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Hypoglycemia in Diabetic and Non-Diabetic Patients of End Stage Renal Disease on Maintenance Hemodialysis

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Abstract

Clinical care of patients with end-stage renal disease (ESRD) is complex and often involves management of conditions outside of dialysis provision. Hypoglycemia is a well recognized complication of chronic kidney disease and hemodialysis, yet its prevalence among patients who are undergoing hemodialysis is subject of much debate as many of these hypoglycemic episodes may be asymptomatic. However, health effects associated with these episodes; both symptomatic and asymptomatic, can be severe, even causing sudden death of the patients. The evaluation of uremic hypoglycemia in patients of diabetes involves exclusion of obvious causes such as insulin and oral hypoglycemic therapy. Spontaneous uremic hypoglycemia in patients who do not have diabetes has been attributed to various factors like, diminished renal gluconeogenesis, poor nutrition resulting in deficiency of precursors of gluconeogenesis, impaired glycogenolysis, impaired renal insulin degradation and clearance and in a few cases, inadequate response from immediate counter-regulatory hormones such as catecholamine and glucagon. However, the mechanism(s) seems to differ from one patient to the other. And when the patients of end stage renal disease are initiated on renal replacement therapy in the form of hemodialysis , many factors related to hemodialysis itself such as of glucose-free dialysis fluid, glucose loss into the dialysate and diffusion of glucose from plasma to erythrocytes may predispose these patients to hypoglycemia. This observational prospective study was carried in the hemodialysis unit of the department of medicine, Acharya Shri Chander college of Medical Sciences and Hospital, Sidhra, Jammu. The 40 patients above 18 years of age, who were receiving maintenance hemodialysis were included in this study. The results showed progressively decreased blood glucose values in majority (80%) of the patients after the start of hemodialysis and out of 11 patients who actually developed hypoglycemia, only four patients exhibited symptoms of hypoglycemia. The aim of the study was to characterize the episodes of hypoglycemia, so that proper care is taken in anticipating, preventing and managing these episodes in future sessions of hemodialysis in this highly vulnerable group of patients .

Keywords: Hypoglycemia; Chronic Kidney Disease (CKD); End Stage Renal Disease [ESRD) Hemodialysis (HD).

Introduction

Hypoglycemia is a potentially lethal complication of chronic kidney disease and hemodialysis in both diabetic and non-diabetic patients on renal replacement therapy. Many studies have demonstrated that plasma glucose concentration decreases during hemodialysis resulting in frequent hypoglycemic episodes mostly asymptomatic[1-5]. These events tend to recur often and this recurrence has been identified as a cause for the absence of symptoms as repeated episodes of relatively mild hypoglycemia have been shown to reduce the counter-

regulatory responses and impaired physiological defenses against hypoglycemia; indeed it has been reported that the response of adrenaline to hypoglycemia was found to be blunted by approximately 50% after repeated episodes of hypoglycemia in one experimental study [6]. Nevertheless, these recurrences expose such patients to the risk of severe health effects including progressive cognitive impairment [5-7].

In addition to hypoglycemic unawareness, severe hypoglycemia can powerfully stimulate the sympathetic nervous system and may bring about acute secondary adverse cardiovascular outcome including sudden death [7]. The increased adrenaline induced by repetitive hypoglycemia promotes intimal thickening and smooth muscle cell proliferation after endothelial denudation in experimental animals. As adrenaline has profound effects on blood constituents, inflammatory cytokine levels, coagulation, and fibrinolysis, so it follows that adrenaline hyperactivity through the sympathoadrenal response to hypoglycemia could play a key role in the progression of atherosclerosis [6,7].

