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Metabolic factors associated with the development of lipodystrophy in patients on long-term highly active anti-retroviral therapy (HAART)

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Dyslipidemia, insulin resistance and diabetes are frequent in patients on highly active anti-retroviral therapy (HAART) and especially in patients with lipodystrophy, and may lead to atherosclerosis. This study described the metabolic alterations associated with lipodystrophy in adults on chronic HAART in Kenya. The prevalence of dyslipidaemia amongst the study participants was (211) 79.6%. Elevated total cholesterol was found in 129, high low-density-lipoprotein cholesterol (LDL-C) in 107, low High-density lipoprotein cholesterol (HDL-C) in 110 and high triglycerides in 131 participants. Lipodystrophic patients were more likely to have dyslipidemia than normal lipids (55.4 versus 35.1%, p = 0.007 OR 2.2 CI 1.3 to 4.6) with 57, 45.9, 65.9 and 45.2% having elevated total cholesterol, elevated LDL-C, elevated triglycerides and low HDL-C, respectively. Hypertriglyceridemia and hypercholesterolemia were significantly associated with lipodystrophy (OR 3.8 CI 2.3 to 6.4; p = 0.000) and (OR 1.94 CI 1.2 to 3.2; p = 0.008), respectively. The odds of lipodystrophy was 2.913 times higher for patients with elevated triglycerides than for those with normal triglycerides (p < 0.001). Sixty-four (24.3%) participants had dysglycemia, with 3.5% having diabetes and 20.8% having impaired fasting glucose (IFG). Among patient with lipodystrophy, 69.8% had normal fasting glucose, 25.1% had IFG and 5.1% were diabetic. Lipodystrophic patients were not more likely to have abnormal blood sugars than normal blood sugars (p value 0.125).

Key words: Dyslipidemia, atherosclerosis, fasting glucose, dysglycemia, lipodystrophy, chronic highly active anti-retroviral therapy (HAART), metabolic alterations.

INTRODUCTION

Dyslipidemia and dysglycemia are very frequent in patients with lipodystrophy (Mercier et al., 2009; Jevtovic et al., 2009). The lipid disturbances, insulin resistance and increased risk of diabetes coupled with fat redistribution seen in lipodystrophic patients have been shown to predispose to premature and accelerated atherosclerosis and thus an increased risk of acute myocardial infarction (DAD study group, 2007).

Saves et al. (2002) reported the prevalence of hypertriglyceridemia in patients without lipodystrophy, those with 1 to 3 signs and those with more than 4 prevalence of hypercholesterolemia were 48, 62 and 62%, respectively. Samaras et al. (2007) found hypertriglyceridemia to be twice as prevalent (61%) in patients with lipodystrophy

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as compared to those without. The pathogenesis of hypertriglyceridemia in HIV-associated lipodystrophy appears to arise predominantly from increased hepatic secretion of very low density lypoprotein tryglycerides (VLDL-TG) rather than reduced clearance. De novo lipogenesis, resting lipolytic rate and hepatic triglyceride stores are also increased in HIV-associated hypertriglyceridemia. Triglyceride clearance may also be impaired in these patients because of reduced lipoprotein lipase activity; however, this appears to play a minor role (Grunfeld et al., 1992).

Insulin resistance and impaired glucose tolerance have been observed with regimens containing protease inhibitors especially Indinavir and regimens containing nucleoside reverse transcriptase inhibitors, chiefly stavudine (Carr et al., 1998; Lawrence, 1946). While Indinavir has been demonstrated *in vitro* to have a direct effect on glucose metabolism and may induce insulin resistance by inhibiting glucose movement through the GLUT4 transporter, the emergence of insulin resistance during antiretroviral therapy is a complex process that is not completely understood. Fasting glucose levels from a group of 1,278 men in the MACS cohort showed that 14% of HIV-infected men on antiretroviral therapy had diabetes mellitus compared with 5% in HIV-negative men adjusted for age and body mass index (BMI) (Palella Jr et al., 2004).

