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Comparing the glucose metabolism derangement in human immunodeficiency virus infection patients on antiretroviral treatment with drug naïve patients at Lagos State University Teaching Hospital

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People living with HIV and AIDS are exposed to the challenges of aging and diet related diseases due to prolonged survival by retroviral drugs. The presence of chronic inflammatory state and the metabolic effects of antiretroviral therapy are additional burden. This study was designed to determine the changes in glucose metabolism in HIV infection. This was a case-control study carried out at the adult HIV clinic. Consenting participants were grouped into four; those on nucleoside reverse transcriptase inhibitor/non-nucleoside reverse transcriptase inhibitor (NRTI/NNRTI) (group 1), those on NRTI/PI (group 2), those that were treatment naïve (group 3) and age and sex matched HIV negative controls (group 4). Questionnaires were used to assess the demography of participants. The weight and height of participants were done. Blood was collected for fasting blood sugar, 2 h post prandial glucose and CD4 count. The body mass index (BMI) was significantly lower in the participants on protease inhibitors. The control group had lower 2HPP glucose despite a higher FBS than the other groups that were HIV positive. Treatment naïve (group 3) tend to have higher 2-hour post-prandial blood sugar (2HPP) glucose tests (p= 0.04). The male HIV positive participants on PI also had significantly higher 2HPP glucose tests (p=0.01). The females had lower fasting blood sugar (FBS) and 2HPP glucose tests than the males. There were no correlations of glucose metabolism with CD4 count, age or BMI. The higher 2HPP glucose tests in participants who are treatment naïve may be explained by insulin resistance associated with chronic inflammatory state. It is therefore recommended that HAART be commenced early.

Key words: Human immunodeficiency virus, glucose metabolism, highly active antiretroviral therapy.

INTRODUCTION

Patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) are increasing in number. This is partly due to improved screening, early diagnosis, improved therapy and greater

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access to treatment, as well as acceptance of therapy (Kalra et al., 2011). With improved survival, HIV patients are exposed to age related diseases such as hypertension, diabetes, cancers, myocardiopathies and dyslipidemia in association with the long term metabolic effects of highly active antiretroviral therapy (HAART) and chronic inflammation of HIV infection (Saves et al., 2002; Levitt and Bradshaw, 2006). The consequences are the emergence of metabolic syndromes such as lipodystrophy, cardiovascular disease and disorders of glucose metabolism among people living with HIV and AIDS (Samaras, 2012).

Since the advent of HAART, diabetes has become a leading cause of morbidity in North American and European patients with HIV (Saves et al., 2002; Samaras, 2012). Emerging data from across Africa also indicate that the prevalence of diabetes and dyslipidemia is increasing as people are living longer on HAART (Levitt and Bradshaw, 2006). However, the rising prevalence of diabetes among PLWHA in Africa is only partly explained by the scale-up of HAART because societal factors including urbanization are having a significant impact on the epidemiology of diabetes across the continent (Kalra et al., 2011).

HAART drugs are classified as non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), fusion inhibitors, integrase inhibitors, and chemokine-CCR5 receptor inhibitors. Abnormal glucose metabolism (e.g. diabetes mellitus) can result from insulin resistance or defects in insulin secretion or both. NRTIs directly affect mitochondrial function (Brown et al., 2005). Mitochondrial dysfunction has been implicated in the pathogenesis of insulin resistance. Short-term exposure to stavudine, for example, can reduce insulin sensitivity in healthy volunteers (Fleischman et al., 2007). It is also associated with accelerated development of lipodystrophy and pancreatitis leading to development of diabetes (Carr et al., 2003; Daar et al., 2011). Some NNRTIs have been implicated in development of dyslipidemia with increase in low density lipoproteins (LDL) and increase in cholesterol and triglyceride (Daar et al., 2011; Van der Valk et al., 2001; Taylor et al., 2010).