In symptomatic patients episodes of cold sweats, agitation, dizziness, disorientation, slurred speech, fatigue, and decreased level of consciousness are typical. A case of hypoglycemia complicated by central pontine myelinolysis and quadriplegia has been described [7]. Information on hypoglycemia associated with kidney disease generally has emerged through various case reports, small series and reviews. In the ADVANCE (Action in Diabetes and Cardiovascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial analysis, higher serum creatinine was an independent risk factor for severe hypoglycemia [8]. ESRD unrelated to the diabetes is the second most frequent cause of hypoglycemia in hospitalized patients [9] and carries a high mortality rate [10]. It has been reported that as many as half the maintenance hemodialysis patients may experience hypoglycemia over a 3 month period [11]. In a systematic review and meta-analysis, severe hypoglycemia was strongly associated with a higher risk of cardiovascular disease (relative risk 2.05). The analysis indicated that co morbid severe illness alone may not explain the association between hypoglycemia and cardiovascular disease [12]. One study suggested a link between hypoglycemia and increased risk of stroke in patients with renal failure [13]. Moreover in symptomatic patients the episodes of hypoglycemia may lead to repeated interruptions in hemodialysis session resulting in inadequate dialysis.

Methodology

This observational prospective study was undertaken in the hemodialysis unit of the department of medicine, Acharya Shri Chander college of Medical Sciences and Hospital, Sidhra, Jammu. The 40 patients of end stage renal disease above 18 years of age, who were receiving maintenance hemodialysis in our hospital were included in the study .The included patients were divided into two groups; Group I 20 ESRD (non-diabetic) patients on regular HD and Group II: 20 diabetic ESRD patient(of type 2 diabetic) on regular HD. Exclusion criteria included patients suffering from severe protein –energy malnutrition, decompensated liver disease, congestive heart failure, history of alcoholism, history of episodes of drug-induced hypoglycemia and patients taking any drug known to interfere with glycemic control. All these patients were dialysed using sodium bicarbonate solutions, glucose free dialysate using polysulfone dialyser system. Patients were asked not to eat during the hemodialysis session.

After the detailed history taking and physical examination, which also included weight and height measurements for calculation of BMI, all the routine lab investigations and specialized tests whenever indicated, were performed. Blood glucose levels were measured just before the beginning of HD session, after two hours and at the end of HD session. The blood glucose levels were also measured whenever patients developed some symptom like decreased levels of alertness, hypotension or whenever they themselves reported some symptoms. Glucose measurements were done in the dialysate passed out from the patients twice, two hours after the start and at the end of HD session. Blood glucose level <70mg/dl were taken as indicative of hypoglycemia.

Results

This study included 40 ESRD patients on HD divided into 2 groups. Group 1 included 20 non-diabetic patients between age of 25-65 years of which 15 were male and 5 were female patients and group 2 included 20 diabetic patients between age of 45-65 years of which 16 were male and 4 were female. Table 1 shows demographic data for all studied ESRD patients on HD; (40) patients, divided into 2 groups: Group 1 having 20 Non-diabetic patients (15 males and 5 females), their mean age in years was 42.15±11.32 years (25-65 years) and Group 2 having 20 patients of type 2 diabetes (16males and 4 females),

their mean age in years was 53.65±8.68 years (45-65years)

At the start of HD session the mean blood glucose level was 114.2±12.81 among non-diabetic patients and 175.5±42.58 among diabetic patients. Two hours after the start of HD mean blood glucose level was 107.9±16.21 among non-diabetics and 155.2±50.76 among diabetics. Post-dialysis mean blood glucose level among diabetics was 99.65±30.72 among non-diabetics and 147.4±68.43 among diabetics. Before the start of HD session, there was a statistically significant difference between blood glucose levels (BGL) between non diabetic (90-138mg/dl) and diabetic (118-250mg/dl) patients. At 2 hours after the start of HD session, there was a statistically significant difference in BGL, between non diabetic (86-130 mg/dl) and diabetic (68-230mg/dl) patients. At the end of HD session, there was again a significant difference between BGL in non diabetic (50-176mg/dl) and diabetic group(50-260mg/dl).

