BLOOD GLUCOSE EXCURSION IN HEMODIALYSIS PATIENTS WITH END STAGE DIABETIC NEPHROPATHY

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Abstract:

Background: Diabetic kidney disease (DKD) refers to the deterioration of kidney function seen in diabetes mellitus (DM) patients. Patients with end-stage kidney disease (ESKD) frequently experience wide glycemic excursions, which is considered a risk factor for the development of diabetic complications. Blood glucose fluctuations have been documented in hemodialysis (HD) patients with and without diabetes mellitus. The aim of this study was to assess the blood glucose excursion in ESKD patients with and without diabetes mellitus on maintenance HD. Methods: 80 patients were enrolled in this study; 20 non-diabetic ESKD patients on HD and 60 diabetic patients including: 20 patients with type 2 DM, 20 DKD patients and 20 diabetic patients on HD. Blood glucose profile and other laboratory investigations were done. For dialysis patients, random blood glucose levels before, during and after the dialysis session and glucose in dialysate flow were measured. Glucose excursion was expressed as the difference between random blood glucose levels before-during and before-after HD session. Results: Regarding blood glucose profile, fasting, postprandial blood glucose and glycated hemoglobin levels were higher in group IIA (DM without DKD) than group IIC (DKD on HD) (P < 0.001). As regard to the dialysis groups, glucose excursion (before-during) was non significantly higher in group IIC than group I(Non-DM on HD), on the other hand there was significant increase in the glucose excursion (before-after) in group IIC when compared with group I (P 0.021). In group IIC, glucose excursion (before-during) and (before-after) were significantly increased in patients treated with insulin than other patients who had not taken antidiabetic medications (P 0.012, 0.016 respectively). In Group I, glucose excursion (before-after) had significant negative correlation with fasting blood glucose (r -0.525, P 0.018). In Group IIC, glucose excursion (before-after) and (before-during) had significant positive correlation with 2 hours postprandial blood glucose (r 0.573, P 0.008) (r 0.506, P 0.023), respectively. Conclusion: Blood glucose excursion occurs more in diabetic hemodialysis patients than non-diabetic patients on hemodialysis, and in patients on insulin therapy more than non-insulin regimens. Hemodialysis decreases blood glucose proved by the presence of glucose in the dialysate outflow. Blood glucose profile is linked to glucose excursion, inferring that good glycemic control is important to decrease blood glucose fluctuations.

Keywords: Glucose excursion, Diabetic kidney disease, Hemodialysis

Introduction:

Diabetes mellitus is a major cause of morbidity and mortality, and it leads to early onset of coronary heart disease, retinopathy, nephropathy, and peripheral neuropathy (1). The plasma glucose concentration is determined by the amount of glucose synthesized, and the one removed from the circulation and metabolized. This concentration must be maintained within a relatively narrow range despite the wide daily fluctuations in glucose ingestion and glucose demands in various tissues (2).

The regulation of endogenous production of glucose is determined by hormonal and neural factors. In the acute phase, glucoregulatory mechanisms involve insulin, glucagon and catecholamines (3). The kidneys are involved in maintaining glucose homeostasis through three different mechanisms: gluconeogenesis; glucose uptake from the blood for its own energy request and reabsorption in tubules to the general circulation (4).

Diabetic kidney disease (DKD) refers to the deterioration of kidney function seen in diabetes mellitus patients. The progression of the disease is known to occur in a series of stages and is linked to glycemic and blood pressure control (5). It develops in approximately 40% of patients who are diabetic and is the leading cause of chronic kidney disease (CKD) worldwide (6).

During hemodialysis, plasma glucose diffuses across the concentration gradient from blood to the dialysate. In addition, the plasma glucose level at the post dialyzer site decreases to less than the glucose concentration of the dialysate, possibly as a result of diffusion of plasma glucose into erythrocytes (7). Counter-regulatory hormones are secreted in response to this hypoglycemic state resulting from the hemodialysis session. The combination of a relative and absolute lack of insulin after hemodialysis, the counter-regulatory hormone response, and the postprandial state leads to hemodialysis-associated hyperglycemia (8).

