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Assessment of Some Biomarkers of Renal Function and Myoglobin Level in Human Immunodeficiency Virus-1 Infected Subjects.

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ABSTRACT

Background: The emergence of highly active antiretroviral therapy (HAART) has led to dramatic improvements in prolonging the life expectancy of HIV-infected patients. However, long-term use may cause kidney derangements that may be life-threatening. **Objective**: This present study seeks to assess the levels of microalbuminuria and myoglobin in HIV positive subjects. **Materials and Methods**: One hundred and fifty subjects [50 HIV negative, 50 positive HAART naïve and 50 HAART treated subjects] were enrolled in the study. Plasma creatinine, urea, uric acid, myoglobin and urine microalbumin were assayed using standard methods. **Results**: Microalbuminuria was significantly higher ($p<0.001$) in HIV positive than HIV negative subjects, while the differences in the levels of urea, creatinine, uric acid and myoglobin were insignificant. The levels of urea ($p<0.001$), creatinine ($p<0.018$) and uric acid ($p<0.001$) were significantly higher in HIV positive HAART naïve than HIV positive on HAART. Even though the levels of microalbuminuria were higher while myoglobin was lower in HIV positive HAART naïve than HIV positive on HAART, the difference was not statistically significant. **Conclusion**: The levels of measured markers of renal function were higher in HIV positive subjects whether or not on HAART treatment. However, HAART treatment did not adversely affect renal function in this study.

Keywords: HIV, HAART, Microalbuminuria, myoglobin.

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INTRODUCTION

The early events in Human Immunodeficiency Virus-1 (HIV-1) disease take place rapidly, and once they occur, infection is permanently established (1). The events associated with primary HIV infection are critical determinants of the subsequent course of HIV disease. Preventing or interfering with these early events is an important goal of all prevention efforts that focus on pathogenic events (2). The introduction of anti-retroviral therapy (ART) in the management of HIV infection has resulted in a significant reduction in the morbidity and mortality associated with the disease (3). It was recently recommended that all HIV-infected individuals with detectable viremia, regardless of their CD4 cell count, should begin antiretroviral therapy (ART) as soon as possible after diagnosis to prevent disease progression, improve clinical outcomes, and reduce transmission (4). The new ART drugs combined excellent potency with greater convenience, safety, and tolerability make lifelong viral suppression achievable and reduce the risk of viral resistance. In HIV-infected persons, ART is effective in preventing HIV transmission (5,6) and provides individual and public health benefits. Antiretroviral drugs are classified according to the step they inhibit in the viral life-cycle and the discovery of the multi-step replicative life cycle of HIV in human CD4+ T-cells has led to the identification of potential drug targets to slow the replicative process. This resulted in unprecedented scientific progress in the drug discovery and drug development process (7). The new trends for the treatment of HIV/AIDS consists of a combination of three to five agents targeting different viral proteins, i.e. the reverse transcriptase, protease, integrase and envelope, and aims to suppress viral replication to undetectable levels. This "highly active antiretroviral therapy" (HAART) has brought a massive benefit for life expectancy and quality in HIV-1-infected individuals (8). HIV-infected subject care has now shifted from complications arising from opportunistic infections with other causes associated to HIV pathogenesis and toxicity of HAART (9). HAART side-effects may be transient or may persist throughout therapy and this usually leads to switching or discontinuing therapy resulting in non-adherence by the patients (10). The increases in access to HAART have made the management of drug toxicities an increasingly crucial component of HIV care in developing countries (11). The severity of adverse effects of HAART varies by ethnicity, individual differences, age, region, and interaction with other drugs, including alcohol and type or class of drug (12). The adverse side effects related to HAART in developing countries may differ from that in developed countries because of the high prevalence of conditions such as anemia, malnutrition, tuberculosis and frequent initial presentation with advanced HIV disease (11). Furthermore, the clinical course of Chronic Kidney Disease (CKD) has become indolent, and survival of HIV-infected persons with End Stage Renal Disease (ESRD) is prolonged. Parenthetically, this in turn has led to increasing prevalence of CKD in HIV populations despite declining incidence (13). Furthermore, the incidence of renal disease and need for dialysis were significantly lower in patients receiving continuous ART compared to those on intermittent ART (13,14). This study was therefore undertaken to evaluate some markers of renal function in HIV-1 infected Nigerians on HAART and HAART naïve.

