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Influence of Period of Diagnosis on Microalbuminuria and Myoglobin level among HIV-1 Infected Adults in a Nigerian Tertiary Hospital

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Abstract

Background: The introduction of anti-retroviral drugs in the treatment of individuals with Human Immunodeficiency Virus-1infection has improved the lifespan of infected subjects. Chronic Kidney disease is increasingly reported in such individuals.

Objective: The objective of this study was to determine if associations exist between some markers of renal function with duration of diagnosis in Human Immunodeficiency Virus-1 infected Nigeria subjects whether or not on Antiretroviral Therapy.

Materials and Methods: One hundred and fifty subjects (50 Human Immunodeficiency Virus negative, 50 positive treatment naïve and 50 subjects on Highly Active Antiretroviral Therapy) were enrolled in the study. Plasma creatinine, urea, uric acid, myoglobin and microalbuminuria were assayed using spectrophotometric and Enzyme Linked Immunosorbent Assay methods. Semi-structured questionnaire was used to obtain socio-demographic data of subjects.

Results: A positive correlation was observed between microalbuminuria ($r=0.341; p<0.05$) and myoglobin ($r=0.319; p<0.05$) with duration (years) of diagnosis in Human Immunodeficiency Virus-1 positive treatment naïve subjects. No such association existed in subjects on Antiretroviral Therapy treated subjects. A positive correlation was also observed between creatinine and Cluster of Differentiation 4 (CD4) count ($r = 0.333, p<0.05$), myoglobin and Cluster of Differentiation 4 (CD4) count($r=0.030, p<0.05$) in Human Immunodeficiency Virus positive subjects on Antiretroviral Therapy.

Conclusion: The levels of microalbuminuria and myoglobin increased with duration of infection in treatment naïve Human Immunodeficiency Virus-1 positive subjects. However, treatment with Antiretroviral Therapy may have restored back the loss of renal function from the initial damage caused by the viral infection.

Keywords: Human Immunodeficiency Virus-1, Highly Active Antiretroviral Therapy, Microalbuminuria, Myoglobin

1. Introduction

Kidney dysfunction,whether acute and chronic renal failure, is a known complication of Human Immunodeficiency Virus-1 (HIV-1) infection [1]. The aetiology of HIV-associated acute kidney disease is thought to involve the virus itself, co-morbid diseases or infections and anti-retroviral therapy [2]. Thus, acute renal failure has been linked to the use of indinavir and tenofovir, and can progress to chronic kidney disease (CKD) if not treated [3]. Sub-Saharan Africa is home to only 12% of the global population, yet accounts for 71% of the global burden of HIV infection. The development of CKD in those infected with HIV is thought to be mediated by viral proteins, host genetic variants, and environmental factors [2]. Chronic immune activation is a hallmark of HIV disease and results in increased viral replication and immune cell depletion, immune cell dysfunction, and aberrant lymphocyte turnover [4]. In addition to endogenous factors such as the effects of pro-inflammatory cytokines; exogenous factors such as the direct interaction between the HIV envelope and various cell types, and the effects of other infecting microbes are associated with increased cellular activation and thus may have significant effects on HIV disease and pathogenesis [4]. The treatment of HIV/AIDS consists of a combination of three to five agents targeting different viral proteins. These anti-retroviral drugs have improved the life expectancy and quality in HIV-1-infected individuals. Chronic viral infections may have strong impact on the clinical course of kidney disease. Viruses therefore may be capable of damaging the kidney in a number of ways often peculiar to specific infections[5]. (The risk of acute and chronic kidney disease remains higher in HIV-infected persons than in the general population, and kidney disease in HIV-infected persons is associated with poor outcomes, including increased mortality and morbidity. It was recently stated that HIV-associated nephropathy occurs less frequently in the era of antiretroviral therapy [6]. Kidney disease in HIV-infected persons manifests in a variety of ways, including HIVAN, non-collapsing focal segmental glomerulosclerosis, immune-complex kidney disease, acute kidney injury (AKI), comorbid chronic kidney disease (CKD), and kidney injury resulting from prolonged exposure to antiretroviral therapy or from opportunistic infections [7].