Insulin resistance has been demonstrated in patients with fat redistribution, even in patients not receiving protease inhibitors. In an Australian study on the prevalence of metabolic syndrome in patients on HAART, the prevalence of fasting glucose greater than 5.6 mmol/L was 19% in those with lipodystrophy versus 11% in those without lipodystrophy (Samaras et al., 2007).

Lipodystrophy and the associated metabolic dysregulation has similar features as those seen in metabolic syndrome and has been shown to put HIV infected patients at risk of premature and accelerated atherosclerosis (Friis-Møller et al., 2003a, b). Samaras et al. (2007) in a multicenter cross-sectional study of 788 HIV positive patients found a prevalence of metabolic syndrome in patients on HAART to be 14% by International Diabetes Federation (IDF) criteria and 18% by National Cholesterol Education Program Adult Treatment Panel III (ATPIII) criteria (NCEP/ATP III, 2001); lipodystrophy was present in the majority of patients with metabolic syndrome: 73% by IDF criteria and 79% by ATP III criteria (Samaras et al., 2007).

The prevalence of lipodystrophy is high in Kenya. There are few studies on its prevalence and on the metabolic alterations associated with its development. The increased cardiovascular risk associated with these changes may lead to increased morbidity and mortality in affected patients who may benefit from intervention strategies such as dietary modification, physical exercise and lipid lowering therapy to reduce their risk constellation (Behrens et al., 2003). We set out to investigate the prevalence and type of dyslipidemia and dysglycemia in patients on chronic HAART in Kenya.

MATERIALS AND METHODS

Ethical considerations

The study was conducted after approval by the Department of Clinical Medicine and Therapeutics, University of Nairobi, and the Kenyatta National Hospital Scientific and Ethical Review Committee.

Study site

The study was conducted at the HIV out-patient clinic at Kenyatta National Hospital, a tertiary National referral and teaching hospital in Kenya.

Study population

The participants were HIV-infected adults on HAART for longer than six months, attending the HIV clinic between August 2007 and 2008. The participants were HIV-1 positive adult patients on combination HAART as recommended by the National HIV program and defined as either dual NRTI (d4T or AZT or TDF with 3TC) with a NNRTI (NVP or EFV) or the dual NRTIs with a PI (LPV/r) for 6 to 72 months who attended the HIV clinic between August 2007 and 2008.

Study design

This was a cross-sectional descriptive study. Random sampling was done daily during routine visits until the desired sample size was reached. The minimum sample size required to determine the prevalence of lipodystrophy was determined at 265 patients. The criteria for statistical significance was p value < 0.05.

Inclusion criteria

HIV-1 infected male and female patients aged 15 years and older on HAART, regularly reviewed and compliant with treatment for six months or more were deemed eligible for this study.

Exclusion criteria

Patients on HAART for less than 6 months, patients on anabolic steroids or immuno-modulatory therapy, patients known to have Cushing's disease or other endocrine disorders, pregnant patients and moribund patients such as patients with malignancy or HIV wasting syndrome were excluded.

Patient assessment

The Comprehensive Care Centre operates five days in a week. All patients underwent full evaluation at initial and subsequent follow-up visits. Data on patient characteristics such as age, gender, marital status, occupation, level of education, WHO clinical staging, current and prior anti-retroviral therapy, physical examination findings and baseline and subsequent laboratory investigations including full blood count, liver and renal function tests, CD4 and CD8 counts were recorded in the patients' charts. Patients deemed eligible for antiretroviral therapy commenced treatment and thereafter

Table 1. Demographic characteristics of the study population.