MATERIALS AND METHODS

Study Participants

This is a cross sectional study involving 150 participants comprised of 50 HIV positive subjects on HAART, 50 HIV positive HAART naïve and 50 apparently healthy individuals of HIV negative status.

Study Area and Ethical Consideration

The study was conducted at Anti- Retroviral Therapy (ART) Clinic, Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital, a referral tertiary hospital located in Osogbo, Osun State, Nigeria. The study participants were HIV infected patients on routine visit to the ART clinic, LAUTECH Teaching Hospital (LTH), Osogbo.
The study protocol was approved by the Ethics Review Committee of the LAUTECH Teaching Hospital, Osogbo. All subjects who gave informed consent and met the inclusion criteria were enrolled for 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 subjects. Age bracket, for males and females subject (18 – 70 years).

Exclusion Criteria

Subjects identified to have acute or chronic kidney disease, taking nephrotoxic drugs, or pregnant; or known to have diabetes mellitus, hypertensive; HBsAg positive; Anti-HCV positive and underaged infected children (<18 years) were excluded.

Sample Preparation and determination

Ten milliliters of random non-fasting venous blood was collected aseptically from each individual into lithium heparin. The blood samples were centrifuged at 5000rpm for 4mins. The HIV status was confirmed using double serological techniques. The plasma samples obtained were used to assay urea, creatinine and uric acid. Random urine specimens were also collected same day the blood samples were collected for microalbumin assay. The serum was stored at −20°C until analyzed for myoglobin assay. 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. Myoglobin was analyzed by ELISA technique using AccuBind reagents kit supplied by Monobind Inc, Lake Forest, CA, USA.

Statistical Analysis

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

RESULTS

The results are as presented in tables 1, 2 and 3. 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 shows the comparison of microalbuminuria, myoglobin, urea, creatinine, uric acid, CD4 count, BMI, and age in HIV Positive patients on HAART, HIV Positive HAART Naïve and HIV Negative controls**.** The mean levels of microalbuminuria in HIV Positive subjects on HAART, HIV Positive HAART Naïve subjects were significantly higher

(p<0.01) when compared with HIV Negative control subjects. The mean levels of myoglobin in HIV Positive subjects on HAART were slightly higher than that of the HIV Negative controls while the mean myoglobin level of HIV positive naïve subjects was slightly lower than that of the HIV Negative controls though these differences were not statistically significant. The mean levels of urea, creatinine and uric acid in HIV positive Naïve subjects were significantly higher (p<0.01) when compared with the HIV Negative controls while those of HIV positive subjects on HAART were not significantly different from the HIV Negative controls. The means CD4 count of subjects with HIV Positive on HAART, HIV Positive Naïve subjects were significantly lower (p<0.01) when compared with HIV Negative controls. The mean BMI of subjects with HIV Positive Naïve was significantly lower (p<0.01) when compared with HIV Negative controls while that of HIV positive patients on HAART was not significantly different from that of the HIV negative controls. The means age of subjects with HIV Positive on HAART, HIV Positive Naïve were significantly higher (p<0.05) when compared with HIV Negative Controls.

Table 2 shows the comparison of renal function markers, and myoglobin between male and female HIV positive on HAART subjects. The levels of creatinine and uric acid were significantly higher (p<0.05) in male subjects than female subjects. However, the levels of urea, microalbuminuria and myoglobin in male subjects when compared with the female subjects were not significantly different (p>0.05).

Table 3 shows a comparison of renal function markers, and myoglobin between male and female HIV positive naive subjects. The level of myoglobin was significantly higher (p<0.05) in male subjects than female subjects in HIV positive naïve subjects. But the levels of urea, creatinine, uric acid and microalbumin in male subjects when compared with the female subjects were not significantly different (p>0.05).

