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IMPACT OF VIRAL INFECTIONS ON UREA AND CREATININE LEVELS IN PATIENTS WITH CHRONIC KIDNEY DISEASE ON HAEMODIALYSIS

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ABSTRACT:
Background: Chronic kidney disease (CKD) has emerged as a world-wide public health problem with substantial morbidity and mortality. Chronic viral infection is associated with a higher risk of death in patients with CKD undergoing haemodialysis. Objective: To evaluate the impact of viral infections on urea and creatinine levels in viral infected CKD patients on haemodialysis. Method: Retrospective study of 164 consecutive CKD patients referred to the laboratory for HIV, HBV, HCV, urea, electrolytes and creatinine from the dialysis unit of Abdullahi Wase Specialist Hospital,Kano, Nigeria between January 2006 and December 2008 was done. They consisted of 114 males and 50 females. The studied parameters were evaluated using standard routine methods. Results: Twenty six (15.9%) out of the 164 patients were positive for viral infections. The mean urea level in viral infected CKD patients was higher (47.5 ± 3.9mmol/L vs 40.8 ± 1.7mmol/L; $p < 0.002$) than non-viral infected patients. Similarly, mean creatinine level in the viral infected patients was higher than the non-viral infected counterparts (1096 ± 116 vs 973 ± 28mmol/L; $p < 0.001$). The mean urea level in the HBV infected patients was higher (54.3 ± 4.3mmol/L) than the HIV (42.7 ± 4.9; $p < 0.05$) and HCV (23.4 ± 0.2mmol/L;$p < 0.001$) infected CKD patients. Conclusion: Viral infections strongly impacted on the kidney in CKD and haemodialysis patients, hence exacerbation of disease progression. Treatment and prevention of viral infections should be promoted.

INTRODUCTION

The main causes of Chronic Kidney Disease (CKD) are diabetes mellitus and high blood pressure, which are responsible for over 60% cases. If uncontrolled, the progressive renal disease may lead to End-Stage Renal Disease (ESRD) requiring haemodialysis. Chronic kidney disease has emerged as a world-wide public health problem with substantial morbidity and mortality. Many cases of viral infections in CKD patients on dialysis may reflect the acquisition of an infection during dialysis. The risk of transmission is proportional to the time spent on haemodialysis and the prevalence of the infection within individual haemodialysis units (1). Chronic viral infection is associated with a 57% higher risk of death in patients with CKD undergoing haemodialysis when compared to non-viral infected subjects (2). This increased mortality may reflect not only hepatic dysfunction but increased cardiovascular disease and anaemia. Viral infections do not only affect the liver or

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heart but have been implicated in the pathogenesis of kidney disease.

Infections with Human Immunodeficiency Virus (HIV), hepatitis B virus (HBV) and hepatitis C Virus (HCV) can cause rapidly progressive renal disease and their recognition and management are critical in patients with ESRD (3). Even though significant progresses have been made in the prevention and control of viral infections in renal dialysis units, transmissions do still occur through contamination of equipment, environmental surfaces and the use of multiple dose vials of drugs (4). Chronic viral infections may have strong impact on the clinical course of kidney disease. Each virus typically causes characteristic histologic pattern, whereas HIV infection often causes collapsing focal sclerosis, HBV causes membranous glomerulonephropathy and HCV causes membranoproliferative glomerulonephritis (5). Viruses therefore may be capable of damaging the kidney in a number of ways that are often peculiar to the specific infection. This study was designed to evaluate the impact of viral infections on urea and creatinine levels in viral infected CKD patients on dialysis. The proportion of the CKD patients on dialysis who have been infected was also documented.