Glucose and insulin metabolism in patients with diabetes are profoundly altered by advanced CKD. Risk of hypoglycemia is increased by failure of kidney gluconeogenesis, impaired insulin clearance by the kidneys, defective insulin degradation due to uremia, increased erythrocyte glucose uptake during hemodialysis. Patients with end-stage kidney disease (ESKD) frequently experience wide glycemic excursions, with occurrences of both hypoglycemia and hyperglycemia and this is considered a risk factor for the development of diabetic complications independent from HbA1c (9).

Assessment of glycaemia by glycated hemoglobin (HbA1c) is hampered by a variety of CKD-associated conditions that can bias the measure either to low or high range. Alternative glycemic biomarkers, such as glycated albumin or fructosamine, are not fully validated. Therefore, HbA1c remains the preferred glycemic biomarker despite its limitations. The use of continuous glucose monitoring in this population suggest promise for more precise monitoring and treatment adjustments to permit fine-tuning of glycemic management in patients with diabetes and advanced CKD (10). The aim of the present study was to assess the blood glucose excursion in the end stage kidney disease patients with and without diabetes mellitus on maintenance hemodialysis.

Methods:

This is a cross sectional descriptive study that was conducted at nephrology and dialysis units of Tanta university hospital and El Mahalla El Kubra general hospital, Gharbia, Egypt, for a duration of 1 year. The study included 80 patients who were classified as follows:

- Group I: 20 non diabetic ESKD patients on hemodialysis.
- Group II: 60 diabetic patients who are further subdivided into:
- Group (IIA): 20 patients with type 2 D.M without nephropathy.
- Group (IIB): 20 Patients with diabetic kidney disease (on conservative therapy).
- Group (IIC): 20 diabetic patients on maintenance hemodialysis.

Diabetic kidney disease (DKD) was defined as eGFR <60 mL/min/1.73 m2 and/ or ACR ≥30 mg/g (11). The dialysis patients were using sodium bicarbonate solutions and glucose free dialysate three times per week the following patients were excluded from the study: patients below 18 years old and above 70 years old, and who are suffering from starvation, depression, decompensated liver disease, sepsis and congestive heart failure. Full history taking and thorough clinical examination were done. Abdominal sonography with emphasize on kidneys was done to non-dialysis patients. Laboratory investigations were done including; fasting blood glucose (FBG), 2 hours postprandial blood glucose level (2hPP BG), glycosylated hemoglobin (HbA1c), blood urea, serum creatinine and estimated GFR by using the Modification of Diet in Renal Disease (MDRD) formula. For non-dialysis patients, urinary albumin/creatinine ratio was done. For dialysis patients, random blood glucose levels before, during and after the dialysis session and glucose in dialysate flow were measured. Glucose excursion was expressed as the difference between random blood glucose levels before-during and before-after the hemodialysis (HD) session.

Ethical consideration:

- The whole study design was approved by the local ethics committee, faculty of medicine, Tanta University. The committee's reference number is 31916/11/17.
- A written informed consent was obtained from all participants before inclusion in the study, explaining the value of the study, plus the procedures that were commenced
- Confidentiality and personal privacy was respected in all levels of the study.
- Patients felt free to withdraw from the study at any time without any consequences.
- Collected data were not be used for any other purpose.
- There was no conflict of interests.
- No fund was supplied.

Statistical Analysis:

The collected data were organized, tabulated and statistically analyzed using Statistical Package for the Social Sciences (SPSS) software version 20. Measurement of data consistent with normal distribution was expressed as mean ± standard deviation (SD). Statistical differences between groups were tested using Chi Square test for qualitative variables, Student's T test between 2 groups of numerical (parametric) data. Kruskal Wallis test was used to compare between more than two groups of numerical (non-parametric) data followed by Mann-whitney for multiple comparisons. Spearman correlation is used to show relationship between different variables. Probability (P) values < 0.05 were considered statistically significant.