Table 1: Comparison of BMI, markers of renal function and CD4 count in HIV Positive Subjects on HAART, HIV Positive HAART naïve and HIV Negative control (Mean±SD)

Variables	HIV positive on HAART	HIV positive naïve	HIV negative Control	F-value	p-value
Age (years)	40.36 ± 8.39[b]	39.67 ± 11.88[b]	34.50 ± 9.27	5.164	0.007
Microalbuminuria (mg/L)	49.54 ± 58.5[a]	53.56 ± 43.70[a]	8.30 ± 7.16	17.474	0.001
Myoglobin (ng/ml)	59.20 ± 54.59	43.70 ± 29.24	52.36 ± 38.67	1.699	0.187
Urea (mmol/L)	3.29 ± 1.05	4.55 ± 2.23[a]	3.30 ± 0.72	11.754	0.004
Creatinine (µmol/L)	91.42 ± 16.02	103.00 ± 30.44[a]	83.30 ± 12.00	11.056	0.001
Uric acid (mg/dl)	4.15 ± 1.25	5.99 ± 2.29[a]	4.42 ± 1.14	18.223	0.001
CD4 count (cells/µL)	583.28 ± 285[b]	235.66 ± 146.43[a]	907.32 ±45.11	136.54	0.001
BMI (Kg/m^2)	23.29 ± 3.88	21.71 ± 2.99[a]	23.87 ± 3.00	5.673	0.004

a: indicates p-value<0.01 which is considered significant when compared with control
b: indicates p-value<0.05 which is considered significant when compared with control

Table 2: Comparison of some markers of renal function between male and female HIV positive on HAART subjects (Mean±SEM)

Parameters	Male N=14	Female N=36	p-value
Urea (mmol/L)	3.47 ± 1.16	3.22 ± 1.01	0.469
Creatinine(µmol/L)	99.28 ± 16.25	88.36 ± 15.16	0.030
Uric acid (mg/dl)	4.74 ± 1.43	3.93 ± 1.16	0.037
Microalbuminuria (mg/L)	36.64 ± 18.63	54.56 ± 67.63	0.336
Myoglobin (ng/ml)	78.21 ± 70.14	51.23 ± 45.10	0.126

Table 3: Comparison of some biomarkers of renal function between male and female HIV positive naive subjects (Mean± SEM)

Parameters	Male	Female	p-value
Urea (mmol/L)	5.25 ± 2.74	4.04 ± 1.65	0.059
Creatinine(µmol/L)	111.90 ± 38.4	96.55 ± 21.40	0.078
Uric acid (mg/dl)	6.13 ± 2.37	5.90 ± 2.28	0.736
Microalbuminuria (mg/L)	58.33 ± 50.55	50.10 ± 38.56	0.517
Myoglobin (ng/ml)	53.28 ± 32.76	36.76 ± 24.73	0.047

DISCUSSION

This study was conducted to assess the renal perturbation that may occur in HIV-1 infection and to know whether treatment with HAART contributes to renal impairment in infected subjects in Osogbo, Nigeria. In this study, microalbuminuria was significantly higher ($p<0.001$) in HIV positive than HIV negative subjects. The levels of urea ($p<0.001$), creatinine ($p<0.018$) and uric acid ($p<0.001$) were significantly higher in HIV-1 positive HAART naïve than HIV-1 positive on HAART. Even though the levels of microalbuminuria were higher while myoglobin was lower in HIV-1 positive HAART naïve than HIV-1 positive on HAART, the difference was not statistically significant.