Protease inhibitors (PIs) have different capacities to induce insulin resistance and the risk of diabetes is dose and duration dependent (Taylor et al., 2010; Lee et al., 2004) Some suggested mechanisms include the down regulation of GLUT-4, inhibition of peroxisome proliferator-activated receptor ϒ activity and reduction in beta cell function (Ruddich et al., 2005; Vigouroux et al., 2003; Woerle et al., 2003; Young et al., 2005; Behrens et al., 1999).

This study was designed to evaluate the changes in glucose metabolism in HIV-AIDS patients in hospital care. The Lagos University Teaching Hospital had been treating HIV and AIDS with free access to HAART for about 8 years before the study was done in 2014. During the period, the guideline recommended commencement of HAART if the CD4 count was less than 350 cells per microliter or if the clinical stage was stage 3 and above. It was an opportunity to investigate treatment naïve patients in care. It was expected that the outcome of the study will increase awareness among clinicians and contribute to knowledge on those at risk, when to screen and the appropriate but simple parameter to monitor.

METHODOLOGY

This was a case-control study carried out in Lagos State University Teaching Hospital (LASUTH) Ikeja. The study populations were HIV and AIDS patients attending the adult hematology clinic and the controls were blood donors. Questionnaires were administered to the participants after obtaining informed consent. Eligibility criteria included subjects with previously documented HIV infection who have been on HAART for more than a month, stable HIV seropositive subjects who are HAART naive, age between 18 and 50 years. This is to limit the influence of underlying asymptomatic glucose intolerance associated with aging. Both sexes were recruited. The following were excluded to avoid the influence of chronic inflammation, multiple organ damage, common chronic non infectious diseases on diet, food consumption and metabolism: History of chronic co-morbid conditions like pulmonary tuberculosis, anemia, hypertension, renal or liver disease predating HIV infection, personal or family history of diabetes mellitus, hyper-insulinemia, impaired fasting glucose, glucose intolerance or diabetes based on 2-hour oral glucose tolerance test before diagnosis of HIV. Subjects exposed to other drugs known to alter glucose metabolism, alcohol, pregnancy or on contraceptives were also excluded. Ethical approval was obtained from the Hospital's Health Research Ethical Committee (LASUTH-HREC- LREC/10/06/226).

The patients were grouped according to the kind of drugs the subjects use: Group 1 were on 1 NNRTI + 2 NRTI; Group 2 were the subjects on 1 PI + 2 NRTI; Group 3 were the HIV subjects not on drugs otherwise called treatment naive and the controls, Group 4, who were non-HIV age and sex matched volunteers. In the clinic, the NNRTI drugs of choice were Efavirenz, Nevirapine; NRTI were Zidovudine, Lamivudine, Abacavir, Tenofovir and PI were Ritonavir, Lopinavir and Atazanavir. The first line combination was one NNRTI combined with two NRTI. While the second line combination was a PI combined with two NRTI.

Blood samples were withdrawn by trained phlebotomist. Free flowing blood samples from the ante-cubital vein were collected into a fluoride oxalate (4 ml) and di-potassium ethylene-diamine tetra-acetic acid (K2-EDTA) vacutainers (4 ml) after a 12 to 14 h fast. After which, 75 g of glucose in 1 L of water was administered to all the participants. Another sample was collected 2 h later into fluoride oxalate bottle for glucose estimation (World Health Organization/International Diabetes Federation (WHO/IDF) criteria for diagnosis of impaired fasting glucose (IFG) Impaired glucose tolerance (IGT) and diabetes mellitus). All glucose estimations were automatically analyzed using a VITROS 350 chemistry analyzer by ortho-clinical diagnostics using its VITROS-GLU slides and VITROS chemistry product calibrator kit 1. CD4 counts were estimated from the K2-EDTA vacutainer within 6 h of sample collection using the counter 2 flow-cytometry by PATHEC. The subject's height and weight were measured for the calculation of body mass index (BMI).