Results:

This cross-sectional observational study included 80 patients classified as 60 diabetic patients and 20 non diabetic patients on hemodialysis. Group I included 9 males and 11 females non-diabetic hemodialysis patients, their mean age was 53.7 years. Group IIA included 10 males and 10 female's diabetic patients, their mean age was 48.5 years. Group IIB included 8 males and 12 females diabetic kidney disease patients, their mean age was 51.1 years. Group IIC included 11 males and 9 females diabetic patients on maintenance hemodialysis, their mean age was 50.6 years. There were no statistically significant difference as regard to age and sex among the studied groups. Clinical data of the studied groups are shown in (table 1). Comparison of fasting and postprandial blood glucose in group IIA when compared with group IIC. The two hours postprandial blood glucose was significantly higher in groups IIA and IIB than group IIC. Also, group IIA had significantly higher HbA1c than group IIC (P <0.001) (table 2).

As regard to the dialysis groups (I and IIC), random blood glucose (RBG) before, during and after hemodialysis session was measured and compared. In both groups, median post-dialysis RBG was lower than mean pre-dialysis RBG. In group IIC, mean RBG before and during the hemodialysis session was significantly higher than group I (P < 0.001, 0.008 respectively), whilst there was no significant difference in mean RBG measured after the hemodialysis session, inferring the effect of HD on lowering blood glucose level. In addition, glucose excursion was calculated. Glucose excursion (before-during) was non significantly higher in group IIC than group I, on the other hand there was significant increase in the glucose excursion (before-after) in group IIC when compared with group I (P 0.021) (table 3). In group IIC, 8 patients were treated with insulin and 12 patients did not take any antidiabetic medications. Glucose excursion (before-during) and (beforeafter) were significantly increased in patients treated with insulin than other patients who had not taken antidiabetic medications (P 0.012, 0.016 respectively). Glucose was measured in the dialysate outflow, it was positive in 70% of patients in group I and 75% of patients in group IIC. There was no significant difference between the two groups. In Group I, glucose excursion (before-after) had significant negative correlation with fasting

blood glucose (r -0.525, P 0.018), non-significant negative correlation with 2 hours postprandial blood glucose and blood urea and non-significant positive correlation with HbA1c, serum creatinine and eGFR. Glucose excursion (before-during) had non-significant negative correlation with fasting blood glucose, 2 hours postprandial blood glucose, serum creatinine and blood urea and non-significant positive correlation with HbA1c and eGFR (table 4). In Group IIC, glucose excursion (before-after) had significant positive correlation with 2 hours postprandial blood glucose (r 0.573, P 0.008), non-significant positive correlation with fasting blood glucose, serum creatinine, blood urea and eGFR, and non-significant negative correlation with fasting blood glucose, serum creatinine, blood urea and eGFR, and non-significant positive correlation with fasting blood glucose, serum creatinine, blood urea and eGFR, non-significant positive correlation with fasting blood glucose, serum creatinine, blood urea and eGFR, and non-significant positive correlation with 2 hours postprandial blood glucose (r 0.506, P 0.023), non-significant positive correlation with fasting blood glucose, serum creatinine and blood urea, and non-significant negative correlation with fasting blood glucose, serum creatinine and blood urea, and non-significant negative correlation with fasting blood glucose, serum creatinine and blood urea, and non-significant negative correlation with fasting blood glucose, serum creatinine and blood urea, and non-significant negative correlation with HbA1c and eGFR (table 5).

Discussion:

Glycemic variability refers to the unstable state of blood glucose level between its peak and valley, which is one of the important characteristics of glycometabolism disorder. It is considered an independent risk factor for diabetic complication (12). This study was conducted to assess the excursion in blood glucose levels in diabetic end stage renal disease patients on maintenance hemodialysis. In the current study, there was a statistically significant increase in the levels of fasting blood glucose (FBG), 2 hours post prandial blood glucose (2hPP BG) levels and HbA1c in the group (IIA) when compared with group (IIC). This contradicts the results of Abe et al. who reported that there is a statistically significant increase of FBG and 2hPP BG in hemodialysis diabetic kidney disease patients when measured in hemodialysis days as compared to non-hemodialysis days, and this was explained by that hemodialysis can lead to hyperglycemia by decreased levels of plasma immune reactive insulin (13). In disagreement with our results, Jin et al. reported that HbA1c was significantly higher in diabetic hemodialysis patients group more than the other groups. This could be explained by that the uremic toxins influence glucose homeostasis by decreasing insulin sensitivity, increasing hepatic gluconeogenesis, and decreasing cellular glucose utilization in end-stage kidney disease patients (14). Our findings might be due to variable carbohydrate metabolism in patients on dialvsis leading to more susceptibility to hypoglycemia, and the fact that the interaction time between hemoglobin and blood glucose is shorter in patients with CKD, which leads to decrease hemoglobin glycosylation (15).