The observed higher levels of microalbuminuria in HIV positive subjects whether on HAART or not, agrees with previous studies (15,16). It was suggested that HIV infection was associated with higher levels of microalbuminuria and that antiretroviral therapy can also contribute to renal impairment either directly; by inducing acute tubular necrosis, nephropathy by crystals deposit, renal tubular disorders or indirectly through pharmacologic

interactions. It was reported that antiretroviral therapy may prevent the loss of protein in urine as a result of kidney damage (17). Although a lower mean value of microalbuminuria was observed among study subjects on HAART than HAART naïve, the difference was insignificant. On the contrary, a recent study reported that excellent potency of the combined ART drugs may be renal protective with greater convenience, tolerance and adherence, and can effectively suppress viral replication thereby reducing the risk of viral resistance (18). Microalbuminuria is one of the earliest indications of renal damage especially in patients with diabetes mellitus and hypertension, and it is correlated with the high occurrence of cardiovascular morbidity (19). Microalbuminuria may reflect a state of increased kidney endothelial permeability and it is regarded as an early biomarker of diffuse endothelial dysfunction since it is the excretion of small quantities of albumin in urine that cannot be detected by ordinary urinalysis test strip. It has been suggested that microalbuminuria may represent the renal manifestation of generalized, genetically conditioned vascular endothelial dysfunction (20,21). The detection of Microalbuminuria in this study is also consistent with previous study which reported elevated levels of Microalbuminuria in 61% of HIV positive subjects with 11% of the subjects having markedly elevated Microalbuminuria levels without changes in the levels of creatinine, uric acid and GFR-MDRG (22). Renal dysfunction in the HIV positive subjects may be due to the effect of both the HIV virus and the use of ART drugs (22). It is well recognized that the presence of renal damage can exacerbates cardiovascular risk and increases the risk of mortality of the patients. It was further suggested that the chances of renal disease increase with risk factors like co-infection with hepatitis C (23), and/or B, hypertension, diabetes mellitus, dyslipidemia and low CD4 cell count (24).These were however excluded from this study.

In this study, an insignificantly higher level of myoglobin was observed among subjects with HIV positive on HAART and HAART naive compared with the HIV negative control subjects. The causes of rhabdomyolysis (the disintegration of striated muscle that can results in the release of muscular cell constituents into the extra cellular fluid and the circulation) differ in individuals with single episodes and those with recurrent diseases. These includes; physical factors (trauma, exercise), infections (viral, bacterial or fungal), metabolic factors and drugs. Higher myoglobin levels were detected in 2 patients with primary HIV infection which was described as non-traumatic rhabdomyolysis with acute renal failure (25). There was a significantly higher ($p<0.05$) mean myoglobin level in male subjects when compared with the female subjects in both HIV positive naïve group. The significantly higher mean level in HIV positive naïve subjects is associated with the continuous replication of the virus with prolonged duration of infection as shown in the comparison of myoglobin level with the diagnosis of infection and this agrees with

earlier studies (26, 27). The authors reported that acute rhabdomyolysis was present in some HIV patients, as a result of complications that may occur in the early and later stages of HIV disease.

The level of CD4 count has been used as a marker of disease progression. The mean CD4 count was significantly higher ($p<0.01$) in HIV negative controls than HIV Positive patients both on HAART and HAART naïve; this is in agreement with the recent study (28). It was observed that the mean CD4 count was significantly higher in controls than HIV infected subjects both on pre-HAART and on HAART. It was reported that HIV infected patients were subjected to immunosuppression with CD4 count <200cell/µL and impaired renal function. Immunological AIDS (CD4+ count <200 cell/µL) was reported to be associated with development of opportunistic infections, malignancies and other diseases that affects kidney functions (28-30). However, the commencement of HAART in HIV-infected subjects has led to an increase in their CD4 count because CD4+ T-cell had a protective role in the development of renal diseases for except acute tubular ischaemia (31). Furthermore, the apparently normal renal function among HIV-1 positive subjects on HAART could be attributed to the fact that HAART, in attempts to suppress the viral loads and increase CD4 counts, leading to a decrease in the rate of damage caused by HIV infection (32). According to Obirikorang (33), the level of the renal markers; creatinine and urea in HIV-infected positive patients showed a picture of an initial derangement but an attempt towards recovery by the system after the administration of HAART restored back their functional capacity. 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 with 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 (34).