MATERIALS AND METHODS

Records of 164 consecutive patients who were referred to the laboratory from the dialysis unit of Abdullahi Wase Specialist hospital, Kano Nigeria for HIV, HCV and HBV antibodies and urea, electrolytes and creatinine were included in the study from January 2006 to December 2008. These were CKD patients who were on regular haemodialysis. They consisted of 114 males and 50 females. The blood samples were collected just before the commencement of a new round of haemodialysis into lithium heparin plastic containers and plasma obtained after centrifugation at 1000g for 10 minutes. HIV antibodies were screened using Determine reagent strip which is an immunochromatographic test strip supplied by Abbot Laboratories and those found to be positive were confirmed using ImmunoComb II technique by Orgenics, Isreal. The samples were also screened for HBsAg by latex agglutination technique. All positive samples were repeated using Enzyme Linked Immunosorbent Assay (ELISA) technique (Pathogyme Omega Diagnostics, UK). While HCV antibody was screened using immunochromatographic strip technique by Clinotech, Canada and positive samples were repeated using ELISA technique (HCV Murex 40, Anhet Laboratories USA). Urea was assayed using Urease-Berthelot technique while creatinine was assayed using alkaline-picrate colorimetric technique (Jaffe's method). Student's t-test was used for comparison of the means of urea and creatinine levels in the patients who were positive for HIV, HBV or HCV antibodies and non-viral infected CKD patients. The urea and creatinine values were expressed as means± SEM and levels were considered significant at $p < 0.05$.

RESULTS

The results are as shown in tables 1,2 and 3. Table 1 shows the mean levels of urea and creatinine in CKD patients on haemodialysis and the reference ranges. Twenty six (15.9%) out of the 164 CKD patients were positive for studied viral infections. The mean urea level was 41.8±4.6mmol/L while the creatinine level was 997±45µmol/L. Table 2 shows the mean urea and creatinine levels in viral infected CKD patients compared to non-

viral infected counterparts. The mean urea level in viral infected CKD patients was higher (47.5 ± 3.9 mmol/L vs 40.8 ± 1.7mmol/L, $p < 0.002$) than non-viral infected CKD patients. In the same vein, mean creatinine level in the viral infected CKD patients was higher than the non-viral infected CKD patients (1096 ± 116µmol/L vs 973 ± 28µmol/L, $p < 0.001$). Table 3 shows the studied parameters in the viral infected CKD patients based on the type of viral infection. The mean urea level in the HBV infected CKD patients was higher (54.3 ± 4.3mmol/L) than the HIV infected CKD patients (42.7 ± 4.9mmol/L). On the other hand, creatinine level in the HBV infected CKD patients (1089 ± 187) was lower than HIV infected CKD patients (1150 ± 137µmol/L). The difference was however not statistically significant ($p > 0.05$). The mean urea and creatinine levels of the HCV infected patients were lower (23.4 ± 0.2 mmol/L and 878 ± 1.2µmol/L) than those of HBV (54.3 ± 4.3 mmol/L, $p < 0.001$; 1089 ± 187µmol/L, $p > 0.05$) and HIV (42.7 ± 4.9 mmol/L, $p < 0.05$; 1150 ± 137µmol/L; $p > 0.05$) infected CKD patients. The mean urea level of non-viral infected CKD patients was lower than HBV ($p < 0.001$) and HIV ($p > 0.05$) infected patients, but was lower ($p < 0.001$) than that of HCV infected patients. In the same vein, the mean creatinine level of non-viral infected patients was lower ($p < 0.001$) than those of HBV and HIV infected CKD patients but higher ($p < 0.001$) than that of HCV infected patients.

Table 1:Plasma Urea and Creatinine levels in chronic Kidney Disease patients on haemodialysis.

Measured Variables	**Chronic Kidney Disease Patients**	**Reference Range**
Number of subjects	164(100%)	-
Number of males	114(69.5%)	-
Number of females	50(30.5%)	-
Number of viral infected patients	26(15.9%)	-
	41.8±4.6	1.7-8.3
Plasma Creatinine (µmol/L)	997±45	53-116

Table 2:Plasma Urea and Creatinine levels in viral infected Chronic Kidney Disease patients compared with non-viral infected CKD patients

Measured Variables	Viral Infected CKD patients	Non-viral infected CKD patients	p-Value
Number of Patients	26(15.9%)	138(84.1%)	-
Number of males	22	96	-
Number of females	04	42	-
Plasma Urea (mmol/L)	47.5±3.9	40.8±1.7	P<0.002
Plasma Creatinine (µmol/L)	1096±116	973±28	P<0.001

Table 3: **Urea and Creatinine levels in Chronic Kidney Disease patients based on type of viral infections**

Measured Variables	**HBV infected CKD patients**	**HCV infected CKD patients**	**p-value**	**HIV infected CKD patients**	**p-value**	**Non-viral infected CKD patients**	**p-value**
Number of patients	14	02	-	10	-	138	**-**
Number of males	12	02	-	08	-	96	**-**
Number of females	02	-	-	02	-	42	**-**
Plasma Urea (mmol/L)	54.3±4.3	23.4±0.2	P<0.001	42.7±4.9c	P<0.05	40.8±1.7	P<0.001
Plasma Creatinine (µmol/L)	1089±187	878±1.2	P>0.05	1150±137	P>0.05	973±28	P<0.001

