



## STUDY OF HYPOGLYCEMIA IN PATIENTS ON MAINTENANCE HEMODIALYSIS

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### ABSTRACT

The dialysate glucose concentration was as high as 1800 mg/dL. At that time, osmotic ultrafiltration (with sodium and glucose being the major osmoles) was the major mode of volume removal.<sup>1,2</sup> Over time, ultrafiltration by hydrostatic pressure was found to be superior to osmotic ultrafiltration and the concentration of glucose in dialysate was drastically decreased. Subsequently, it became less clear what the ideal concentration of glucose should be in the dialysate. Many units switched to a glucose-free dialysate. The study was done in maintenance hemodialysis unit of Gandhi Hospital, Secunderabad over a period of one year from December 2013-December 2014. 50 patients were chosen by random sampling, 25 of them were diabetics and 25 non-diabetics.

Hypoglycemia is not uncommon (26%) in CKD V patients on maintenance hemodialysis, both in diabetics and nondiabetics. Incidence of hypoglycemia is more in diabetics than in nondiabetics, both with glucose-free hemodialysis solution and glucose-added hemodialysis solution. There was a decrease in the occurrence of hypoglycemia when glucose-added hemodialysis solution is used, both in diabetics and nondiabetics. Asymptomatic hypoglycemia is very common, both in diabetics and nondiabetics.

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### INTRODUCTION

The use of glucose in dialysate has played different roles over the course of time. Early in the history of hemodialysis, the use of glucose in dialysate was important for effective osmotic ultrafiltration.

In the 1960s, the dialysate glucose concentration was as high as 1800 mg/dL. At that time, osmotic ultrafiltration (with sodium and glucose being the major osmoles) was the major mode of volume removal.<sup>1,2</sup> Over time, ultrafiltration by hydrostatic pressure was found to be superior to osmotic ultrafiltration and the concentration of glucose in dialysate was drastically decreased. Subsequently, it became less clear what the ideal concentration of glucose should be in the dialysate. Many units switched to a glucose-free dialysate.

In 1978, Wathen *et al.* demonstrated a statistically significant drop in glucose concentration with the glucose-free dialysate, while with the glucose-containing dialysate the glucose concentration remained stable.<sup>3</sup> Several other studies have confirmed a small fall in glucose concentration with either stable or lower insulin concentration with the glucose-free dialysate.<sup>4,5</sup>

In reviewing the metabolic effects associated with glucose-free dialysate, it is clear that the patient enters into a catabolic state, similar to a fasting state. The decrease in serum glucose concentration is not as high as would be expected by the amount of glucose loss in the dialysate. Therefore, the fall in glucose concentration is counteracted by endogenous glucose production from gluconeogenesis and glycogenolysis. While many patients are able to tolerate this state, the more debilitated/malnourished patients will not have the reserve to respond and therefore placing them at risk for hypoglycemia. The diabetic patient would also be at particular risk for hypoglycemia especially if they are taking long-acting insulins or oral hypoglycemic agents. Thus, an argument could be made for a standard physiological concentration of glucose in the dialysate to minimize these metabolic effects. A dialysate containing 100 mg/dL is FDA approved and currently commercially available in the United States. However, while many studies have been done comparing 200 mg/dL glucose dialysate vs. glucose-free dialysate, various studies have been performed comparing this more physiologic glucose dialysate (i.e., 100mg/dL) to other glucose concentrations. Clearly, the first question is whether a switch to a lower glucose bath is safe (especially in diabetic patients).

#### Aim of the study

1. To study the incidence of hypoglycemia in diabetic and non-diabetic CKD patients on maintenance hemodialysis.

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- To study the incidence of symptomatic and asymptomatic hypoglycemic episodes in patients on maintenance hemodialysis.
- To evaluate the repercussions of a HD session on glycaemia at different times in two groups of patients--DM and non-diabetics--using dialysis solutions with and without glucose.

## MATERIALS AND METHODS

The study was done in maintenance hemodialysis unit of Gandhi Hospital, Secunderabad over a period of one year from December 2013-December 2014. 50 patients were chosen by random sampling, 25 of them were diabetics and 25 non-diabetics.

### Inclusion Criteria

Minimum 18 yrs old and on regular, stable dialytic management for the last 60 days at least

### Exclusion Criteria

- Patients with an ongoing systemic infection at the time of the study
- Patients hospitalized for decompensation of diabetes mellitus or any other comorbidity
- Those who were not able to understand the characteristics and implications of the study

## METHODS

Both diabetic and non diabetic CKD patients on maintenance hemodialysis were randomly selected, 25 in each group. All DM patients were on insulin therapy. All of them had reasonably well-controlled glycaemias without significant fluctuations for the last several weeks. The patients' dietary habits were not changed either before or during the period of the study. Previous individual regular doses of insulin therapy before breakfast were maintained for all the DM patients.