As regard to blood glucose excursion, Massimo et al. agreed with our results by finding that glucose levels measured by mean amplitude of glycemic excursions (MAGE) in patients with type 2 DM on hemodialysis are more variable than type 2 DM patients not on hemodialysis, as there is decrease in glucose levels during hemodialysis session than increase of blood glucose levels after the session, and this variability phenomena is evident in patients with poor DM control (16). Moreover, Xu et al. noted that glucose

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variability was significantly evident in diabetic nephropathy patients with glucose excursions became wider by deteriorating kidney function (17). In addition, Jin et al. found that mean amplitude glycemic excursion (MAGE) of blood glucose was significantly higher in diabetic nephropathy patients on HD than that in ESRD patients (14). Also, Riveline et al. showed that the mean glucose concentration was significantly lower in type 2 DM patienrs in hemodialysis days than non-hemodialysis days, although only two patients had intra-dialytic hypoglycemia (18). In agreement with our results, Berra et al. noted that the use of insulin enhanced glucose variability (19). Regarding the correlation between blood glucose excursion and glycemic parameters, Nalysnyk et al. agreed with our findings and stated that the changes in the blood glucose levels through time representing glucose variability showed good correlation with both fasting and postprandial blood glucose values (20). Also, Mirani et al. agreed with our results and found a direct correlation between the mean glucose concentration and glycated hemoglobin, whereas no association existed between the glucose profile variability and glycated hemoglobin (21). Moreover, Hsu et al. concluded that in diabetic patients, the postprandial hyperglycemia led to glucose variability (22). On the other hand, our results disagreed with Nasr-Allah et al. who found that there was a significant correlation between glucose variability with blood glucose profile (FBG, 2hPP BG, and HbA1c) in DM group and in diabetic nephropathy group, but no significant correlation was found between glucose variability and blood glucose profile in the hemodialysis patients group (23).

Several studies that investigated the association between these metabolic effects and glucose-free dialysates have shown that patients enter a catabolic state similar to the fasting state. During a glucose-free dialysis session, 15–30 g of glucose is removed from the patient and this loss can result in clinically manifest or undiagnosed hypoglycaemia (24, 25). Padmanabhan et al. noted that glucose-containing dialysate at 100 mg/dL significantly reduced the hypoglycemic episodes and their intensity. Hence, glucose-containing dialysate appeared to offer better glycemic control and lesser glycemic fluctuations during HD days for both diabetic and nondiabetic ESRD patients (26).

Study Limitations:

- The small number of patients who were enrolled in our study.
- We couldn't asses' blood glucose levels by continuous blood glucose monitoring (CGM) due to its high cost and it was unavailable at the time of the study.
- We didn't assess short-term and long-term health effects of glucose excursion in hemodialysis patients.

Conclusion:

Blood glucose excursion occurs more in diabetic hemodialysis patients than non-diabetic patients on hemodialysis, and in patients on insulin therapy more than non-insulin regimens. Hemodialysis decreases blood glucose proved by the presence of glucose in

the dialysate outflow. Fasting and postprandial blood glucose levels had significant positive correlations with blood glucose excursion in hemodialysis patients with type 2 DM, inferring that good glycemic control is important to decrease blood glucose fluctuations.