C=p>0.05

DISCUSSION

Even though all the viral infected CKD patients did not demonstrate identical trend in their urea and creatinine levels, the mean urea and creatinine levels in the HBV and HIV infected CKD patients on haemodialysis were higher than non-viral infected CKD patients. It may suggest that viral infections exacerbate the complications associated with CKD. The impact of HBV on kidney disease was greater than those of HIV and HCV infected CKD patients. The impact of viral infections on the clinical course of kidney disease has been reported in some studies (5-6). It was observed that one of the parameters that are undoubtedly influencing the natural course of viral infections in CKD and dialysis patients was an impaired immune system leading to high susceptibility to many other viral and bacterial infections (5). Those immunological abnormalities affect both acquired and innate immunity. The impaired immune response may be the possible explanation for the differences between the consequences of HBV exposure of an immune-competent adult host and those infected CKD and dialysis patients (5,7). The observed differences in the impact of viral infection may be due to deficiency in CD8-cytotoxic and CD4 helper lymphocytes, whose functions are important in the destruction of viral infected cells and for ß-lymphocyte antibody production (8). Acquired immunity disturbances demonstrated by low expression of many adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), low CD80/CD86 receptors in antigen presenting cells as well as altered CD28 expression in T-lymphocytes have been reported (9-11). These antigen presenting cells and T-lymphocyte interactions are impaired in CKD and dialysis patients. The pathophysiological mechanism of glomerular deposition of immune complexes in CKD and dialysis patients consists of viral particles, viral antibodies and rheumatoid factors (13). Viral infections may impact strongly on kidney disease in a number of ways that are peculiar to the specific infection. The immune complexes which are formed from viral or endogenous antigens that are within the glomerular basement may combine with antibodies that also enter the glomerulus and are deposited within the kidney. This may be associated with deposition of extracellular matrix proteins in glomerular loops and mesangium since progressive renal disease is characterized by increased accumulation of acellular material within the glomerular mesangium.

In addition, viral proteins or inflammatory factors are commonly expressed in HIV associated nephropathy (3, 14). Viruses have been observed to have direct cyto-pathogenic effects on glomerular cells such that many of the glomerular filters are collapsed. Most HIV infected CKD and dialysis patients may present with heavy proteinuria with very high urea and creatinine levels (15). The kidney glomeruli are thus target organs for every haematogenous infections. Viral infections can cause primary glomerulonephritis since nephrotoxic agents precipitate renal disease that affects the interstitium and the tubular apparatus (16). Studies have shown also that the problems with kidney function in HIV infected people may be due to medications or HIV itself. Kidney disease in HIV infected subjects has been associated with more advanced HIV disease, low CD4 cell counts, diabetes, hypertension and acute bacterial infection of the kidney and sepsis (17). Kidney disease in HIV infection has been linked

with drug use but our records did not show drug use neither where the patients aware of their HIV status before evaluation. Studies have shown that there was a significant difference in creatinine clearance values of HIV infected patients but anti-retroviral drug use improved the patients outcome by reducing patients susceptibility to kidney disease (18).Despite the fact that the mean urea level in the HBV infected patients was higher than the HIV infected subjects, the observed mean creatinine level in HIV infected was however higher because of muscle wastages usually associated with HIV infection.

The number of HCV infected patients observed in this study may be too few to be subjected to meaningful independent statistical analysis. However, Johnson et al (19) reported that mixed cryoglobulinaemia was one of the most common extrahepatic manifestations in HCV infection which may impact and exacerbate kidney disease. Cryoglobulinaemia was defined as the presence in circulation of immunoglobulins that are reversibly precipitated in the serum. Type II cryoglobulinaemia was associated with membranoproliferative glomerulonephritis. The proportion of viral infected CKD patients on dialysis was observed to be 15.9% in this study. But the proportion of specific viral infections which was 8.5% for HBV, 6.1% for HIV and 1.2% for HCV was consistent with 0-10% reported by Burdick et al in a survey of three continents (20).

CONCLUSION

Viral infections strongly impacted on the kidney in CKD and dialysis patients and exacerbated disease progression. Treatment and prevention of viral infection should be promoted.

