Glycemic disturbances in diabetic and non-diabetic patients undergoing hemodialysis

معدل شيوع الاختلاطات الوعائية واتباطها بعوامل الخطورة لدى مرضى السكري في مدينة المكلا/ حضرموت– اليمن

Balqis AL-Sayeed Abdulla Ebrahim [1]

Mohammed Omer Bahwal [2]

Maysa Saeed Al-Noban [3]

1) Assistance Pro, Internal Medicine.
2) Assistance Pro, Internal Medicine.
3) Lecturer , Community Medicine

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Alandalus University For Science & Technology

(AUST)

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Abstract :

Chronic kidney disease is a significant risk factor for the development of metabolic disturbance with or without presence of diabetes mellitus, this metabolic disturbance should be considered an important patient safety outcome in patients on hemodialysis, thus this cross-sectional study aimed to determine the effect of end stage renal failure on the blood glucose level in hemodialysis patients with or without diabetes mellitus and correlate of these parameters with the presence or absence of glycemic changes during hemodialysis. In this blood samples was assayed in 60 participants: 20 patients with end-stage kidney disease with type II diabetes mellitus (group I), 20 with end-stage kidney disease without diabetes mellitus (group II) and 20 with healthy volunteers (group III, control).Different available assays were used for blood glucose and the glycated hemoglobin. In this no significant difference was found in the post prandial of patients groups and control group. The glycosylated hemoglobin and fasting blood glucose significantly differed between patients groups and control group. The fasting blood glucose was significantly different between group I and II. It can be concluded from this study that glycated hemoglobin and fasting blood glucose strongly correlate with intra dialysis changes in patients with diabetes mellitus and non-diabetic patients. This finding indicates the importance of careful assessment and control of glycaemia during hemodialysis.

Keywords: Diabetic and non-diabetic Hemodialysis patients, glycatedhemoglobin, fasting and random blood sugar.

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Introduction :

In healthy non diabetic people, the pancreatic beta cells secrete half of the daily insulinrequirement (about 0.5 units/kg/day) at a steady basal rate independent of glucose levels, the other half is secreted in response to prandial glucose stimulation into the portal system passes through the liver, where about 75% is metabolized, with the remaining 25% metabolized by the kidneys. About 60% of the insulin in the arterial bed is filtered by the glomerulus, and 40% is actively secreted into the nephric tubules. [1] Most of the insulin in the tubules is metabolized into amino acids, and only1%of insulin is secreted intact. For diabetic patients receiving exogenous insulin, renal metabolism plays a more significant role since there is no first-pass metabolism in the liver. As renal function starts to decline, insulin clearance does not change appreciably, due to compensatory peritubularinsulin uptake. [2] But once the glomerulus filtration rate drops below 20 mL/min, the kidneys clear markedly less insulin,an effect compounded by a decrease in the hepatic metabolism of insulin that occurs in uremia.[3] Thus, despite the increase in insulin resistance caused by renal failure, the net effect is a reduced requirement for exogenous insulin in end stage renal failure (ESRD). [4] Diabetes mellitus is a leading cause of ESRD, [5] and glucose metabolism alterations due to insulin resistance, decreased insulin degradation, and blunt insulin secretion are common in ESRD patients. [6] It is known that intermittent hemodialysis dialyzes out blood glucose, and that hemodynamic change during hemodialysis induces stress hormones and inflammatory cytokines, which also affect blood glucose homeostasis. Indeed, type 2 diabetic patients with ESRD now represent a substantial proportion of patients undergoing chronic hemodialysis. [7] Diabetic patients have a high mortality rate, this is particularly marked in diabetic patients on chronic hemodialysis, and these patients have a poorer outcome than non-diabetic subjects. [8]

Though most uremic patients are insulin-resistant with associated glucose intolerance, hypoglycemia occurs in some patients undergoing hemodialysis,both impaired insulin

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degradation and reduced renal gluconeogenesis in uremic patients increase the risk of hypoglycemia.[9] Using sugar-containing dialysate further complicates blood glucose control in diabetic patients undergoing chronic hemodialysis. The altered glucose metabolism and dialysis process in CKD poses a great problem in blood glucose control in dialysis patients. [10], however, it is still unclear which factors play an important role in diabetic hemodialysis patients, who have a complicated glucose metabolism.