Statistical analysis

The variables were presented in averages and one way ANOVA

Table 1. Demography of Subjects recruited in this study.

S/N	Groups	Number	% Female	Age (years)	BMI (kg/m^2)
1	NNRTIs +NRTIS	93	75	36.98 ±6.6	28.31± 4.83
2	Pls + NRTIs	31	71	36.48 ±7.31	21.17 ±3.74
3	NAÏVE HIV	60	73	34.86 ±8.45	26.28 ±3.87
4	NON-HIV	56	71	37.00 ±6.76	24.21 ±3.69

Table 2. Descriptive statistics of the subjects analyzed (mean and standard deviation-SD)

S/N	Groups	FBS (mmol/L)	2HPP (mmol/L)	Drug comm. (Months)	CD4 (cells/uL)
1	NNRTIs+NRTIS	4.36 ±0.71	5.08 ±1.00	44.24 ±30.34	397 ±222
2	Pls + NRTIs	4.29 ±0.54	5.14 ±1.09	35.09 ±28.15	454 ±177
3	NAÏVE HIV	4.32 ±0.76	5.41 ±1.36	N/A	271 ±154
4	NON-HIV	4.44 ±0.59*	4.94 ±0.99*	N/A	851 ±270

N/A = Not applicable. Drug Comm= Period of Drug Commencement (months).

was done to evaluate the differences in the variables. This was followed by post-test to explore the significant differences between groups. The differences were considered to be statistically significant provided the p-value was less than 0.05 ($p<0.05$). Multiple regression was used to test the correlation of the glucose levels with age, BMI, CD4 counts and period on retroviral drugs. Further tests were done to estimate the contribution of each variable to changes in the glucose level. The contribution was statistically significant if p- value was less than 0.05 ($p<0.05$). The statistical package used was the GraphPad InStat.

RESULTS

The total number of subjects was 241, of which 73% were females. The age range was 22 to 50 years with a mean of 38 ± 7 years. The mean body mass index was 25 kg/m^2 ± 4. There was no significant difference in the age of the different groups ($p = 0.29$) as shown in Table 1.

There was significant difference when the means of the BMI were compared among the four groups ($p = < 0.0001$), a post test done showed that there were significant differences in BMI of the control group and the other groups ($p< 0.05$). The average BMI in subjects on PIs was less than the BMI in control. While BMI of participants on NNRTIs and of treatment naïve subjects were higher than in control subjects (Table 1).

The mean of the fasting blood sugar was 4.35±0.65 mmol/L and that of the 2 h post prandial was 5.14±1.11 mmol/L and all the subjects had fasting blood sugar and 2 hour post prandial sugar within the normal range (<6.1 mmol/L and <7.8 mmol/L respectively) (WHO/IDF, 2006). Using analysis of variance (ANOVA), there was no significant difference in the means of fasting blood sugar in the four groups ($p= 0.3654$). Similarly, there was no significant difference in the means of the 2 hour post prandial blood sugar of the four groups ($p=0.2370$).

In Table 2, the fasting blood sugar (4.44 ±0.59) was slightly higher in controls while the 2 hour post prandial sugar (4.94 ±0.99) was slightly lower compared to those of HIV patients though this was not statistically significant.

Comparing the means of each group with that of the control, HIV patients who were naïve to HAART had significantly higher 2HPP ($p= 0.04$). But there was no statistical difference between the control and those on HAART (Table 2).

There was a sex difference when the means of FBS and 2HPP in males and females were compared. From Table 3, the FBS in all groups of HIV females were significantly lower than in controls ($p=0.045$, $p=0.014$, $p=0.026$). Whereas, there was no statistical difference in the FBS of males in all HIV groups compared to the control ($p=0.53$).

However, in males, the 2HPP sugar of HIV patients on Protease inhibitor was statistically higher than that of control ($p=0.01$) (Table 4). While in females, the 2HPP was statistically higher in treatment naïve HIV patients as against controls ($p=0.02$).