Variable		No. of patients	Mean/ (%)
Age	All patients aged ≥ 15 years	265	40.69±23.41
Gender	Female	158	(59.6)
	Male	107	(40.4)
WHO stage	I	24	(8.9)
	II	47	(17.3)
	III	99	(37.3)
	IV	95	(36)
CD4 counts	Nadir	256	119±49
	Most recent	265	335±76.50
Duration of HAART (Months)	6-18	83	(31.2)
	19-36	123	(46.4)
	>3	59	(22.4)
HAART combinations	d4T based	188	(70.9)
	AZT based	41	(15.5)
	TDF based	36	(13.6)

were given individualized appointments depending on their clinical condition. They also returned to the clinic monthly for supply of antiretroviral medication. Recruitment was done among patients who had been on anti-retroviral therapy for more than six months. The patients were informed about the study and their eligibility assessed. Those who met the inclusion criteria and gave signed informed consent were recruited. A study questionnaire was used to collect baseline and clinical data. Lipodystrophy was assessed by patient report and physician examination using a modified version of the lipodystrophy case definition questionnaire (Carr, 2003). After an overnight fast of 9 to 12 h, blood was taken from all the patients for measurement of lipid profiles and fasting blood glucose. Lipid profile was done at the Pediatric Laboratory, University of Nairobi using the HUMALYZER 2000 machine through a direct method to measure LDL-C and HDL-C and enzymatic hydrolysis to measure triglycerides and total cholesterol. Fasting blood glucose was measured by the glucose oxidase method on the medisense glucometer (Gochman et al., 1972).

Outcomes

Lipid disturbances were classified as per NCEP/ATP III guidelines as high total cholesterol, high LDL-cholesterol, high triglycerides or low HDL-cholesterol. Study participants were considered diabetic if they had history of self report of diabetes, or use of hypoglycemic medication, or Fasting plasma glucose (FPG) ≥ 7.0 mmol/L. Impaired fasting glucose (IFG) was defined as FPG of 5.6 to 6.9 mmol/L.

Statistical analysis

All data was entered into data base using Microsoft Excel. Qualitative variables were described in frequencies or percentages and compared between groups using Chi square (χ^2) test. Quantitative variables were described with medians or means and compared between groups using Wilcoxon rank sum test. Cox proportion hazard regression modeling was used to determine variables that predicted the outcomes. Statistical analysis was performed using Statistical Package for Social Sciences, version 15.0. Results were presented in form of tables. The criteria for statistical significance was p value < 0.05

RESULTS

We screened 318 HIV-seropositive patients on chronic HAART therapy and excluded 53 (16.6%) patients; 40 had been on HAART for less than 6 months, 5 had opportunistic infections, 3 were moribund, 2 had HIV wasting syndrome, 2 declined consent and 1 had a malignancy. Two hundred and sixty five patients were thus enrolled at the Comprehensive Care Centre at the Kenyatta National Hospital.

Patients' baseline characteristics

The mean age of the study population was 40.69 years with 59.6% being female. The mean baseline CD4 count and reconstituted CD4 count of the study participants was 119 and 335/mm^3, respectively as depicted in Table 1. Majority of the patients (73.3%) were in WHO stage III and IV at initiation of HAART. The mean duration of treatment of the study participants was 29.7 months, with 66.8% having used HAART for longer than 18 months. Stavudine based regimens were in use by 70.9% of patients whereas 15.5% of patients were on AZT-based regimen. Twenty six of these patients had switched from a d4T based regimen prior to enrolment into the study. It

Table 2. Metabolic variables of the 265 study participants.

Variable (mmol/l)	Male (n=107)	Female (n=158)
TC Mean± SD	5.2±1.38	5.35±1.32
Median (IQR)	5.08 (2.15-10.08)	5.16 (2.54-9.87)
HDL-C Mean± SD	1.097±0.39	1.179±0.44
Median (IQR)	1.08 (0.24-2.67)	1.11 (0.20-3.03)
LDL-C Mean± SD	3.28±1.26	3.18±1.25
Median (IQR)	3.03 (1.08-7.92)	3.02 (0.08-7.67)
TG Mean± SD	2.00±1.54	2.21±1.79
Median (IQR)	1.62 (0.49-10.6)	1.70 (0.47-11.26)
FBS Mean± SD	5.5 ± 2.1	5.18±0.9
Median (IQR)	5.4 (2.8-20.1)	5.1 (3-9.3)

was also noted that of 36 (13.6%) patients who were on a TDF based regimen, 30 had switched from a d4T based regimen and 6 from an AZT based regimen prior to the time of enrolment.