In patients with diabetes, strict glycemic control lowers the risk of cardiovascular events which are the main cause of death in this setting [11] and improves prognosis among those with CKD who undergo regular hemodialysis,[12] therefore, the accurate assessment of glycemic control is important to optimize outcomes .

Moreover, mild degrees of hyperglycemia in non-diabetic dialysis populations have been associated with reduced survival. [13] An accurate assessment of glycemic control in the dialysis population is therefore critical, to improve outcomes and survival. Several clinical tests are useful for measuring long-term glycemic control in the general diabetic population.[14] The hemoglobinA1c (HgbA1c) concentration is a marker of hyperglycemia and reflects average blood glucose concentration over 3 months in diabetic individuals. [15]

This test is routinely performed in diabetic subjects with chronic kidney disease and ESRD.[16] HbA1c , the most widely used assay, measures the percentage of circulating hemoglobin that has chemically reacted with glucose and reflects ambient blood glucose control over the prior 120 days, with the most profound effect in the preceding 30 days.[17]

Factors that shorten red blood cell (RBC) survival, including severe nephropathy, may reduce HbA1c since the time necessary for glucose to chemically bond with RBCs decreases.[18] If this significantly impacts HbA1c, dialysis patients and clinicians would be falsely comforted by relatively low HbA1c values despite high risk for subsequent cardiovascular disease and infectious complications. [19]

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However, ESRD significantly alters glycemic control, the results of hemoglobinA1c testing, and the excretion of anti-diabetic medications. The various and opposing effects of ESRD and dialysis can make blood glucose levels fluctuate widely, placing patients at risk of hypoglycemia and presenting a challenge for nephrologists and internists. [20]

HbA1c does not accurately reflect the actual status of glycemic control in some conditions where plasma glucose changes during short term, and in patients who have diseases such as anemia and variant hemoglobin. In comparison, another index of glycemic control, glycated albumin (GA), more accurately reflects changes in plasma glucose during short term and also postprandial plasma glucose. Although GA is not influenced by disorders of hemoglobin metabolism, it is affected by disorders of albumin metabolism. [21]

Despite these limitations, the hemoglobinA1c level is considered a reasonable measure of glycemic control in ESRD.Glycatedfructosamine and albumin are other measures of glycemic control with some advantages over HbA1c in dialysis patients. However, they can be affected by conditions that alter protein metabolism, including ESRD. [22]

The importance of accurately assessing glycemic status in the management of diabetic patients cannot be overemphasized. Various parameters including fasting glucose level, postprandial glucose level, and glycated hemoglobin are used to great effect in determining the glycemic status of patients, and their clinical significance has already been proven through numerous epidemiological and clinical studies. [23]

Thus, the relative amount of glycated protein serves as an indirect record of glycemic status over the period of protein turnover. Of the glucose monitoring markers using protein glycation, HbA1c, is considered the gold standard in the clinical setting. In addition, recent efforts addressing reference method standardization have empowered HbA1c as a diagnostic tool for diabetes.[24] Chronic kidney disease remains as one of the major complications for individuals with diabetes and contributes to

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considerable morbidity. Individuals subjected to dialysis therapy, half of whom are diabetic, experience a mortality of ~20% per year. Understanding factors related to mortality remains a priority. Outside of dialysis units,Hb A1c is unquestioned as the "gold standard" for glycemic control. However, there is evidence in large cohorts of diabetic dialysis patients that HbA1c at both the higher and lower levels was associated with mortality. Given the unique conditions associated with the metabolic dysregulation in dialysis patients, there is a critical need to identify accurate assays to monitor glycemic control to relate to cardiovascular endpoints. [25]