There was no difference in the means of the age, BMI and CD4 counts of males and females. Except in group 1 where there was a significant difference among the sexes in age ($p<0.001$) (Tables 3 and 4).

There was no correlation between FBS/2HPP with other variables that is Age, BMI, CD4 count, period on drugs, using the correlation matrix of all groups.

The correlation coefficient, r, between CD4 and FBS/2HPP were -0.239 and -0.136 respectively. Indicating an inverse or opposite relationship and covariation of 23.9 and 13.6% respectively. The period on HAART had a statistically significant contribution ($p = 0.0485$).

DISCUSSION

From Table 3, demographic characteristics indicate that

Table 3. Descriptive statistics for female subjects in this study.

S/N	Groups	Age (years)	BMIkg/m^2	FBSmml/L	2HPPmmol/L	CD4cells/ul
1	NNRTIS+NRTIS	35.89±6.20	28.77±4.85	4.27±0.61	4.96±0.85	420±226
2	Pi +NRTIS	35.77±7.28	27.57±4.06	4.20±0.40	4.75±0.69	483±180
3	NAÏVE-HIV	34.00±8.86	26.25±3.58	4.34±0.84	5.50±1.26	271±163
4	NON-HIV	35.68±6.99	24.15±3.61	4.51±0.59	4.95±0.90	826±245

Table 4. Descriptive statistics for male subjects in this study.

S/N	Groups	Age (years)	BMIkg/m^2	FBSmmol/L	2HPPmmol/L	CD4cells/ul
1	NNRTIS+NRTIS	40.30±6.86	26.89±4.61	4.62±0.93	5.43±1.34*	327±196
2	Pi +NRTIS	38.22±7.53	26.19±4.06	4.52±0.79	6.10±1.34*	383±156
3	NAÏVE-HIV	37.25±6.88	26.38±4.71	4.27±0.50	5.16±1.64*	270±130
4	NON-HIV	40.31±4.94	24.38±4.00	4.27±0.55	4.93±1.22	913±327

there were no differences in the sex ratio and age between the groups though there were more females in the study which reflected the proportion of females attending the clinic. The only difference within the groups is seen in the BMI. Therefore the differences in glucose metabolism might be explained by the difference in BMI.

Subjects did not show abnormality in glucose metabolism, the FBS and 2HPP being within normal limits in all the groups. This is contrary to other findings where 2 to 40% of HIV patients have been found to have diabetes (Brown et al., 2005, Hadigan et al., 2001; Glass et al., 2006). This may be due to the facts that these subjects have been on HAART for a short period (mean period of 44 months, from Table 4); the sample size might be small; the exclusion criteria that excluded history of impaired glucose metabolism and the fact that the drugs frequently involved in glucose metabolism like stavudine and didanosine were not being used by these subjects. The mean period subjects were on lopinavir and ritonavir (PI) was also short (35 months) (Lee et al., 2004; Ruddich et al., 2005).

This study also showed that treatment naïve HIV subjects had significantly higher 2HPP than the control group (p=0.04) (Table 4), while those on HAART showed no significant difference in FBS and 2HPP when compared to controls (p>0.05). This suggests that the increased inflammatory state in untreated HIV infection may have been antagonistic to insulin. This is in agreement with findings that the inflammatory states lead to decrease adeponectin levels and an increased insulin resistance (Reid et al., 2012). Presence of a chronic inflammation may also explain why treatment naïve HIV subjects also had significantly Lower BMI.

The study showed that female HIV subjects seem to tolerate glucose better than their male counterpart. When the sexes were considered, the females showed a significantly lower FBS than the control. While the males had higher FBS than the controls, though not statistically significant. This is in agreement with several studies from high income countries which suggest that HIV-infected women on HAART have a lower risk of developing diabetes (Reid et al., 2012).