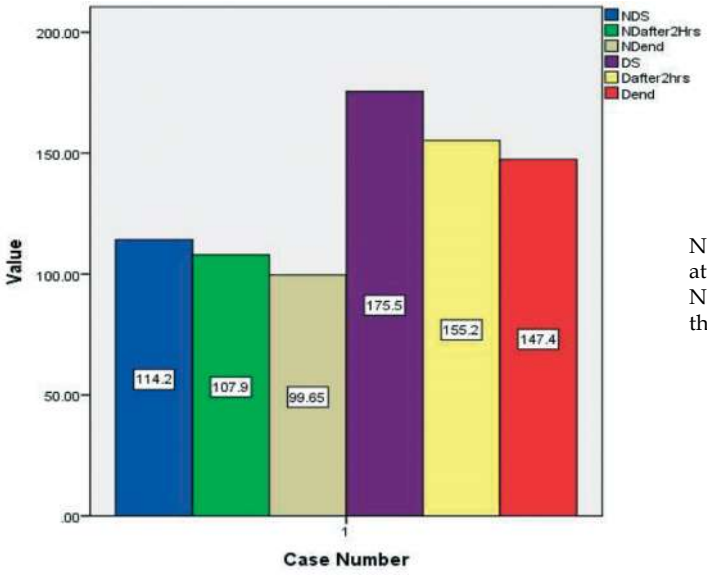
In group one, 5 patients developed hypoglycemia and in group two, 6 patients developed hypoglycemia. However, hypoglycemia was symptomatic in only two patients from each group and asymptomatic in rest of the patients .

Table 1: Showing blood glucose values in both groups at the start, 2 hours after and at the end of hemodialysis

Variable	Group 1 Non-Diabetic N=20	Group 2 Diabetic N=20	T	P
Sex Male	15	16		
Female	5	4		
Blood glucose(mg/dl) before the start of HD session	90-138	118-250	6.16	0.0001
Blood glucose(mg/dl) 2 hours after the start of HD session	86-130	68-230	3.96	0.0003
Blood glucose(mg/dl) at the end of HD session	50-176	50-260	2.86	0.007

Table 2: Showing the prevalence of hypoglycemia in ESRD patients

ESRD patients on HD	Hypoglycemia Blood glucose <70mg/dl	Decrease at 2 hours after the start of HD	Decrease at the end of HD	Before the start of HD	2 hrs. after the start of HD	At the end of HD	Increased At 2 hours after start of HD	Increased at the end of HD
All patients N=40	N=11 27.5%	N=28 70%	N=32 80%	None	2	11	8	3
Group 1 Non-Diabetic N=20	N= 5 25%	N=16 80%	N=16 80%	None	None	5	3	None
Group 2 Diabetic N=20	N= 8 40%	N=12 60%	N=16 80%	None	2	4	5	3



NDS-Non-diabetic Blood glucose at the start of HD
NDafter2Hrs – Blood glucose at the end of 2 hours

Fig. 2: Comparison of glucose levels in blood in both diabetic and non-diabetic patients at the start,2 hours after and at the end of HD session

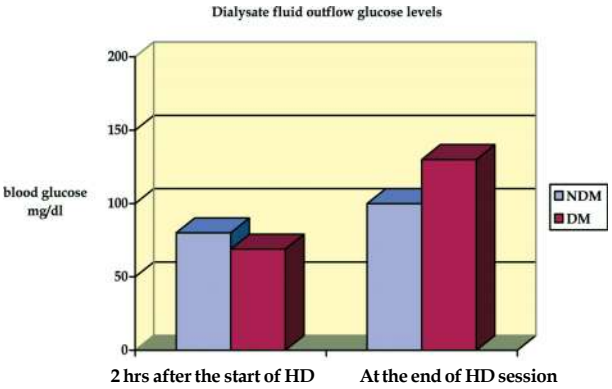


Fig. 4: Dialysate Fluid Outflow Glucose Levels

Discussion

Hypoglycemia is a well recognized complication of chronic renal failure and hemodialysis, yet its prevalence among patients who are undergoing hemodialysis is subject of much debate as many of these hypoglycemic episodes may be asymptomatic [1-5]. In ESRD, it has been reported more frequently than in CKD stage 3 and 4, and also during hemodialysis sessions, and even more frequently in diabetic subjects. The health effects of hypoglycemia can be severe [6,7] in both symptomatic and asymptomatic patients.