The objective of this study was to determine whether association exists between early markers of renal dysfunction and duration of HIV-1 diagnosis among adult Nigerians.

2. Materials and Methods

Study Area:

The study was conducted at Anti Retroviral Therapy (ART) Clinic, Ladoke Akintola University of Technology Teaching Hospital, a referral tertiary hospital located in Osogbo, Osun State, Nigeria. Diagnosis of HIV in this clinic was based on a positive ELISA reaction and confirmed by a Western blot.

Study Participants:

This is a cross sectional case-control study involving 150 participants comprised of 50 HIV positive patients on HAART, 50 HIV positive HAART naïve and 50 apparently healthy HIV -1 negative individuals.

Ethical Consideration:

The study protocol was approved by the Ethical Review Committee of the LAUTECH Teaching Hospital, Osogbo. All subjects who gave informed consent and met the inclusion criteria were enrolled in the study.

Inclusion Criteria:

HIV positive males and females subject on treatment, HIV positive male and female subjects who are not yet on drugs (naive), HIV negative males and female subject. Age bracket, for males and females subject (18-70 years).

Exclusion Criteria:

Patients known to have acute or chronic kidney disease, taking nephrotoxic drugs, or pregnant; or known to have diabetes mellitus, known to be hypertensive; HBsAg posiitive; Anti-HCV positive and under aged infected children (<18 years).

Sample Preparation and determination:

Five milliliters of random non-fasting venous blood were collected aseptically from each individual into lithium heparin. The blood samples were centrifuged at 5000rpm for 4mins. The plasma samples obtained were used to assay urea, creatinine and uric acid. The plasma was stored at −20° C until analyzed for myoglobin assay. Random urine was collected for microalbumin determination. The CD4 count, body weight and height were obtained from patient's medical records. The renal function markers were assayed using VIS Spectrophotometer 721(D) UK with standard procedures and methods as previously described [8]. Myoglobin was analyzed by ELISA technique using AccuBind reagents [8].

3. Statistical analysis

The SPSS (statistical package for social sciences) software version 21.0 was used for the statistical analysis. Values obtained from the study expressed as mean ± standard deviation were compared using the independent student T- test and ANOVA to compare the measured variables between groups. The significance was measured at $P<0.05$.

4. Results

The results are as presented in tables [1-7]. The study participants were 50 (14 males, 36 females and mean age 40.36 ± 8.39) HIV-1-positive individuals on HAART, 50 (21 males, 29 females and mean age 39.67 ± 11.88) HIV-1-positive individuals HAART naïve and 50 (30 males, 20 females and 34.50 ± 9.27) HIV-1-negative controls.

Table 1: Comparison of measured parameters with duration of treatment in HIV positive subjects on HAART (Mean± SEM)

Duration	No of Subjects	Urea (mmol/L)	Creatinine (µmol/L)	Uric acid (mg/dl)	Microalbuminuria (mg/L)	Myoglobin (ng/ml)	CD4 count (cells/µL)
<1 Yr	5	4.18 ±2.85	95.60 ± 25.25	5.90 ± 1.66	46.00 ± 35.06	40.60 ± 30.23	256.20 ± 115.94
1-2Yrs	6	3.72 ± 0.94	93.83 ± 17.72	4.62 ± 1.21	47.83 ± 41.30	49.50 ± 43.02	203.83± 196.51
3-4 Yrs	5	4.24 ± 1.43	95.60 ± 19.96	5.80 ± 2.48	25.80 ± 18.84	42.60 ± 13.16	368.0 ± 196.51
5-6 Yrs	13	4.38 ± 1.33	100.69 ± 16.65	6.04 ± 2.74	53.85 ± 44.04	42.15 ± 17.02	261.38 ± 187.34
>6Yrs	21	5.05 ± 2.89	10.57± 41.26	6.44 ± 2.34	63.43 ± 49.52	44.00 ± 35.02	192.53 ± 103.59
F-value		0.529	0.607	0.730	0.825	0.078	1.777
P-value		0.715	0.660	0.576	0.517	0.989	0.150