The study was a single-blind randomized clinical trial and consisted of two phases. In phase 1, the patients of both groups (diabetics and nondiabetics) were submitted to a regular 4-h HD procedure with a bicarbonate solution without glucose; in phase 2, the same patients were submitted to another dialysis session using a bicarbonate solution containing glucose 100 mg/dl. There was 1 week to 10 days interval between each of the phases. For phase 1, regular glucose-free bicarbonate dialysis solution (from Oasis Nephrocare) was used. For phase 2, a specially prepared glucose added solution (from Oasis Nephrocare), 100 mg/dl in the final dialytic fluid, was used.

Hypoglycemia was defined as serum glucose level below 70 mg/dl with or without symptoms. The patients carefully observed directly for any sign or symptom of hypoglycemia throughout the period of the sessions. If there was any suspicion of such a situation, they were submitted to capillary glycaemia evaluation using a glucometer. If capillary glycaemia below 70 mg/dl was found, the patient treated appropriately.

The blood glucose level of each patient was measured four times during the HD session--at 1, 2, 3 and 4 Hr (end of the session). For this purpose, blood samples were collected from the arterial line of the dialysis system, e.g. coming from the patient immediately before entering the dialysis circuit. Plasma glucose level was measured by hexose kinase method. Glucose

levels and the number of symptomatic and asymptomatic hypoglycemic events were compared in each group.

### Statistical analysis

Statistical analysis was performed using the GraphPadInStat software version 3.10 for Windows. Data are expressed as mean $\pm$ -SD. The Fisher's exact test was used for comparison of categorical variables. Student's unpaired t-test was used to compare continuous variables. Statistical significance was set at P <0.05.

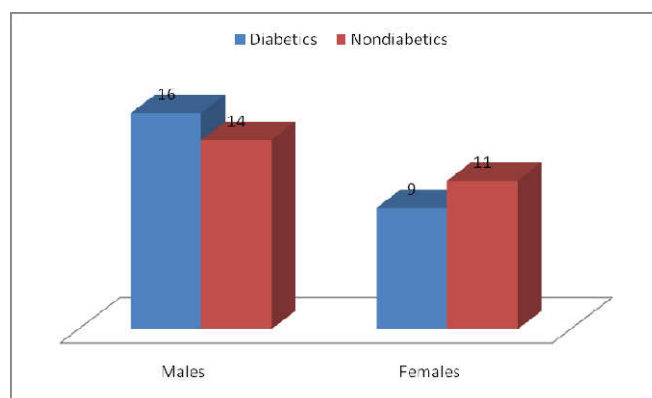
## RESULTS

### Age distribution

	Mean age	p value
Diabetics(n=25)	43.9 $\pm$ 5.5	
Nondiabetics(n=25)	40.0 $\pm$ 10.2	0.0989

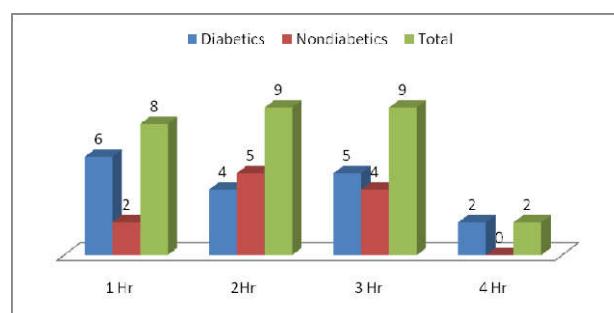
### Sex distribution

	Males	Females	p value
Diabetics(n=25)	16	9	
Nondiabetics(n=25)	14	11	0.773



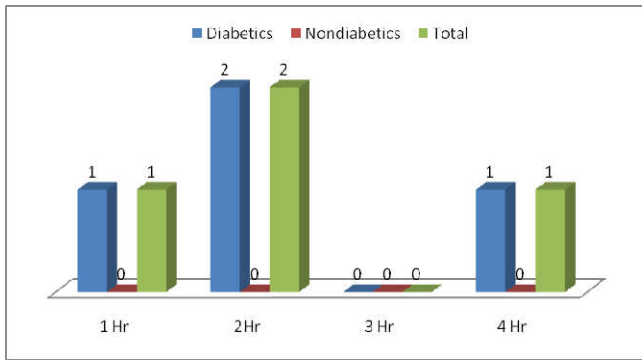
### Hypoglycemic events without glucose in dialysate

	At 1 Hr	At 2 Hrs	At 3 Hrs	At 4 Hrs	Total glucose measurements
Diabetics	6	4	5	2	100
Nondiabetics	2	5	4	0	100