Metabolic variables of the study population

The median total cholesterol, HDL-cholesterol, LDL-cholesterol and fasting blood sugar were normal whereas the median triglycerides were marginally elevated in females as shown in Table 2.

Prevalence of dyslipidemia

Overall dyslipidaemia was found in 211 (79.6%) patients, of whom 58.3% were females. Elevated total cholesterol (>5.17 mmol/l) was found in 129 (48.6%) patients, elevated LDL-cholesterol (>3.34 mmol/l) in 107 (40.3%) patients, low HDL-cholesterol levels (<1.03 mmol/l) in 110 (41.5%) patients and high triglyceride levels (>1.69 mmol/l) in 131 (49.4%) patients as depicted in Figure 1.

Dyslipidaemia and lipodystrophy

Dyslipidaemia was found in 117 (55.4%) patients with lipodystrophy and normal lipids in 18 (34.6%) patients with lipodystrophy. Presence of dyslipidaemia was significantly associated with lipodystrophy (p = 0.007 OR 2.2 CI 1.3 to 4.6) as shown in Table 3.

Types of dyslipidemia and lipodystrophy

Hypertriglyceridemia was the most common type of dyslipidaemia associated with lipodystrophy occurring in 89 (65.9%) of the patients. The association was found to be statistically significant (OR 3.8 CI 2.3 to 6.4 p = 0.000). Hypercholesterolemia was found in 77 (57%) of the patients with lipodystrophy and this also achieved statistical significance (OR 1.94 CI 1.2 to 3.2 p = 0.008). Neither elevated LDL-C nor low HDL was significantly associated with lipodystrophy. The associations between the various types of dyslipidaemia with lipodystrophy are summarized in Table 4.

Dysglycemia and lipodystrophy

Abnormality in blood glucose was not found to be significantly associated with the presence of lipodystrophy. Among patients with lipodystrophy, 93 (69.8%) had normal fasting blood sugar, 34 (25.1%) had impaired fasting glucose and 7 (5.1%) were diabetic as shown in Table 5.

Logistic regression analysis

A logistic regression model was constructed to find which of the associated factors independently predicted lipodystrophy while controlling for the other factors and to quantify this association (Table 6). From logistic regression analysis model, we estimated that for patients with abnormal triglycerides (that is, triglycerides levels > 1.69) who had the same levels of total cholesterol, the odds of lipodystrophy was 2.913 times higher compared to those with normal triglycerides. This estimate was statistically significant (p < 0.0001). From the same model we estimated that for patients with abnormal total cholesterol levels (that is, total cholesterol levels > 5.17) who had same levels of triglycerides and HAART duration, the odds of lipodystrophy is 1.288 times higher compared to those with normal total cholesterol, though this estimate was not statistically significant (p = 0.388).

In conclusion, we observe from the logistic model that abnormal levels of triglycerides was significantly associated with a higher likelihood of developing lipodystrophy for patients in this study.

DISCUSSION

Prolonged use of HAART has led to recognition of long term complications of these therapies such as lipodystrophy which manifests with distressing morphologic changes in body habitus and has been associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolemia, insulin resistance (raised C-peptide and insulin concentrations), impaired glucose tolerance and type 2 diabetes mellitus (Carr, 2000). This study was conducted between August 2007 and 2008 at Kenyatta National Hospital, a referral and teaching hospital in Kenya. It comprised 59.6% females (female to male ratio

Table 3. Association between dyslipidaemia and lipodystrophy.

Variable	Prevalence of lipodystrophy n(%)	Total	P value
Dyslipidemia	117 (55.4)	211	0.007
No dyslipidemia	18 (34.6)	54	

Table 4. Types of dyslipidaemia associated with lipodystrophy.

