Dyslipidaemia and dysglycaemia in HIV- infected patients on highly active anti-retroviral therapy in Kumasi Metropolis

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Abstract

Back ground: Diet and genetic predisposition significantly affect lipid metabolism in the individual. This metabolic effect is further challenged in patients infected with HIV and on HAART. The prolonged use of HAART is associated with lipodystrophy, dyslipidemia, and insulin resistance.

Objective: To determine the prevalence of lipid dysregulation and dysglycaemia in HIV infected patients on HAART in the Kumasi metropolis.

Methods: This cross sectional study was conducted between October 2009 and June 2010, and 305 HIV-infected patients consisting of 164 patients on HAART for at least six months and 141 HAART-naive patients constituted HIV-positive patients, not on HAART and whose CD4 were not below 320 cell/ml as the control. Data was analyzed using Graph Pad Prism (version 5.0). Unpaired t-test, linear and multivariate regression analyses, was used to predict glucose level from the various parameters. Anthropometric parameters consisting of body weight, waist and hip circumferences, height, bicep and triceps skin fold were measured with a pair of calipers. Lipid profile and fasting blood glucose were determined by enzymatic methods. CD4 counts and hemoglobin were determined.

Results: Fasting plasma, glucose (3.81±0.08mmol/l, 4.48±0.17mmol/l), total cholesterol (3.05± 0.0 8mmol/l, 4.54±0.08mmol/l) LDL (2.24±0.07mmol/l, 2.87±0.07mmol/l) and HDL (0.85±0.04mmol/l, 0.97±0.03mmol/l) between the control and case respectively were significantly raised (P< 0.001), though within the physiological range. The significantly increased hip and waist circumferences, waist-to-hip ratio (0.85±0.22, 0.88±0.01) of the control and case correlated with lipodystrophy.

Conclusion: HAART was associated with lipodystrohy and, the risk of developing type II diabetes among the HAART experienced group was 5 times higher than the HAART naive group.

Keywords: HIV, HAART, non-nucleoside reverse transcriptase inhibitor, nucleoside reverse transcriptase inhibitor, Hypertriglyceridemia

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Introduction

The search for vaccines to protect against HIV/AID has continued to elude the science world. However, the use of highly active antiretroviral therapy (HAART) has dramatically improved the prognosis of HIV-infected individuals[1, 2].The beneficial effect of reduced risk of early death from opportunistic infections and other consequences of HIV infection, is however, reduced because other possible causes of death have replaced this beneficial effect[3]. Myocardial infarction has become a matter of particular concern. Two of the main sources of cardiovascular disease are believed to be vascular inflammation and dyslipidemia. Unfortunately, the use of these agents have given rise to metabolic and morphological abnormalities termed lipodystrophy syndrome and cardiovascular diseases[4,5]. There is sufficient evidence that lipodystrophy is linked to hypercholestrolaemia, hypertriglyceridaemia, hyperinsulinaemia, peripheral insulin resistance and even to overt diabetes[6, 7].

Although there are differences between the individual drugs with respect to the resulting metabolic abnormalities, treatment with protease inhibitors (PI) and to some extent nucleoside analogues such as reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are known to be associated with hyperlipidaemia, hypertriglycereldaemis,lypodystrophy, hyperglycaemia and increased insulin resistance[5,8]. Low levels of total and high-density lipoprotein cholesterol (HDL-C) are also known to be associated with chronic HIV infection[9]. Although this

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dyslipidaemia has been attributed to PI therapy, dyslipidamia has also been observed in treatment-naïve HIV-infected individuals suggesting that HIV infection itself has a lipid metabolic derangement[10,11].

Treatment with retonavir in healthy volunteers resulted in hypertriglyceridaemia which is not associated with impaired lipoprotein lipase activity[9] and treatment with indinavir may lead to insulin resistance and lipid metabolic dysregulation[12]. However, the exact mechanism by which the HIV infection or HAART induces dyslipidaemiais still being researched into. Carpentier, et al.[13] showed that insulin-mediated suppression of plasma free fatty acid concentrations was impaired both prior to and following introduction of HAART, compared to healthy, matched controls.VLDL-apoB and VLDL-TG concentrations rose significantly from normal levels after HAART. Compared to healthy control subjects, VLDL fractional catabolic rate and clearance in HIV-seropositive individuals was reduced approximately by 40%, and this defect was not corrected after HAART. The increase in VLDL after HAART was associated with an increased VLDL-apoB and VLDL-TG secretion towards the normal while the impaired VLDL clearance remained unchanged.