There was an insignificant difference($p>0.05$) in the serum uric acid level of HIV positive on HAART patients compared to the HIV negative control; this observation is not in agreement with previous studies (35,36). These authors reported that some antiretroviral drugs have been associated with mitochondrial dysfunction which may lead to increase lactate formation, which competes with uric acid for tubular secretion in the kidneys leading to hyperuricemia. The serum uric acid level in HIV positive HAART naïve patients was significantly higher ($p< 0.01$) when compared with the HIV negative control and this observation is consistent with previous studies (36,37). This is attributed to increased cell turnover as a result of HIV-infection (36). Hyperuricemia has been shown to be a common finding among individuals with HIV infection compared to the general population. (37). High level of uric acid is an indication of

either renal insufficiency or an adaptive measure to combat increased level of free radicals generated as a result of HIV infections.

In this present study, there was a significant increase ($p< 0.01$) in the urea level of HIV positive naïve subjects when compared with HIV Negative control subjects and this is in agreement with Eneyew et al(28) who reported that the urea level can be affected by the degree of dehydration and protein metabolism. There was a slight decrease in the urea level of HIV positive subjects on HAART when compared with HIV Negative subjects but not statistically significant. The mild lower level can also be an indication that the antiretroviral drugs were able to suppress HIV replication effects on the kidney thus ameliorating kidney derangement. Serum urea concentration is an important renal marker to determine if the kidneys are functioning properly. A significant decrease ($p< 0.01$) level of urea was observed in HIV subjects on HAART when compared with the HIV positive naïve subjects. This high level of serum urea is an indication that the kidneys are not filtering adequately (28,38). This elevated urea concentration in HIV positive naïve subjects may suggest pre-renal uremia. It could also be as a result of high protein intake or hyper catabolic states including muscle wasting in these patients. In addition, there is a significant increase ($p< 0.01$) in the serum urea level of HIV positive naïve when compared to HIV negative control and this is an indication that the filtering ability of the kidneys is affected.

The mean serum creatinine of subjects with HIV positive on HAART and HIV positive naïve were significantly higher ($p< 0.01$) when compared with HIV negative control subjects and this is not in agreement with Kamga *et al* (39) that reported that the mean serum creatinine of HIV negative subjects was higher than in HIV positive subjects (39). The HAART administration seems to have had a positive impact by preventing loss of muscle mass among the HAART treated group in this study and this supported the findings advocating for ART to be started in HIV patients with HIV-associated nephropathy HIVAN. The significantly lower ($p< 0.05$) level of serum creatinine among HIV positive patients on HAART when compared to HIV positive naïve was observed and this is consistent with Ani *et al* (40) which reported that administration of early combined therapy with different nucleoside analogues or with newer agents, such as protease inhibitors may profoundly suppress viral replication, translating into prolonged survival.

The significantly lower ($p<0.001$) level of mean serum creatinine in HIV positive naïve when compared to HIV negative control subjects is not in agreement with the previous study (39). These authors reported that the mean serum creatinine level of HIV Negative control subjects was higher than HIV positive naïve subjects. This observation pointed to the fact that replication of HIV exists in glomerular epithelial cells despite undetectable serum viral loads thereby allowing the kidneys to perform a possible role as a reservoir of the virus. This resulted in glomerular

abnormality occurrences in HIV-associated nephropathy. Possible pathogenic mechanisms for this abnormality include direct injury of renal epithelial cells by the virus, injury by HIV gene products, or injury by cytokines and growth factors released by infected lymphocytes and monocytes or released by renal cells after the uptake of viral gene products (41).

CONCLUSION

The levels of measured markers of renal function were higher in HIV positive subjects whether or not on HAART treatment. However, HAART treatment did not adversely affect renal function in this study, but subjects on long-term treatment with HAART may be routinely monitored to ensure that renal impairment is detected early among HIV-1 positive subjects.

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CONFLICT OF INTEREST

None declared.

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