An ideal assay for long-term glycemic control in diabetes would accurately reflect serum glucose concentrations and predict hypoglycemia- and hyperglycemia-related complications,Hb A1c remains a widely used and trusted tool for assessing glycemic control in those patients. The accuracy and predictive ability of the HbA1c in those with ESKD has recently been called into question. The relationship of HbA1c to serum glucose concentrations changes markedly in advanced nephropathy, as a lower Hb A1c level is seen for similar glucose levels compared with patients without nephropathy. This observation likely reflects shortened erythrocyte (red blood cell) survival resulting in less time for hemoglobin and glucose to chemically interact. Incorrectly low HbA1c results in the dialysis clinic produce a false sense of security for patients and clinicians, potentially contributing to the dismal survival rates on dialysis, this controversies surrounding the clinical application of Hb A1c in patients with advanced kidney disease. Unadjusted HbA1c values do not predict outcomes in patients on dialysis. [26]

Methods :

This study is hospital control based study. It was performed on 60 adult persons who were 35 years or older and were incorporated in this study for about 7 months period (February to August 2014). The studied groups included 20 diabetic patients with end stage-renal failure (group I), 20 non-diabetic patients with end stage-renal

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failure (group II), and 20 apparently healthy volunteers as control group (group III).

All samples that were collected in the unit of hemodialysis of the Al-Gomhuria hospital (Aden governorate) were tested for glucose and glycosylated hemoglobin in a biochemical laboratory. Present and absence of diabetic mellitus in studied groups was confirmed by biochemical assay.

Studied patients (group I and II) were hemodialysis using glucose -free dialysis fluid. They did not take any medications prior to dialysis and were asked HbA1c and blood glucose level was measured in all subjects. Blood samples were collected from studied groups in plane tubes (1ml whole blood for fasting blood glucose of which 50 micron for HbA1c test and 1ml whole blood not in fasting state for random blood glucose) from each one and using EDTA asanticoagulants. HbA1c was measured by Chromatographic –spectrophotometric ion exchange and blood glucose measured by Digital color meter .

Data are expressed as means ± standard deviation (SD). Statistical significance between individual samples was determined by a two tailed t test, and correlations between various measurements were assessed. Statistical analysis was performed using the SPSS.

Results :

Group I consisted of 8 male and 12 female patients with a mean age of 44.8 years (range 35-60 years); group II consisted of 11 male and 9 female patients with a mean age of 43 years (range 38-63 years); and group III consisted of 10 male and10 female patients with a mean age of 45.8 years (range 38-52 years). HbA1c, FBS and 2-hour postprandial blood sugar test, for each group are presented in Table 1 .

The physiologically normal range for HbA1c, based on reference values from the laboratory, is less than 7%.HbA1c and FBS parameters were significantly different between patients and control group. The mean random blood sugar did not significantly differ between study groups and group III. In compare between

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studied groups and control group the mean FBS was significantly differed Table (1).

The mean of HbA1c showed statistically significant in studied groups (Iand II) when compared to control group (III) where the P value for the group I and II (0.01*, 0.000 * respectively).

The mean of RBS showed no differ in studied groups when compare to control group. The mean of FBS showed statistically significant in studied groups (I and II) when compared to control group III where the P value for the studied patients (0.000*) .Table2

There is a related correlation in HbA1c and FBS between studied groups. Table 3

Table 1: Glycemic tests measurements in each group of patients Characteristic

Characteristic	Group I n =20 (Mean ±SD)	Group II n =20 (Mean ±SD)	Group III n =20 (Mean ±SD)
HbA1c (%)	9 ± 0.1	6 ± 0.3	5 ± 0.3
Post prandial (mg/dl)	270 ± 2.6	170 ± 32.8	150 ± 2.4
Fasting glucose (mg/dl)	190 ± 0.02	90 ± 0.43	85 ± 0.03

Data are presented as mean ± SD

Table 2: Paired Samples Test of means against reference constants, and correlations for the Glycemic tests in each study group.

	Mean (±SD)	p-value	Confidence interval 95%	
			lower	upper
Hb A1c group I group III	7.05000 (4.53611)	0.01*	4.92703	9.17297
Hb A1c group II group III	7.6 00000 (3.9 85632)	0.000*	5.34667	9.4 653
Hb A1c group I group II	4.6 60000 (3.5 05394)	0,120	-6 005	-3 0194
RBS group I	5.45000 (3.64872)	0.250	3.742	7.1576