REFERENCES

1. Carrion AF, Martin P. Hepatitis C viral infection in patients with chronic kidney disease. Clin Liver Dis 2012;1(3):91-94.

2. Fabrizi F, Takkouche B, Lunghi G, Dixit V, Messa P, Martin P. The impact of hepatitis C virus infection on survival in dialysis patients: meta-analysis of observational studies. J Viral Hepatitis 2007; 14:697-703.

3. Gerald A. Viral infections and the kidney: HIV, hepatitis B and hepatitis C. Cleveland Clin J Med 2007; 74(5):353-360.

4. Ayodele OE, Salako BL, Kadiri S, Arije A, Alebiosu CO. Hepatitis B virus infection, implications in chronic kidney disease, diagnosis and transplantation. Afri J Med Med Sci 2006; 35(2):111-119.

5. Urbanek P. Viral hepatitis infections in chronic kidney disease patients and Renal Transplant Recipients. Kidney Blood Press Res 2012;35:454-467.

6. Bruggeman L. Viral subversion mechanisms in chronic kidney disease pathogenesis. Clin J Am Soc Nephrol 2007;2:S13-S19.

7. Fabrizi F, Messa P, Basile C, Martin P. Hepatitis disorders in chronic kidney disease. Nat Rev Nephrol 2010; 7:395-403.

8. Eleftheriadis T, Antoniadi G, Liakopoulos V, Kartsios C, Stefanidis I. Disturbances of acquired immunity in hemodialysis patients. Semin Dial 2007;5:440-451.

9. Coutin C, Pitard V, Delmas Y, Pelletier N, Defrance T, Moreau JF, Merville P, Dechanet-Merville J. Potential role of soluble CD40 in the humoral immune response impairment of uraemic patients. Immunology 2003;110:131-140.

10. Ori Y, Korzets A, Malachi T, Gafter U, Breitbart H. Impaired lymphocyte Calcium metabolism in end-stage renal disease: enhanced influx, decreased efflux and reduced response to mitogen. J Lab Clin Med 1999;4:391-400.

11. Sester U, Sester M, Hauk M, Kaul H, Kohler H, Girndt M. T-cell activation follows Th1 rather Th2 pattern in haemodialysis patients. Nephrol Dial Transplant 2000;8:1217-1223.

12. Meier P, Dayer E, Blanc E, Wauters JP. Early T cell activation correlates with expression of apoptosis markers in patients with end-stage renal disease. J Am Soc Nephrol 2002; 13:204-212.

13. Agnello V, De Rosa F. Extrahepatic disease manifestations of HCV infection. Some current issues. J Hepatol 2004; 40:341-352.

14. Casanova S, Mazzucco G, Barbiano di Belgiojoso et al. Pattern of glomerular involvement in human immunodeficiency virus-infected patients; an Italian study. Am J Kidney Dis 1995;26:446-451.

15. Winston JA,Bruggeman LA, Ross MD et al. Nephropathy and establishment of a renal reservoir HIV-type 1 during primary infection. N Engl J Med 2001; 344: 1979-1984.

16. Fokunang CN, Banin AN, Kouanfack C, Ngogang JY. Evaluation of hepatotoxicity and Nephrotoxicity in HIV patients on highly active anti-retroviral therapy. J AIDS HIV Res 2010;2(3):048-057.

17. Migueze-Burbano MJ. Renal disease in HIV infected subjects: the deleterious effect of smoking. Fifteen Int AIDS conference, Bangkok. Abstract MoPeB3274.

18. Kamga HLF, Assob JCN, Njunda AL, Nde Fon P, Nsagha DS, Atanga MBS, Weledji P, Puinta DP, Achidi EA. The kidney function trends in human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) patients at the Nylon District Hospital, Douala, Cameroon. J AIDS HIV Res 2011;3(2):30-37.

19. Johnson RJ, Gretch DR, Yamabe H, Hart J, Bacchi CE, Hartwell P, Couser WG, Correy L, Wener MH, Alpers CE .Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. N Engl Med J 1993;328:465-470.

20. Burdick RA, Bragg-Gresham JL, Woods JA, Hedderwick SA, Kurokawa K, Combe C, Saito A, La Bracque J, Port FK, Young EW. Patterns of hepatitis B prevalence and seroconversion in hemodialysis units from three continents: the DOOPS. Kidney Int 2003;63:2222-2229.