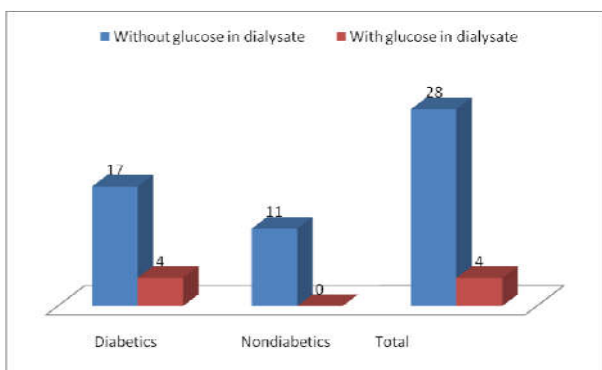
### Hypoglycemic events with 100 mg/dl glucose in dialysate

	At 1 Hr	At 2 Hrs	At 3 Hrs	At 4 Hrs	Total glucose measurements
Diabetics	1	2	0	1	100
Nondiabetic	0	0	0	0	100



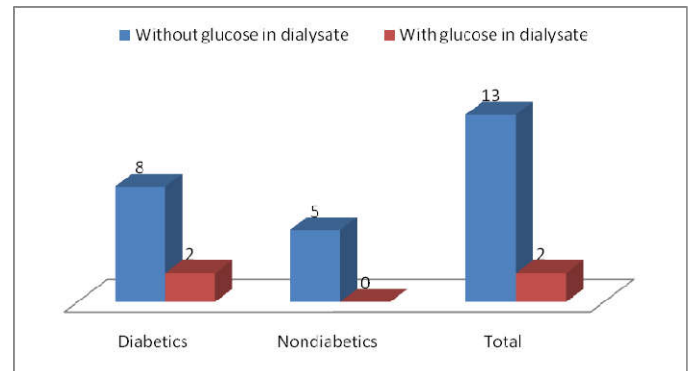
Total No. of hypoglycemic events

	Without glucose in dialysate	With glucose in dialysate	Total glucose measurements
Diabetics	17	4	200
Nondiabetics	11	0	200
Total	28	4	400



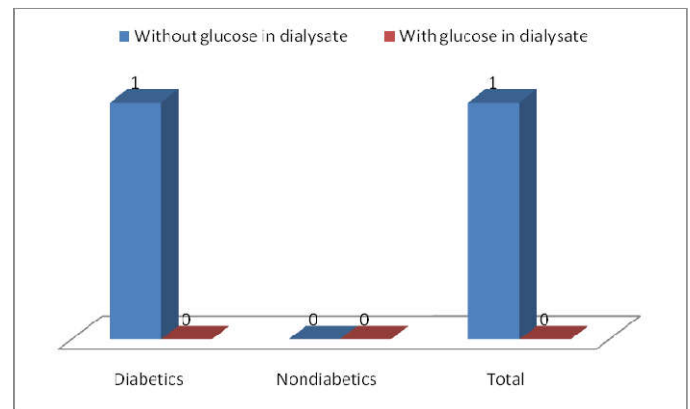
No. of patients with hypoglycemia

	Without glucose in dialysate	With glucose in dialysate
Diabetics	8(16%)	2(4%)
Nondiabetics	5(10%)	0
Total	13(26%)	2(4%)



No. of patients with symptoms of hypoglycemia

	Without glucose in dialysate	With glucose in dialysate
Diabetics	1	0
Nondiabetics	0	0
Total	1(2%)	0



Mean plasma glucose measurements in hypoglycemic patients without glucose in dialysate

Mean plasma glucose measurements in hypoglycemic patients with 100mg/dl glucose in dialysate

Mean plasma glucose measurements in hypoglycemic patients

	Without glucose in dialysate	With glucose in dialysate	p-value
Diabetics	54.2±7.8	64.5±1	<0.0001
Nondiabetics	63.4±2.9	-	
All	57.8±7.8	64.5±1	<0.0001

	At 1 Hr	At 2 Hrs	At 3 Hrs	At 4 Hrs
Diabetics	66.0	64.0	-	64.0
Nondiabetics	-	-	-	-

Mean plasma glucose measurements in all patients

	Without glucose in dialysate	With glucose in dialysate	p-value
Mean plasma glucose	100.3±13.47	104.5±13.42	0.0019

Mean plasma glucose measurements in all patients at different times during hemodialysis

	At 1 Hr	At 2 Hrs	At 3 Hrs	At 4 Hrs
Without glucose in dialysate	102.18±25.57	98.72±24.65	97.92±23.28	102.4±20.75
With glucose in dialysate	105±15.42	104.12±14.72	104.04±11.85	105.08±11.61
p value	0.5058	0.1866	0.1008	0.4274