Table 1 shows the comparison of parameters with duration of treatment in HIV Positive patients on HAART. The level of each parameter showed no significant difference ($p>0.05$) when compared with the duration of treatment of the patients.

Table 2: Comparison of measured parameters with duration of diagnosis of infection in HIV positive ART naïve subjects (Mean± SEM)

Diagnosis of Infection	No of Subjects	Urea (mmol/L)	Creatinine (µmol/L)	Uric acid (mg/dl)	Microalbuminuria (mg/L)	Myoglobin (ng/ml)	CD4 count (cells/µL)
1-2 Yrs	9	3.85 ± 1.14	101.63 ± 23.39	6.14 ± 1.95	27.75 ± 25.05	22.38 ± 23.73	401.00 ± 187.66
3-4 Yrs	17	4.42 ± 2.66	96.71 ± 41.89	5.15 ± 2.51	40.53 ± 39.10	81.59 ± 84.61	255.59 ± 115.04
5-6 Yrs	24	4.63 ± 2.17	106.43 ± 26.16	6.83 ± 2.43	69.64 ± 56.05	112.79 ± 102.49	174.36 ± 96.87
>6 Yrs	10	5.45 ± 2.18	111.10 ± 18.19	6.35 ± 1.75	72.00 ± 30.34	167.10 ± 105.04	136.50 ± 80.59
F-value		0.888	0.419	1.299	2.247	3.247	7.254
P-value		0.479	0.794	0.285	0.079	0.019	0.001

Table 2 shows the levels of measured parameters in study participants and duration of diagnosis of infection. The level of myoglobin was significantly higher ($p<0.05$) in patients with longer duration of infection. Also, a significantly lower level of CD4 count ($p<0.01$) was observed with longer duration of diagnosis.

Table 3: Correlation of measured parameters with duration of treatment in HIV Positive patients on ART

Parameters	**R-value**	**P-value**	**Significant**
Urea (mmol/L) vs Duration of Treatment (years)	0.009	0.948	p>0.05
Creatinine (µmol/L)vs Duration of Treatment (years)	-0.220	0.240	p>0.05
Uric acid(mg/dl) vs Duration of Treatment (years)	-0.192	0.181	p>0.05
Microalbumin (mg/L) vs Duration of Treatment (years)	-0.870	0.546	p>0.05
Myoglobin (ng/ml) vs Duration of Treatment (years)	-0.233	0.103	p>0.05

Table 3 shows the correlation of renal function biomarkers and myoglobin with duration of treatment in HIV Positive patients on HAART. There was no significant correlation ($p>0.05$) between the measured renal function markers and myoglobin with duration of treatment in HIV Positive subjects on HAART.

Table 4: Correlation of measured variables with duration of diagnosis of infection in HIV Positive Naïve patients

Parameters	R-value	p-value	Significant
Urea (mmol/L) vs Diagnosis of Infection (years)	0.268	0.060	p>0.05
Creatinine (µmol/L)vs Diagnosis of Infection (years)	0.173	0.230	p>0.05
Uric acid(mg/dl) vs Diagnosis of Infection (years)	0.199	0.181	p>0.05
Microalbumin (mg/L) vs Diagnosis of Infection (years)	0.341	0.015	p<0.05
Myoglobin (ng/ml) vs Diagnosis of Infection (years)	0.319	0.024	p<0.05

Table 4 shows the correlation of measured variables with diagnosis of infection in HIV Positive Naïve patients. There was a significant positive correlation (R= 0.341; p<0.05) between microalbuminuria and diagnosis of infection. Also, a significant positive correlation (R= 0.319; p<0.05) was observed between myoglobin and diagnosis of infection. On the other hand, no significant correlation (p>0.05) was observed between urea, creatinine, uric acid and diagnosis of infection in HIV Positive Naïve patients.