Type of lipid	Prevalence of lipodystrophy n (%)	Total	Odds ratio (95% CI)	P value
Hypercholesterolemia	77 (57)			
Normal total cholesterol	59 (43)	136	1.94 (1.2-3.2)	0.008
High LDL-C	62 (45.9)			
Normal	74 (54.1)	136	1.5 (0.95-2.6)	0.076
Hypertriglyceridemia	89 (65.9)	136	3.8 (2.3-6.4)	0.000
Normal triglycerides	47 (34.1)			
Low HDL-C	61 (45.2)	136	1.3 (0.8-2.2)	0.257
Normal HDL-C	75 (54.8)			

Table 5. Association between fasting blood glucose and lipodystrophy.

FBS	Prevalence of lipodystrophy n (%)	Total	P value
Normal	95 (69.8)	136	
IFG	34 (25.1)	136	0.124
DM	7 (5.1)	136	

Table 6. Logistic regression model.

Variable	Odds ratio	P	95% CI	
Abnormal Triglycerides	2.913	<0.0001	1.635	5.191
Abnormal total Cholesterol	1.288	0.388	0.725	2.286

1.5:1). Most of the individuals in the study population were young individuals with a median age of 40 years. Females were younger than their male counterparts where 60.7% were below 40 years compared to 44% of males. These findings reflect the National AIDS and STI Control Programme (NASCOP) estimates (Ministry of Health Kenya, 2010) that at least two-thirds of all HIV infected individuals in Kenya are young women. Therefore, the age and gender distribution of this study population is fairly representative of the sample of AIDS patients in Kenya.

Dyslipidemia was found in 79.6% of our study participants. All four types of lipid abnormalities (high total cholesterol, high LDL cholesterol, high triglycerides and low HDL cholesterol) were encountered in our patients and were more prevalent in patients with lipodystrophy.

The pathogenesis of the dyslipidemia is thought to be due to increased apoliporotein B levels, increased dense LDL 2 levels and a shift towards hepatic secretion of VLDL-triglycerides. Circulating cytokines and acute phase reactants may also play a role (Grunfeld et al., 1992).

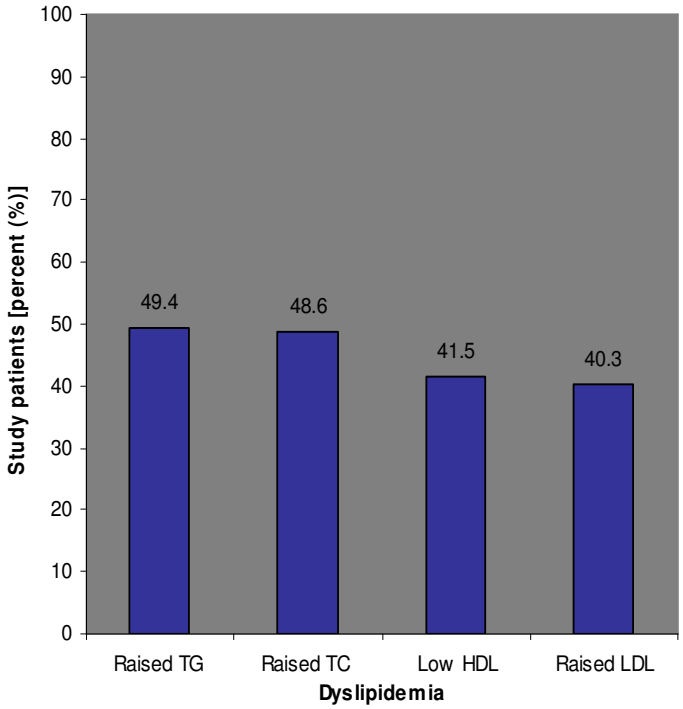

Figure 1. Prevalence of dyslipidemia in the study population.

