EVALUATING THE GLYCEMIC CONTROL INDEX OF CHRONIC KIDNEY DISEASE (CKD) PATIENTS IN SOKOTO

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ABSTRACT

Diabetes is a clinical condition characterized by increased blood glucose level (hyperglycemia). Prolonged diabetes is life threatening and is one of the major risk factors of CKD. If not properly monitored could predispose an individual to a high risk of cardiovascular complication and hasten the progression of CKD to attain end stage renal disease (ESRD). As such the maintenance of glucose homeostasis is crucial in preventing pathological consequences that may result from hyperglycemia. This study therefore aims to investigate the glycemic control index of CKD patients at each stage of the disease. This study was conducted on sixty seven CKD patients attending the nephrology units of Usmanu Danfodiyo University Teaching Hospital and Specialist Hospital Sokoto. The subjects were grouped into stages based on their estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) 4-variable equation. Blood samples were collected into lithium heparinised tubes and used to measure the glucose, glycated hemoglobin (HbA1c) and creatinine levels. The glucose level decreased from stage 1 ($p > 0.05$) to stage 5 while the HbA1c significantly increased as CKD advances. The HbA1c showed a highly significant negative correlation with eGFR ($p = 0.0002$). This study has shown there is poor glycemic control even in normoglycemic condition which could increase their progression to end stage renal disease (ESRD) and worsen the morbidity/ mortality rate among the CKD patients.

Keywords: Chronic Kidney Disease, Diabetes mellitus, Glycated hemoglobin

INTRODUCTION

Chronic Kidney Disease (CKD) is one of the most common diseases worldwide. In Nigeria, the incidence of CKD is about 1.6-12.4% population (Egbi *et al*., 2014; Makusidi *et al*., 2013; Odubanjo *et al*., 2011; Akinsola *et al*., 2009) with the patients progressively developing End Stage Renal Disease (ESRD). CKD is a pathophysiological process associated with renal function abnormalities and progressive reduction of glomerular filtration rate (GFR) for 3 months or more, with or without signs of kidney damage (George and Neilson, 2008; NKF-KDOQ1, 2002).

Diabetes is recognized as a leading cause of CKD and end stage renal failure. Its world prevalence was estimated at 422 million in 2016, and has been rising more rapidly in middle- and low-income countries (WHO, 2016). A key goal for diabetic treatment in patients with chronic kidney disease (CKD) is rigorous glucose control to prevent ESRD (Lubowsky *et al*., 2007). However, diabetes management in the CKD population warrants special considerations. Insulin is renally cleared and patients who have CKD with reduced eGFR (< 60 ml/min per 1.73 m^2) frequently have lower insulin requirements (Biensenbach *et al*., 2003; Rave *et al*., 2001). Likewise, with a decline in renal mass, patients with CKD may experience reduced renal gluconeogenesis (Synder and Bernds, 2004). Moreover, commonly used antidiabetic drugs are renally excreted and have a prolonged half-life in patients with CKD, predisposing them to episodes of hypoglycemia (Moen *et al*., 2009).

Glycated hemoglobin (HbA1c) is widely accepted and used as the most reliable test for assessment of chronic glycemia (Saudek *et al*., 2006). Normally when blood plasma glucose is elevated, the non-enzymatic glycation of hemoglobin increases, this

alteration reflects the glycemic history over the previous 2-3 months, since the erythrocytes have an average life span of 120 days (Braunwald *et al.,* 2001). Blood glucose was considered as a prime test for optimizing treatment of diabetes mellitus. But the HbA1c determination is the new better method to monitor the long term glucose control irrespective of glucose measurement for patient management. It would prevent or delay further diabetic complications (Seedahmed and Ahmed, 2013).

In this study, we aim to assess the glycemic control of CKD patients at each stage of the disease.

MATERIALS AND METHODS

Ethical approval was obtained from the Research Ethics Committee of Usmanu Danfodiyo University Teaching Hospital, Sokoto. Blood samples were collected from 67 patients attending dialysis centers of Usmanu Danfodiyo University Teaching Hospital and State Specialist Hospital Sokoto. The inclusion criteria were all the patients with the various stages of CKD present in the clinics who are willing to participate in the study while the exclusion criteria were the patients not willing to participate and those with established sepsis. 5mls of blood was collected into a lithium heparin vacutainer after an overnight fast. The concentration of creatinine of all the subjects was determined using colorimetric method. The value of the creatinine obtained was used to estimate the glomerular filtration rate (eGFR) using the 4 variable MDRD equation (Levey *et al.,* 1999).

$$eGFR = 186.3 \times (creatinine^{-1.154}) \times (age^{-0.203}) \times 1.212 \,(\text{if patient is black}) \times 0.742 \,(\text{if female})$$

The creatinine is measured in mg/dl, age is in years, and eGFR is expressed in ml/min per $1.73m^2$. This eGFR was used to assign CKD patients to each stage of CKD according to the KD0Q1 (2000) CKD classification method. Glucose is determined after enzymatic oxidation in the presence of glucose-oxidase. The hydrogen peroxide formed reacts under catalysis of peroxidase with phenol and 4-aminophenazone to form a red violet quinoneimine dye as indicator. Glycated hemoglobin is determined using an ELISA kit from Biotain Pharma Co. China.