In the present study, the patients were divided into Group 1 having 20 Non-diabetic patients (15 males and 5 females), their mean age in years was 42.15±11.32 years (25-65 years) and Group 2 having 20 patients of type 2 diabetes (16males and 4 females), their mean age in years was 53.65±8.68 years(45-65years). The difference in the age distribution between the two groups seen in our study can be explained by the fact that in our country many non-diabetic young individuals with no history of long standing hypertension presumably uxexplained renal failure, but chronic glomeulonephritis is most likely cause of ESRD in in these individuals [14]. Blood glucose measured 2 hours after the start of HD session showed decreased values in 28 cases (70%) but they did not reach the hypoglycemic levels(i.e less than 70 mg/dl) and their number increased to 32(80%) at the end of hemodialysis. This implies that 80% of our patients had progressively decreased blood glucose values after the start of hemodialysis**.** Before the start of HD session, there was a very significant difference between blood glucose levels (BGL) between non diabetic (90-130mg/dl) and diabetic (118-250) patients. At 2 hours after the start of HD session, there was a highly significant difference in BGL, between non diabetic (86-130 mg/dl) and diabetic (68-230mg/dl) patients. At the end of HD session, there was a highly significant difference between BGL in non diabetic (99.3±38.5 mg/dl) and diabetic (150.6±97.8 mg/dl) patients. As regards dialysate fluid outflow glucose levels at 2 hours after the start of HD session, there was a very highly significant difference between non diabetic (37.6±18.3 mg/dl) and diabetic (63.4±27.8 mg/dl) patients. Within each group, there was a significant difference in blood glucose levels before, 2 hours after the start and at the end of HD session. At the end of HD session, the dialysate outflow fluid glucose levels showed a highly significant difference between non diabetic (70.3±30.2 mg/dl) and diabetic (101.6±37.6 mg/dl) patients.

In our study larger percentage of patients showed progressively decreased blood glucose levels as compared to some other studies, this difference could be because of the reason that patients included in the study were not given any instructions, different from the usual advise given to these patients, regarding the eating pattern before or after the start of hemodialysis. There is possibility that patients who presented with hypoglycemia may have not had a proper meal prior to the commencement of HD. Although the causes and mechanisms of hypoglycemia in ESRD are multifactorial, it is possible that food intake during HD was an important and significant predictor of the sustainability of normal blood glucose level during HD as diminished glucose availability due to reduction in substrate is thought to be one of the most important mechanism leading to hypoglycemia. This may partially explain the slight variability in the prevalence of hypoglycemia between the current study and others

In our study, 11 patients developed hypoglycemia, 5 in non-diabetic group and 6 in diabetic group. We found that out of 11 patients who developed hypoglycemia; only 4 were symptomatic, rest of the seven patients did not exhibit any signs and symptoms suggestive of hypoglycemia. In group one all 5 patients developed hypoglycemia at the end of hemodialysis session where as in diabetic group, in 2 patients, hypoglycemia was diagnosed 2 hours after the start of dialysis and in rest after that or at the end of the session. In this study, patients presenting with hypoglycemia reported or exhibited confusion, cold sweats, and generalized weakness as the most common symptoms. Some study patients had to be discontinued from the hemodialysis due to severe hypoglycemia within the last hour of the session. A positive correlation between glucose levels in blood and dialysate fluid outflow in diabetic and non-

diabetic patients at the end of HD session was seen; however no correlation was found between blood glucose levels and glucose levels in dialysate outflow 2 hours after starting HD session, in diabetic or non diabetic patients.

The evaluation of uremic hypoglycemia in patients of diabetes involves exclusion of obvious causes such as insulin and oral hypoglycemic therapy [7]. Spontaneous uremic hypoglycemia which occurs in patients who donot have diabetes has been attributed to deficiency of precursors of gluconeogenesis, (e.g alanine) because of poor nutrition, impaired glycogenolysis, diminished renal gluconeogenesis and impaired renal insulin degradation and clearance and, in a few cases, deficiency in an immediate counter-regulatory hormone such as catecholamine and glucagon [7,10-12,14-16]. However, the mechanism(s) seems to differ from one patient to the other. Haemodialysis-induced hypoglycaemia occurs more frequently in patients with diabetes than in those without [16]. Additional triggering events for hypoglycemia are alcohol consumption, sepsis, acute caloric deprivation in already malnourished patients, concomitant liver disease, congestive heart failure, and an associated endocrine deficiency [12-14]. The drugs known to cause hypoglycemia like propranolol, salicylates, and disopyramide should also be reviewed while evaluating hypoglycemia [10,11].