The commonest type of dyslipidemia in this study was hypertriglyceridemia. This finding is not surprising in this population who had multiple risk factors for development of hypertriglyceridemia. These include HIV infection where the pathophysiology is thought to be due to cytokine mediated (especially IFN-α) suppression of lipases with decreased clearance of triglycerides from blood (Grunfeld et al., 1992). In addition, use of HAART, especially protease inhibitors as well as having lipodystrophy are cited as risk factors for elevated triglycerides.

The prevalence of elevated total cholesterol in our study (>5.17 mmol/l) was 48.6%, high LDL-cholesterol was found in 41.5%. Majority of the patients who had elevated total and LDL-cholesterol had borderline elevation. LDL cholesterol is atherogenic and this is therefore of concern in this young population on long term HAART and who probably have other cardiovascular disease risk factors. It may be important to institute therapeutic lifestyle modification and lipid lowering agents in these patients.

Low HDL-cholesterol was found in 40.3% of patients. This is also expected, as HIV infection has been shown to suppress HDL-cholesterol (Grunfeld et al., 1992). This finding however is in contrast to those reported by Manuthu et al. (2008) who found HDL not to be reduced in patients on HAART.

Patients with lipodystrophy were more likely to have dyslipidemia than normal lipids (55.4 versus 35.1%, p = 0.007 OR 2.2 CI 1.3 to 4.6). Similar findings were reported by the data collection on adverse events from anti-HIV drugs (D: A: D) study group who found dyslipidemia in 57% of patients with lipodystrophy. The D: A: D study also reported on a follow up study that after the initial 7 years of HAART, the risk of myocardial infarction was 27% per year (Friis-Moller et al., 2003).

In our study, triglycerides were 3.8 likely to be elevated and total cholesterol 1.94 likely to be elevated in patients with lipodystrophy. Samaras et al. (2007) found significantly elevated total cholesterol and triglycerides in patients with lipodystrophy who did not have other features of metabolic syndrome. Saves et al. (2002) found the prevalence of hypertriglyceridemia in patients without lipodystrophy and those with lipodystrophy was 20 and 42%, respectively that of hypercholesterolemia was 48 and 62%, respectively. Hypertriglyceridemia was found to be an independent predictor of lipodystrophy in the multivariate analysis with the odds of lipodystrophy being 2.9 times higher in those with hypertriglyceridemia compared to those with normal lipids. These patients may benefit from long-term follow-up with regular cardiovascular risk assessment and institution of intervention strategies to reduce their risk constellation.

Impaired fasting glucose was seen in 24.4% and diabetes mellitus in 3.5% of our study participants. Insulin resistance and diabetes have been seen with regimens containing Indinavir and stavudine (Brown et al., 2005). It is thought to be due to inhibition of glucose movement through GLUT 4 transporter (Murata et al., 2000). Manuthu et al. (2008) and the Rwanda study (Mutimura et al., 2007) also reported the prevalence of dysglycemia as 20.7 and 17.3%, respectively. Abnormalities in fasting blood glucose were not found to be associated with lipodystrophy in this study. IFG was reported in 25.1% and diabetes in 5.1% and normal blood glucose in 68.8% of patients with lipodystrophy. Samaras et al. (2007) found abnormalities in blood glucose to be more common in lipodystrophy than those without (19 versus 11%) while Saves et al. (2002) reported that glucose alteration was 16% in patients without lipodystrophy and 28% in patients with lipodystrophy.

It is noteworthy that although metabolic alterations were more common among patients with lipodystrophy, they were also present in patients without lipodystrophy implicating the role of viral and antiretroviral therapy in the etiology.

Conclusion

Dyslipidemia was common in patients with lipodystrophy and this is likely to increase the risk of cardiovascular disease. However, dysglycemia was not associated with lipodystrophy. Hypertriglyceridemia was found to be independent predictors of lipodystrophy. We recommend that lipid profiles should be performed before HAART initiation and be routinely monitored especially in patients who develop lipodystrophy, and regular cardiovascular risk assessment should be done in patients on HAART and

and institution of intervention strategies done to reduce their risk constellation.

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