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group III				
RBS group II group III	5.7 20000 (3.138823)	0.450	42.509	71.890
RBS group I group II	5.1 75000 (3.297667)	0.115	67.835	36.316
FBS group I group III	0.067 50 (0.04 063)	0.000*	4. 848	8.651
FBS group II group III	0.075 600 (0.042 305)	0.000*	55 8005	95 39
FBS group I group II	0.068 850 (0.043 994)	0.000*	-8.9 43	-4 826

Table 3: Correlation between HbA1c and FBS in patients groups

	Group I	Group II
Hb A1c& FBS	0.02	٠.8

Discussion:

HbA1c is an incorporated in almost all the glycemic assessment for diabetes used worldwide and used in making major therapeutic decisions, such as those regarding hemodialysis patients.[27] Large changes in a person's blood glucose levels over the past month will show up in their HbA1c test result, but the Hb A1c does not show sudden, temporary increases or decreases in blood glucose levels. Even though the HbA1c represents a long-term average, blood glucose levels within the past 30 days have a greater effect on theHb A1creading than those in previous months.[28] Virtually all patients with diabetes have interadialysis blood glucose level disturbance. The uremic state indirectly affects the accuracy of the HbA1c assay through altered erythropoiesis but also through direct interactions with glycated hemoglobin analyses. Uremia-induced hemoglobin modification, forming carbamylated hemoglobin, also interferes with the laboratory analysis of the HbA1cassay. [29]

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There is a paucity of data in patients across a wide spectrum of CKD, and it is logical to assume the validity of the HbA1c assay will diminish in the context of advancing renal failure. [30]

However, patients with CKD were excluded from the study, it is possible that the metabolic fluctuations seen with hemodialysis may weaken the relationship between Hb A1cand average glucose.[31]

This is despite the fact that hyperglycemia is frequently reported in patients with chronic renal disease. [32] HbA1c is recognized as an accurate predicator of glycemic disturbance and the likelihood of progression to ESRF. It has thus been incorporated into commonly used prognostic indices of chronic renal disease. [33]

In our study, HbA1c values in patients with ESRF without diabetes were significantly different with to those in healthy participants (P<0.000). On the other hand, HbA1c values were significantly different in patients with diabetic than in healthy participants (P<0.0 1) .

A given value of HbA1c expressed in percentage may have little meaning in geographical areas where diabetic is prevalent, because even the "normal" reference values used by laboratories in these areas will be not true as a result of impaired synthetic kidney function in the population. [34] In our study, patients with elevated biochemical uremic markers had HbA1c values that differed significantly from those of control participants. Patients with diabetes tend to have nephropathy and ESRF leading to decreased levels of erythropoietin a marker that we suggested for effect onHbA1c level . As shown by Williamson glycated hemoglobin testing in CRF, HbA1c does not adequately reflect glycemic abnormalities in patients with severe uremia. Nevertheless, this parameter does give a good estimate of the synthetic function of the

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kidney and, thus, may be used as a prognostic marker for glycaemia. [35]

The HbA1c and FBS are used to assess diabetic and the maintenance of sugar during hemodialysis. (36(Our data indicate that FBS differed significantly between groups II and III (Table 2). On the other hand, FBS differed significantly between groups I and II, RBS does not adequately reflect glycemic disturbance in patients on hemodialysis .

However, it is of the utmost importance to realize that both HbA1c and FBS have substantial intra-laboratory variation in these patients. [37]The intra-laboratory variation of the Hb A1c is well known and was shown by Jordeand Sunds ,also to exist in patients with ESRF .[38]

Diabetic Care Associationconcluded that different reagents that act as glycated protein do not result in the same HbA1c from the same samples. (39)Ricks et al. comparedglucose values in 164 patients with renal impairment on hemodialysis, using baseline glucose, and reported difference in glucose measurement between the three groups and found a glucose ≥ 200 mg/dL was associated with a higher risk of mortality. [40] Our data have indicated that only FBS were significantly different between groups I and II (P<0.001), and, thus, a marker for the absence or presence of glycemic disturbance in hemodialysis patients .

Among risk factor reductions for mortality in dialysis patients with diabetes, improved glycemic control is widely recommended.

For these reasons, HbA1c accurate prognostic marker of glycemic disturbance in the presence of renal failure. However, in the future, there should be an attempt to either standardize the HbA1c and/or FBS in these patients or identify a better marker of synthetic function of the kidney

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