Table 5: Correlation of measured biomarkers of renal function and myoglobin with CD4 count in HIV Positive patients on HAART

Parameters	R-value	P-value	Significant
Urea (mmol/L) vs CD4 count (cells/µL)	-0.050	0.733	p>0.05
Creatinine (µmol/L)vs CD4 count (cells/µL)	0.333	0.014	p<0.05
Uric acid(mg/dl) vs CD4 count (cells/µL)	0.009	0.148	p>0.05
Microalbumin (mg/L) vs CD4 count (cells/µL)	0.217	0.130	p>0.05
Myoglobin (ng/ml) vs CD4 count (cells/µL)	0.303	0.032	p<0.05

Table 5 shows the correlation of renal function markers and myoglobin with CD4 count in HIV Positive patients on HAART. There was a significant positive correlation (R=0.333; p<0.05) between creatinine and CD4 count. Also, a significant positive correlation (R= 0.303; p< 0.05) was observed between myoglobin and CD4 count in HIV Positive patients on HAART. On the other hand, no significant correlation (p>0.05) was observed between urea, uric acid, microalbumin and CD4 count in HIV Positive patients on HAART.

Table 6: Correlation of measured biomarkers of renal function and myoglobin with CD4 count in HIV Positive ART Naïve patients

Parameters	R-value	P-value	Significant
Urea (mmol/L) vs CD4 count (cells/µL)	-0.091	0.532	p>0.05
Creatinine (µmol/L)vs CD4 count (cells/µL)	0.094	0.516	p>0.05
Uric acid(mg/dl) vs CD4 count (cells/µL)	-0.060	0.680	p>0.05
Microalbumin (mg/L) vs CD4 count (cells/µL)	0.117	0.417	p>0.05
Myoglobin (ng/ml) vs CD4 count (cells/µL)	-0.206	0.152	p>0.05

Table 6 shows the correlation of measured renal function biomarkers and myoglobin with CD4 count in HIV Positive Naïve patients. There was no significant correlation (p>0.05) between the measured renal function biomarkers, myoglobin and CD4 count in HIV Positive naïve patients.

Table 7: Correlation of measured parameters of renal function and myoglobin with CD4 count in HIV Negative Control subjects

Parameters	R-value	p-value	Significant
Urea (mmol/L) vs CD4 count (cells/µL)	-0.102	0.483	p>0.05
Creatinine (µmol/L)vs CD4 count (cells/µL)	0.105	0.469	p>0.05
Uric acid(mg/dl) vs CD4 count (cells/µL)	-0.017	0.908	p>0.05
Microalbumin (mg/L) vs CD4 count (cells/µL)	-0.125	0.389	p>0.05
Myoglobin (ng/ml) vs CD4 count (cells/µL)	0.049	0.736	p>0.05

Table 7 shows the correlation of measured renal function biomarkers and myoglobin with CD4 count in HIV Negative Control subjects. There was no significant correlation (p>0.05) observed between the renal function biomarkers, myoglobin and CD4 count in HIV Negative control subjects.

5. Discussion

Renal disease is a common complication of HIV-infected patients, associated with increased risk of cardiovascular events, progression to AIDS, AIDS-defining illness, and mortality (both all-cause and AIDS-related) [9]. Moreover, HIV-infected patients have a faster decline in renal function and are at higher risk of progression to end stage renal disease (ESRD), requiring costly renal replacement therapy in the form of dialysis or transplantation [10].