To understand the changes in regulation of carbohydrate metabolism in patients of CKD and ESRD on dialysis, it is important first to review the role, normal kidneys play in maintenance of blood glucose under various circumstances. In the post-absorptive state, glucose must be continuously delivered into the circulation and liver and kidneys are the only organs which can perform this function as other tissues lack glucose- 6-phosphatase. Release of glucose into the circulation occurs by the means of gluconeogenesis and glycogenolysis [17].

Gluconeogenesis is referred to *de novo* synthesis of glucose from non-glucose precursors; and Glycogenolysis to the process of breakdown of glycogen, a carbohydrate polymer formed directly from glucose or indirectly via gluconeogenesis. Both processes contribute about equally to the glucose delivered into the systemic circulation.The normal human kidney contains negligible amounts of glycogen and kidney cells other than proximal tubules, that could theoretically store glucose, lack glucose-6-phosphatase.Thus, essentially all renal glucose release is probably due to gluconeogenesis. Gluconeogenesis accounts for about 40-50%> of systemic glucose release in postabsorptive state. Since renal glucose release is responsible for 20-25% of systemic glucose release under this condition, it follows that the human kidney should account for approximately half of all gluconeogenesis and thus be as important a gluconeogenic organ as the liver [17,18]. It has even been reported in many animal experiments that on a gram-for-gram tissue basis, the gluconeogenic capacity of the kidney exceeds that of the liver [17-19].

These results thus refuted textbook wisdom that the human kidney plays only a minor role in glucose homeostasis. Moreover, observations in animals that removal of liver and kidney results in more rapid and more profound hypoglycaemia than mere removal of the liver also support the fact that renal glucose release is important for the prevention of hypolgycaemia. Thus, if human kidney were a gluconeogenic organ comparable to the liver, it can be concluded that it should play an important role in glucose homeostasis under. a variety of conditions, e.g. hypoglycaemia, fasting, diabetes mellitus, acidosis and also when renal insufficiency develops [18,19].

Thus, it follows from above discussion that multifactorial alterations in glucose homeostasis occur when kidney function declines. Many studies and reviews have examined the mechanisms and clinical significance of insulin resistance in CKD. Insulin resistance in CKD is an acquired defect as even patients of ESRD , who are not obese and do not have diabetes mellitus, have significant insulin resistance. Proposed additional determinants of insulin resistance in CKD include accumulation of uremic toxins, chronic inflammation, oxidative stress, metabolic acidosis, and vitamin D deficiency. The increased insulin secretion which normally follows as a result of insulin resistance, is not seen in patients of ESRD as there is reduced pancreatic insulin secretion, possibly because of presence of chronic metabolic acidosis, deficiency of 1,25 dihydroxy vitamin D and secondary hyperparathyroidism. On the other hand, less insulin is removed from the circulation as after liver, the kidneys represent the main site for insulin degradation, and as kidney function declines, so does the ability to remove insulin. Again, one would assume that the patient with insulin resistance would need more supplemental insulin to manage blood glucose levels but this is not the case as there is reduced renal gluconeogenesis (due to reductions in kidney mass and diminished kidney function) [20,21].

Thus, glycemic management is complicated by many opposing processes when patient is diagnosed

with renal insufficiency. Although aggressive glycemic control has been shown to alter the clinical course of early diabetic kidney disease, data supporting the benefits of tight glycemic control on outcome in patients with advanced CKD (including ESRD) is lacking. In fact, diabetic patients with lower, though normal, pre-HD glycemia seem to present higher risk of developing intradialytic hypoglycemia when using a dialysis solution without glucose [2]. These findings suggests that diabetic CKD patients who are in best glycemic control present higher risk of hypoglycemia during HD sessions.