STATISTICAL ANALYSIS

The results were expressed as Mean ± SEM. Student's t-test was used to compare the healthy control and the CKD patients. ANOVA was used to compare between the different stages and the control with Dunnet post test. Pearson's correlation was used to determine the relations between the different variables. $P<0.05$ was considered as statistically significant. Statistics was by Graphpad instat3 version 3.02, USA.

RESULTS

The results of the plasma creatinine and eGFR of the CKD patients at various stages of the disease are shown in Fig 1. There was steady increase ($p < 0.05$) in the mean concentrations of creatinine and consequent decrease ($p < 0.05$) in eGFR from stage 1 to stage 5 of the CKD patients as compared to the apparently healthy control subjects.
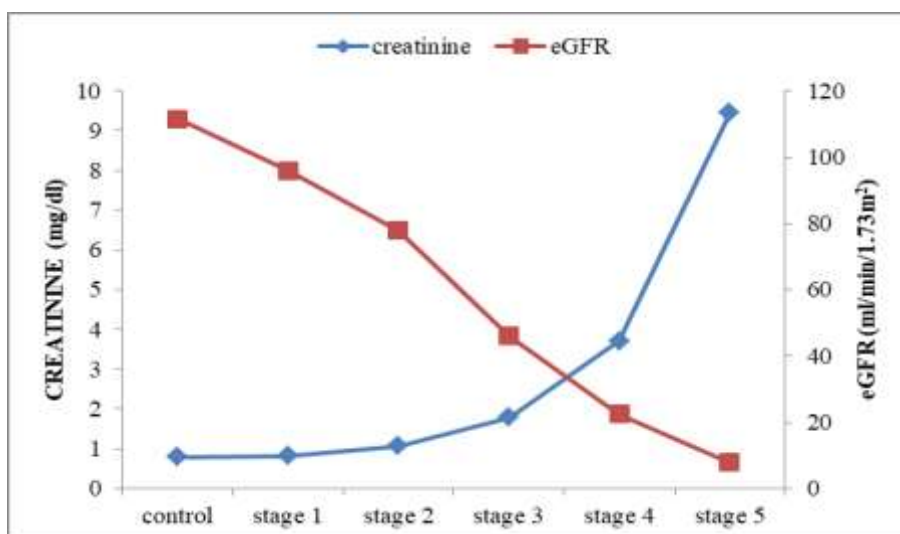

Fig 1: Plasma Levels of Creatinine (mg/ml) and eGFR (ml/min/1.73m²) at Various Stages of CKD.

Table 1 shows the results of the glycemic control markers of the CKD patients. It was observed that the glucose level significantly increased (P < 0.05) when compared to the healthy control subjects. Likewise, the HbA1c significantly increased (P < 0.05) in the CKD patients when compared to the healthy control subjects.

Table 1: Plasma glucose and HbA1c Levels of the CKD Patients and Apparently Healthy Control Subjects in Sokoto

Parameters	CKD Patients (n = 67)	Control (n = 15)	P-Value
Glucose (mmol/l)	5.61 ± 0.27	4.53 ± 0.14	0.0007
HbA1c (ng/ml)	45.32 ± 4.07	25.72 ± 5.00	0.0045