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Tables:

		Group I Non-DM on HD	Group IIA DM	Group IIB DM+CKD	Group IIC DM on HD	
DM	Minimum		3	5.5	6Y	
duration	Maximum	_	6	14.5	20Y	
duration	Mean		4.4+_0.89	9.4+_2.8	11.4+_4.3	
Svetelie	Minimum	110	110	110	120	
Systolic BP	Maximum	135	140	130	145	
51	Mean	125+-7.5	125+_9.4	121+_8.3	132+_8.5	
Diastalia	Minimum	75	70	70	80	
Diastolic BP	Maximum	90	90	95	95	
	Mean	84+_7.9	84+_7.3	85+_8.3	89+_5.16	
Dialyzia	Minimum	1Y			1Y	
Dialysis years	Maximum	10Y	-	-	7Y	
years	Mean	5.5+_1.2			4.0+_1.1	
	Insulin N		11	7	8	
Treatment	%	-	55.0%	35.0%	40.0%	
	Oral N		9	13	0	
	%		45.0%	65.0%	0.0%	

Table 1: Clinical characteristics in the studied groups

Table 2: Comparison of fasting, 2 hours postprandial blood glucose and HbA1c in
the studied groups

		Groups				Tests of significance		
		Group I Non-DM on HD	Group IIA DM	Group IIB DM+CKD	Group IIC DM on HD	Total	Test statistic	P value
	Minimum	95.0	118.0	87.0	85.0	85.0		<.001
Fasting	Maximum	130.0	170.0	179.0	171.0	179.0	15.00	
Fasting	Mean	111.9	142.1	143.5	122.5	130.0	15.99	
	SD	11.7	14.8	26.7	25.0	24.3		
2h	Minimum	130.0	231.0	163.0	161.0	130.0	32.47	<.001
	Maximum	230.0	360.0	320.0	310.0	360.0		
postpra ndial	Mean	175.8	279.1	261.6	222.0	234.6		
nulai	SD	30.0	40.8	47.4	40.6	56.2		
	Minimum	5.0	6.8	6.4	6.4	5.0	66.35	<.001*
HbA1c	Maximum	6.4	9.5	8.5	8.4	9.5		
	Mean	6.0	8.0	7.6	7.4	7.2		
	SD	.4	.8	.6	.6	1.0		

		5			
		Hemodialysis	Tests of significanc		
		Group I Non-DM on HD N=20	Group IIC DM on HD N=20	Test statistic	P value
	Minimum	119.0	139.0		
RBG before HD session	Maximum	183.0	310.0	3.99	<.001*
110 36331011	Mean± SD	151.2±20.3	197.1 ±47.3		
	Minimum	76.0	98.0		.008*
RBG during HD session	Maximum	210.0	226.0	2.81	
	Mean± SD	132.8±32.5	164.1±37.9		
	Minimum	55.0	53.0		
	Maximum	220.0	236.0		
RBG after HD session	Median	101.0	122.5	.69	.495
	IQR	88.5-121.0	76.5-144.0		
	Mean rank	19.22	21.78]	
	Blood g	lucose excursion		Mann-White	ney U test
		Group I Non-DM on HD N=20	Group IIC DM on HD N=20	Z _{mw}	P value
Glucose excursion (before- during)	Median	31.50	45.50		
	IQR	13.50-35.50	-30.0-75.50	1.78	.076
	Mean rank	17.20	23.80		
Glucose excursion	Median	55.50	105.0		
	IQR	32.0-66.0	16.0-128.50	2.30	.021*
(before-after)	Mean rank	16.25	24.75		

Table 3: Random blood glucose and blood glucose excursion in hemodialysisgroups

 Table 4: Correlation between glucose excursion and laboratory parameters in group I

Group I Non-DM on HD	Glucose excursion (before-during)		Glucose excursion (before-after)		
	r	р	r	р	
Fasting BG	383	.096	525	.018*	
2h PP BG	247	.295	351	.129	
HbA1c	.210	.374	.325	.163	
Urea	350	.130	275	.241	
Creatinine	152	.530	.021	.928	
eGFR	.206	.383	.003	.991	

Table 5: Correlation between glucose excursion and laboratory parameters in
group IIC

Group IIC	Glucose excursion (before- during)		Glucose excursion (before-after)		
DM on HD	r	р	r	р	
Fasting BG	.255	.279	.184	.438	
2h PP BG	.573	.008*	.506	.023*	
HbA1c	310	.184	221	.350	
Urea	.288	.219	.316	.175	
Creatinine	.092	.794	.051	.830	
eGFR	318	.127	.331	.154	