In the absence of better clinical trial data, glycemic management in patients of advanced kidney disease continues to be based on individualized decision making [7,20]. Annually, each patient with type 1 diabetes is at risk of experiencing 1–3 episodes and every other person with type 2 diabetes may have at least one episode of severe hypoglycemia. Patients with diabetes and declining kidney function are at even higher risk for hypoglycemia [21]. Thus, with increasing emphasis on tight glycemic control targets, in last few decades, hypoglycemia, often iatrogenic, is a growing concern, in a clinical scenario complicated by missed or irregular meals, advanced age, long duration of diabetes, and unawareness of hypoglycemia elderly. It should be noted that current evidence suggests avoiding strict glycemic control in ESRD patients and it has been seen that hemoglobin A1c between 7.0 and 7.9% is associated with the lowest mortality in dialysis patients [22]; as a result of mounting concerns about hypoglycemia, the American Diabetes Association ’s Standards of Medical Care in Diabetes recommends less stringent HbA1c targets (ie, 7.5%-8.0%) for patients with advanced complications and extensive comorbid conditions [7,8,12,21,22].

Regarding the relationship between different treatment modalities in patients of chronic renal disease and risk of hypoglycemia; the insulin traditionally has been considered the safest antidiabetic agent in this subset of patients [7,22]. There are few head-to-head clinical trials comparing various antidiabetic agents, and none has been conducted in patients with CKD. In a study to determine which anti-diabetic therapies are associated with more frequent episodes of hypoglycemia in patients undergoing long-term hemodialysis, it was reported that overall the oral hypoglycemic agents did not pose a higher risk of hypoglycemia than insulin in diabetic patients undergoing hemodialysis [11].

Now, coming to other factors which may also contribute to hypoglycemia, some authors have suggested that severe carnitine deficiency because of malnutrition and carnitine loss during dialysis , the inability to release glycogen secondary to vitamin B6 and chromium deficiency, may be another factor responsible for hypoglycemia in both diabetic and non-diabetic patients [23,24]. In addition, the various multivariate analysis have revealed that hypoalbuminemia and frequent episodes of intradialytic hypotension are powerful clinical predictors of hypoglycemia in diabetic patients undergoing hemodialysis [23,24]. It has also been postulated that hemodialysis induced decrease in plasma glucose could also result from diffusion of glucose from plasma into the erythrocytes, probably due to the consumption of glucose resulting from the accelerated anaerobic metabolism induced by the changes in the cytoplasmic pH of erythrocytes.

When these patients with all the above discussed complexities of carbohydrate metabolism, start hemodialysis ,the other factors related to the hemodialysis itself , predisposes these patients to increase risk of hypoglycemia; One of the factor ,which has been repeatedly discussed in many studies is the use of glucose –free dialysis fluid. During the early days of hemodialysis, the dialysis fluid used to contain glucose, both to achieve hypertonicity and consequent ultrafiltration and to prevent hypoglycemic episodes. Currently, majority of hemodialysis centres use sodium bicarbonate solution that does not include glucose in its composition, which provides advantages such as cost reduction and less risk of contamination. Thus, the association of high blood flow with the continous flow of this non-glucose dialytic solution through a dialyser lead to loss of serum glucose through dialytic fluid leaving the dialyser, leading to more frequent episodes of hypoglycemia. Indeed, many studies which compared the hemodialysis using dialysis fluid both with and without glucose, reported less incidences of hypoglycemia with the former [26-30]; because of this some authors have advocated use of glucose containing dialysate in patients prone to hypoglycemia and more so in patients in whom episodes are usually asymptomatic [26]. In fact ,in an important study, Bermeister et al concluded that glucose was lost in dialytic fluid leaving the dialyser in significantly lower amounts when using glucose-added solution than glucose-free solution [26]. It has also been claimed that 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 has not been defined, but it can be assumed that it should be the minimum that could prevent HG [29,26]. So, in future more studies using dialysate containing optimum amount of glucose are required and contrary to present practice of using glucose free dialysate in majority of dialysis centres; it is advisable to use dialysate containing glucose at least in patients who are prone to repeated episodes of hypoglycemia during hemodialysis [26-30].

Conclusion

We conclude that during HD, blood glucose tends to decrease in most patients; diabetic and non diabetic and some of them develop hypoglycemia, which may be symptomatic or asymptomatic, so patients should be monitored carefully so that proper care is taken in anticipating, preventing and managing these episodes of hypoglycemia so as to avoid serious health consequences for patients of ESRD on maintenance hemodialysis.

Ethical Approval

The study was approved by the ethical committee of Acharya Shri Chander College of Medical Sciences And Hospital.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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