In this study, the 2HPP was significantly higher in male subjects (p=0.01) on PI and in female treatment naïve subjects (p=0.02). The 2HPP therefore seems to be more sensitive than FBS in detecting abnormality in glucose metabolism (See glucose concentrations for 2HPP in Tables 3 and 4).

The study did not find any correlation between FBS or 2HPP with age, BMI, CD4 count and period of therapy (Tables 5 to 8). This supports Capeau et al. (2012) study in that there is no direct relationship between CD4 and risk of diabetes in HIV subjects (Capeau et al., 2012). Age and BMI may have a threshold effect rather than trend on glucose metabolism.

The CD4 was significantly higher in control subjects (p=0001). CD4 count was improved in subjects using HAART both in males and females compared to treatment naive HIV subjects. Therefore, treatment not only restored immunity, it prevents inflammatory state and thereby reduce insulin resistance except in men on protease inhibitors.

Limitations

The main challenge to this study is the sample size especially in the group on PI. This may have been the reason why we could not demonstrate glucose intolerance. The subjects were on therapy for a short period of 44 months. A longer cohort study might show significant derangement in glucose metabolism.

Conclusion

From this study, 2HPP test is a more sensitive screening

Table 5: The Correlation Matrix For Group one

Age	BMI	Drug C	FBS	2HPP	CD4
1.000	0.096	0.182	0.128	0.072	-0.013
0.096	1.000	0.330	-0.061	0.080	0.170
0.182	0.330	1.000	-0.260	-0.137	0.315
0.128	0.061	-0.260	1.000	0.216	-0.239
0.072	0.080	-0.137	0.216	1.000	-0.136
0.013	0.170	0.315	-0.239	-0.136	1.000

*Drug C = Drug commencement; BMI = Body mass index; FBS = Fasting blood sugar; 2HPP = 2 hour post prandial; CD4

Table 6: Correlation Matrix for Group 2

Age	BMI	Drug C	FBS	2HPP	CD4
1.000	0.406	0.239	0.128	0.384	0.265
0.406	1.000	0.372	0.125	0.286	0.335
0.239	0.372	1.000	0.065	-0.006	0.347
0.128	0.125	0.065	1.000	0.134	-0.076
0.384	0.286	-0.006	0.134	1.000	-0.289
0.265	0.335	0.347	-0.076	-0.289	1.000

*Drug C = Drug commencement; BMI = Body mass index; FBS = Fasting blood sugar; 2HPP = 2 hour post prandial; CD4

Table 7: Group 3 Correlation Matrix

Age	FBS	2HPP	CD4	BMI
1.000	-0.031	-0.177	-0.045	0.161
-0.031	1.000	0.345	-0.073	0.009
-0.177	0.345	1.000	-0.074	0.058
-0.045	-0.073	-0.074	1.000	-0.046
0.161	0.009	0.058	-0.046	1.000

*Drug C = Drug commencement; BMI = Body mass index; FBS = Fasting blood sugar; 2HPP = 2 hour post prandial; CD4

Table 8: Group 4 Correlation Matrix

Age	BMI	FBS	2HPP	CD4
1.000	0.112	0.135	0.253	-0.022
0.122	1.000	-0.124	0.290	0.013
0.135	-0.124	1.000	0.224	0.103
0.253	0.290	0.224	1.000	-0.051
-0.022	0.013	0.103	-0.051	1.000

*Drug C = Drug commencement; BMI = Body mass index; FBS = Fasting blood sugar; 2HPP = 2 hour post prandial; CD4

test for monitoring glucose metabolism in HIV patients than FBS alone. The 2HPP is significantly higher in treatment naïve subjects than subjects on HAART and controls. This may be due to effect of chronic inflammation which is reduced on commencing HAART. Early commencement of HAART is therefore recommended. Those on PI should have their glucose tests done at regular intervals. Female HIV subjects tend to tolerate glucose better than the male counterparts. Therefore, the need to have separate reference values in HIV patients may be determined by further studies.

Conflict of Interests

The authors have not declared any conflict of interests.

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