There was a significant decline in the CD4 count in HIV positive HAART naïve group as shown in (table 2) as the year of diagnosis of infection increases and this is in agreement with [11] that CD4 count decline with time thereby leading to the suppression of the immune system. Also, there was a significant increase in myoglobin level of HIV positive HAART naïve subjects when compared with the duration of diagnosis of infection. This is in agreement with [12] that acute renal failure as a result of HIV infection may lead to high level of myoglobin. There is no significant difference in the level of renal function biomarkers and myoglobin when compared with duration of treatment in HIV positive patients on HAART.

Meanwhile, the duration of treatment with HAART did not adversely affect the levels of Microalbuminuria. This observation is consistent with previous studies elsewhere [13,14].These authors opined that the use of HAART was not influenced by the occurrence of microalbuminuria but kidney disease can be associated with the presence of intrinsic factors such as genetic predisposition. It was reported that antiretroviral therapy may prevent the loss of protein in urine as a result of kidney damage [15].

In addition, a significant positive relationship ($R=0.341$; $p<0.05$) was observed between microalbuminuria and duration of diagnosis of infection (years) in HIV positive HAART naïve subjects and this is consistent with previous studies [16, 17]. The authors observed that the levels of microalbuminuria were higher in patients with moderate to severe immunosuppression or advanced HIV infection. In our study however; we did not observe significant correlation in the levels of Microalbuminuria with CD4 cell count which is a marker of disease progression. Treatment with HAART in HIV positive subjects did not adversely affect the levels of microalbuminuria in this study.

There was a positive significant relationship ($R= 0.319$; $p<0.05$) in the correlation of myoglobin with the diagnosis of infections (years) in HIV positive HAART naïve subjects and this is an indication that the myoglobin level increases with prolonged years of infection without treatment. This observation of increased myoglobin levels is in agreement with [18] where increased level of myoglobin in their study participants was related to HIV infection and other complications of HIV infection such as opportunistic infections (viral, fungal and bacteria) thus leading to rhabdomyolysis.

A positive significant relationship was observed ($R= 0.333$; $p<0.05$) in the correlation of creatinine with CD4 count in HIV infected subjects group on HAART. This could be attributed to the fact that the use of HAART suppress the viral loads and increase CD4 counts thus leading to a decrease in the rate of damage caused by HIV infection [19]. However, in an attempt by HAART to increase the CD4 count, the initial derangement by the virus on the renal function is restored back after the administration of HAART to their normal functional capacity which can be reflected with apparently normal renal function biomarkers. These effects are indicative of a positive prognosis with regard to HIV/AIDS infection which resulted from the initiation of HAART. However, alteration in renal functions may be associated to the side effect of the drugs. HAART can cause renal injury through a variety of mechanisms such as direct renal tubular toxicity (Fanconi-like syndrome and distal tubular acidosis), crystal deposition in the kidney thereby causing obstructions and glomerular lesions [20].

6. Limitation of the Study

The toxicities of HAART are generally modest or severe. This depends on the level of genetic predisposition of the HIV patients. The limitation of the study is most of the HIV patients were not certain of the period when they contacted the viral infections and also the sources of infections. However, proper monitoring needs to be put in place in various antiretroviral clinics within and outside the country for effective study.

7. Conclusion

Renal insufficiency remains prevalent in HIV patients. Changes in renal function occur in HIV infection and during administration of HAART. Human Immunodeficiency Virus (HIV) infection is associated with decline rate of CD4 count, and long term viral infection without treatment may lead to renal impairment and damage. Meanwhile, HAART treatment did not adversely affect renal function in this study, but long-term treatment with HAART may be associated with a higher incidence of renal impairment as demonstrated by the correlation of microalbuminuria with duration of treatment in HIV positive subjects.

Recommendation

Close monitoring of patients before and during HAART administration

Microalbuminuria and other biomarkers of renal function should be periodically measured in subjects on HAART treatment.

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Conflict of Interest

None declared.

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