers are used, and while this does not alleviate intra-dialysis hypoglycemia, this can have an effect on the post-dialysis period causing relative post-dialysis hyperglycemia.[4,5] These factors may have elevated glucose readings on the morning of the day off dialysis, returning to baseline by the day on dialysis.

Asymptomatic hypoglycemia seen in our study suggests an important role of real-time CGM in such patients. However, there is a lack of guidance on use of intensive monitoring devices in patients with uremia especially on hemodialysis.

Our study has a few limitations: firstly, the sample size was small (n = 10). Secondly, just wearing the sensor (though masked) might have influenced the life style. Thirdly, since the recordings were masked, the health care team could not identify the ways to provide any therapeutic management pertinent to the recordings. Finally, the limitation of AGP as a monitoring tool, especially in patients with uremia is to be considered, as it can over-diagnose both hypoglycemia and hyperglycemia, making it a suboptimal tool during rapid glucose fluxes.[6]

Nevertheless, our study does re-emphasize that it is important to detect asymptomatic intra-dialysis hypoglycemia in subjects with diabetes by intensive monitoring. Using glucose-based dialysate fluid, giving a snack prior to dialysis, and reducing pre-dialysis anti-diabetes medications are proposed strategies to counter this.[7] The latter two measures were already being

carried out in these patients, despite which the fluctuations occurred, suggesting the need for both stricter implementation and further research on solutions.

Conclusion

These glycemic fluctuations need to be considered in the management of subjects with diabetes related end stage renal disease ,undergoing hemodialysis.

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Conflicts of interest

There are no conflicts of interest.

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