Values are mean ± standard error of means. HbA1c = Glycated hemoglobin

Fig 2 shows the results of the glucose level at various stages of CKD. The glucose levels slightly decreased (p > 0.05) from stage 1 to a deceptively normal blood glucose level at stage 5. Healthy control subjects 4.53 ± 0.14 mmol/l; CKD stage 1, 7.23 ± 0.93 mmol/l; CKD stage 2, 5.38 ± 0.24 mmol/l; CKD stage 3, 5.35 ± 0.39 mmol/l; CKD stage 4, 5.29 ± 0.46mmol/l; CKD stage 5, 4.66 ± 0.32 mmol/l.
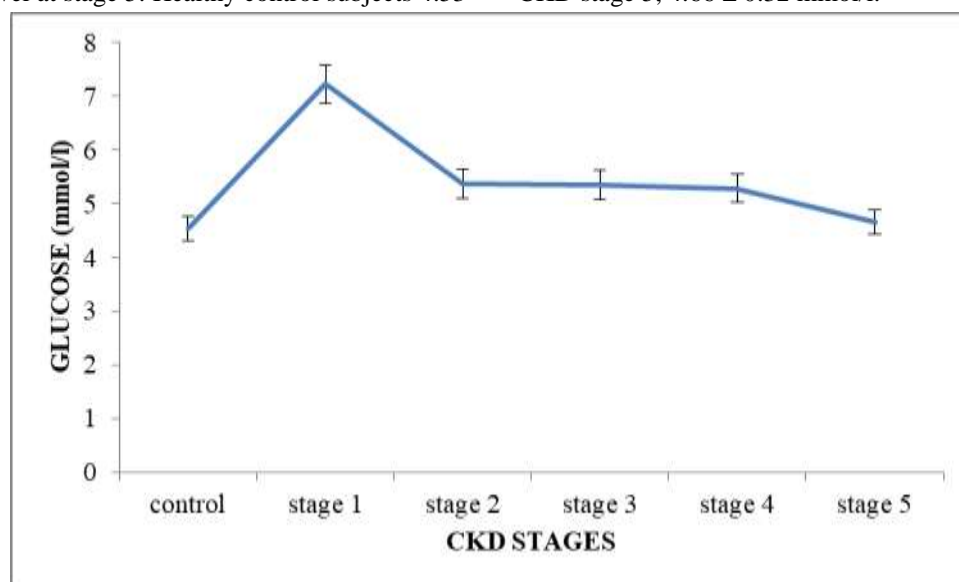

Fig 2: Levels of Glucose (mmol/l) at Various Stages of CKD.

Figure 3 shows the results of the glycated hemoglobin at various stages of CKD. HbA1c increased significantly (p < 0.05) as CKD advances confirming poor glycemic control. Healthy control subjects, 25.72 ± 5.00ng/ml; CKD stage 1, 30.59 ± 3.90ng/ml; CKD stage 2, 31.85 ± 3.06ng/ml; CKD stage 3, 34.83 ± 5.46ng/ml; CKD stage 4, 48.15 ± 7.51ng/ml; CKD stage 5, 76.38 ± 12.3ng/ml. Furthermore, there is a negative correlation between eGFR and HbA1c (Fig 4) which is statistically significant (p = 0.0002).
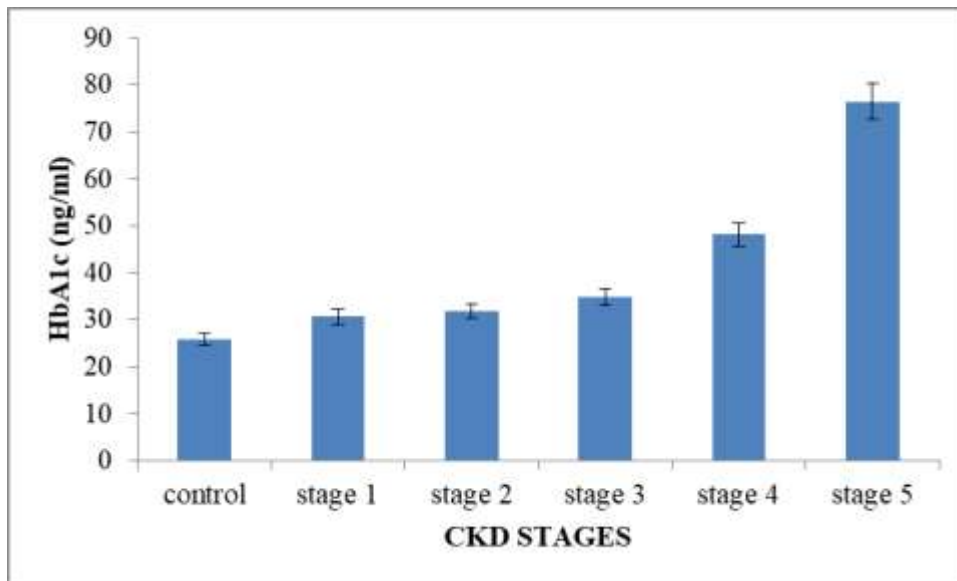
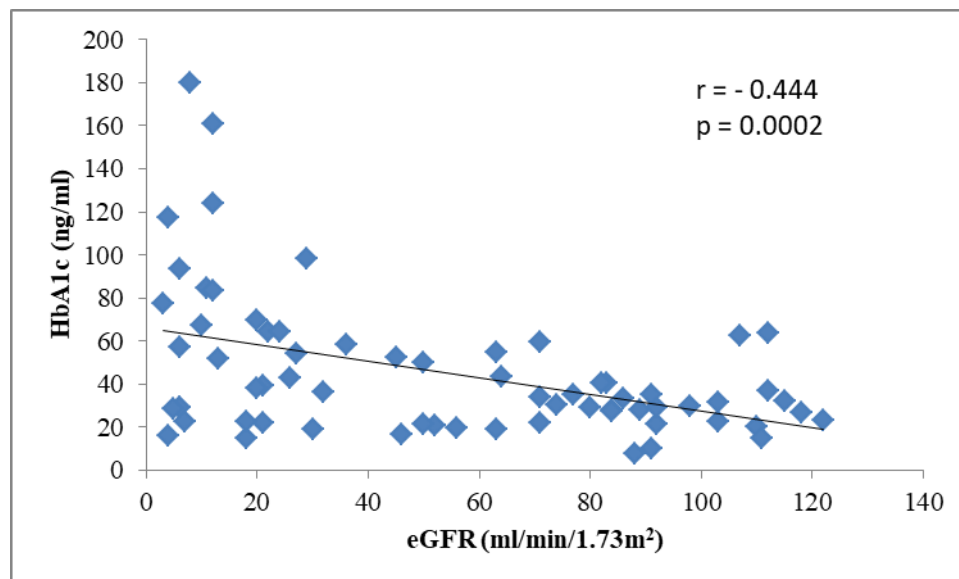*Fig 3: Mean HbA1c (ng/ml) levels at various stages of CKD*