## DISCUSSION

A total of 50 patients of Chronic Kidney disease stage V on maintenance hemodialysis were included in study, 25 were diabetics and 25 were nondiabetics. Of the 50 patients studied, 30 were males and 20 females with a mean age 43.9± 5.5 in diabetics, 40.9± 10.2 years in nondiabetics (range, 22 to 62 years). Patients had been on dialysis treatment for 19 months (range, 6 to 64 months). Hemoglobin A1c levels were 6.66 ± 0.3 in patients with diabetes and 6.06 ± 0.19 in patients without diabetes. All diabetic patients were on insulin therapy. The presence of glucose in hemodialysis solutions appears to greatly reduce the risk of intradialytic episodes of hypoglycemia. Glucose-containing solutions offer other general beneficial effects, such as protection of erythrocytes, low and stable blood pressure levels, and improved stability of blood glucose levels during dialysis. The optimum concentration of glucose in the dialysate in Indian patients has not been defined, but it can be assumed that it should be the minimum that could prevent hypoglycemia.

In the present study, when a glucose-free dialytic solution is used, the prevalence of hypoglycemia is 26% which is comparable to a study by Burmeister JE<sup>7</sup> *et al*, where 23.6% patients had hypoglycemia. However, Jackson<sup>6</sup> *et al* found

hypoglycemia in 38% patients including both diabetics and nondiabetics.

With glucose-free dialysate, 13 patients, 8 diabetics and 5 nondiabetics, presented 28 measures of hypoglycemia, and with glucose-added dialysate, only 2 diabetics presented 4 measures of hypoglycemia which are significantly low. There was no hypoglycemia in nondiabetic patients when glucose-added dialysate is used.

The lowest observed glucose value in the present study, when a glucose-free dialytic solution used, is 44 mg/dl in diabetics and 60 mg/dl in nondiabetics, whereas in a study by Burmeister *et al* it was 21 mg/dl in diabetics and 60 mg/dl in nondiabetics. In a study by Jackson *et al*, these values were 50 mg/dl in diabetics and 38 mg/dl in nondiabetics. When a glucose added dialytic solution is used, lowest glucose value is 64 mg/dl which is similar to a study by Burmeister *et al*.

For all patients, the mean plasma glucose level (mg/dl) in phase 1 was 100.3±13.47, where in phase 2 this was 104.5±13.42, which is significantly high with a p-value of 0.009. This finding is similar to a study by Burmeister *et al* and Maren *et al*<sup>8</sup> which can be explained by the increase in insulin secretion in the period with glucose in the dialysis fluid.

However, there were no significant higher levels of blood glucose at different time periods (1hr, 2hr, 3hr, 4hr) in patients treated with the dialysate containing glucose than in those treated without glucose in the dialysate which is similar to another study by JE Burmeister *et al*<sup>9</sup>.

Among diabetic patients, values for hypoglycemia measures in phase 1 was 54.2±7.8 mg/dl, which is significantly lower than in phase 2, 64.5±1 mg/dl with a p-value of 0.0001. This finding is again comparable to a study by JE Burmeister *et al* and a Maren *et al*<sup>8</sup>.

There was an occurrence of hypoglycemia throughout the study period in the present study similar to a study by JE Burmeister *et al*. Majority of the hypoglycemic episodes, 17 of 28, were occurred during the first half of the hemodialysis which can be explained by the main biochemical changes in the glucose metabolism that occur during this period.

Jackson *et al* and JE Burmeister *et al* reported asymptomatic hypoglycemia in all patients in their study. Only one patient presented with symptoms of hypoglycemia in the present study at the end of the hemodialysis session, who is diabetic had asymptomatic hypoglycemia at 2<sup>nd</sup>hr and at 3<sup>rd</sup>hr when glucose-free dialytic solution is used.

Overall the results of the present study are comparable to previous studies.

## CONCLUSIONS

1. Hypoglycemia is not uncommon (26%) in CKD V patients on maintenance hemodialysis, both in diabetics and nondiabetics.
2. Incidence of hypoglycemia is more in diabetics than in nondiabetics, both with glucose-free hemodialysis solution and glucose-added hemodialysis solution.

3. There was a decrease in the occurrence of hypoglycemia when glucose-added hemodialysis solution is used, both in diabetics and nondiabetics.
4. Asymptomatic hypoglycemia is very common, both in diabetics and nondiabetics.

## Limitations

1. The small sample size of 50 patients.
2. Each dialyser was reused different number of times before the study.
3. Limited number of blood glucose levels measurements.
4. Different schedule of dialysis -afternoon, evening and night-in relation to the time of insulin administration.

However, the fact that this study was conducted under the day-to-day clinical conditions implies that it can be interpreted as reflecting the daily reality of the dialysis treatment of these patients.

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