Fig 4: Correlation graph of HbA1c and eGFR in the CKD patients

DISCUSSION

Diabetes mellitus is one of the leading causes of CKD and has been a major health problem of increasing magnitude worldwide (Ardhanari *et al.*, 2014). If not maintained, diabetes mellitus may result in CKD and consequent end stage renal disease (ESRD), as well as cardiovascular complications in the CKD patients. As such the maintenance of glucose homeostasis is crucial in preventing pathological consequences that may result from hyperglycemia or hypoglycemia (Triplitt, 2012).

As observed in this study, the patients' plasma creatinine level increased from stage 1 to stage 5 and consequently, the glomerular filtration rate was greatly reduced when compared to the healthy control. This indicated the kidney status of these patients as malfunctional and confirmed the chronic kidney disease patients status.

The present study showed normal glucose level as CKD advances but increased glycated hemoglobin. The normoglycemia observed could be due to the measures taken for the glucose control, use of antidiabetic drugs which are renally excreted and have a prolonged half-life in patients with CKD (Moen *et al.*, 2009). It could also be due to the level of circulating insulin in the patients as CKD advances. As the glomerular filtration rate decreases, there is decreased clearance of insulin leading to

persistent circulating insulin (Sampanis, 2008) and consequently may result in reduced blood glucose. The normoglycemia observed in this study could also be due to loss of appetite of the CKD patients, especially from stage 3 to 5. Moreover with a decline in renal mass, patients with CKD may experience reduced renal mass gluconeogenesis (Synder and Bernds, 2004). Previous studies also suggested that hemodialysis patients could have hypoglycemia because of the prolonged persistence of circulating insulin, altered dietary and exercise patterns (Goldberg *et al.,* 1980).

In addition, the low blood glucose levels observed in these CKD patients may not be indicative of excellent glycemic control because an increase was observed in the glycated hemoglobin from stage 1 to stage 5 of the CKD patients. Hemoglobin is non-enzymatically glycosylated when blood glucose enters the erythrocytes (Murray *et al.,* 2000). Normally when blood plasma glucose is elevated, the non-enzymatic glycation of hemoglobin increases. However, this study contrasts previous studies of reduced HbA1c in CKD patients (Vijatha *et al*., 2014). Shanthi *et al.,* (2013) found out that HbA1c levels are not only affected by blood glucose levels only but could be altered by other coexisting factors such as iron

deficiency anaemia, reduced red blood cell life span, recent transfusion, accelerated erythropoiesis due to erythropoietin therapy, and metabolic acidosis (Ansari *et al.,* 2003; Joy *et al.,* 2002). However, in anaemic patients, the concentration of glycated hemoglobin has been reported to be increased despite the shortened life span of the erythrocytes (Shanthi *et al.,* 2013). According to Vijatha *et al*., 2014, increased HbA1c may be due to carbamylation of erythrocytes interfering with HbA1c.

A highly significant negative correlation was observed between eGFR and HbA1c. This has clearly shown that among these patients, the HbA1c increases as the glomerular filtration rate diminishes even in the normoglycemic condition, an evidence of poor glucose control in the patients.

CONCLUSION

This study has clearly shown that there is poor glycemic control which could increase their progression to end stage renal disease (ESRD) and worsen the morbidity/ mortality rate among the CKD patients. However, further studies can be done to ascertain the causes of the increased glycated hemoglobin.

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