Susceptibility to the development of these metabolic defects varies with the individual and could be influenced by genetic difference[14]. The recently observed association between the APOC3-related rs10892151 polymorphism and serum triglyceride levels led to the believe that genetic differences may play a major role in human immunodeficiency virus (HIV) antiretroviral therapy-induced dyslipidemia[15]. Although similar result have been reported in Asia, America and Europe very little work in Ghana has been done to determine the effect of HAART on lipidystrophy in HIV patients and particularly in the Ashanti region of Ghana, a population with a difference in ethnicity and dietary (from Europe and America) which may all have effect on fat and carbohydrate metabolism.

Methods

The study was carried out at Kumasi South Hospital with the permission ofthe National Aids Control Programme. All procedures were approved by the Committee on Human Research Publication and Ethics of School of Medical Sciences, KNUST (*CHRPE/Student/113*/09). A written informed consent form was completed by all the participants who were recruited into the study after the study was explained in a language they understand. Pre-tested questionnaires were used to record information of the participants. Information on demography, life style, physical examination and anthropometric measurements were taken.

Study design

A cross sectional comparative study of 305 HIV-infected patients conducted between October 2009 and June 2010. Out of this number, 164 patients were on highly active antiretroviral therapy for at least six months and above (HAART- experienced) and 141 HAART- naïve, patients constituted HIV-positive patients, not on HAART and whose CD4 was not below the critical value of 320 cell/ml). The age range of the HAART experienced was 22 to 60 years, (mean ± S.E.M of 38.18±0.65 years) and that of the HAART naïve, between 20 to 64 years (mean ± S.E.M of 38.81±0.76 years). Of the 164 HAART experienced participants, 122 (74.4%) were females and 42 (25.6%) were males, (mean ± S.E.M of 37.33±0.77 and 40.64±1.16 respectively). The HAART-naïve group had 86 (61.0%) participants being females and 55 (39.0%) males (mean ± S.E.M of 36.59±1.01 and 42.27±1.01 respectively).

WHO recommended antiretroviral medicines were used: Stavudine, lamivudine, Efavirenz, Zidovudine and Nevirapine. All the HAART experienced participants involved in the study used a combination of these medicines, grouped under NRTI consisting:Stavudine, lamivudine and Zidovudine and NNRTI consisting of Nevirapine and Efavirenz. The combination consisted of a Stavudine based lamivudine with either Nevirapine or Efavirenz and a Zidovudine based lamivudine combined with either Nevirapine or Efavirenz.

Participants with opportunistic infections, pregnant women and patients with known type I and II diabetes and (or) hypertension before HAART were excluded.

Anthropometric measurement

Body weights were measured (to the nearest 0.5 kilogram), with the subject standing on a weighing scale after it was adjusted to zero kg, and calibrated using known weights. Heights were measured (to the nearest 1.0 centimeter), with the subject standing in an erect position against a vertical scale of portable standiometer and an L-square placed on the head, and the head positioned tolevel with the inferior margin of the bony orbit. The waist measurements

were taken from the middle point between the iliac crest and the last rib, as recommended by the World Health Organization. Hip circumference was measured as the maximal circumference over the buttocks. Hip and Waist circumferences were measured twice to the nearest centimeter and the mean were used for subsequent analysis. Skin fold measurement was done with a pair of calipers (Body care CV47 OD, UK) at four standard points: subscapular (on the Back below shoulder blade), suprailiac (Side of waist), bicep and triceps skin folds. All measurements were read in centimeters (cm) but the height was converted to meters. BMIs were then calculated as weight in kilograms divided by the height in meter squared.

Sample preparation and Biochemical assay

Fasted blood samples (overnight fast between 8-12 hours) were drawn from the median cubital vein on the anterior forearm into plain and fluoride oxalate tubes, BD vacutainer®, (BD, Plymouth, PL6 7BP. UK), to prevent glycolysis.

The clotted blood was centrifuged using centrifuge (D-78532, Tuttlingen, Germany) at 2000 rpm for 5 minutes to separate out the serum. The serum was used to estimate the lipid profile: Total cholesterol (TC), High density lipoprotein cholesterol (HDL), low density lipoprotein(LDL) and triglycerides (TRG) were estimated by direct enzymatic assay with Selectra Junior (Vital Scientific, N.V. Netherlands) automated assay. Protocol for assay by the kit manufacturer (ELITECH DIAGNOSTICS) was strictly adhered to. Interassay coefficient of variation (2.3% and 2.1% for low and high total cholesterol controls respectively comply with National Cholesterol Education Programme recommendation[16.] The remaining serum which was not immediately used was stored at -20°C. Anticoagulated blood was gently mixed with blood mixer (Sarstedt, D-5223, Numbrecht, West Germany). Haemoglobin concentration was estimated with Sysmex (KX-21N) and Cluster of differentiation 4 (CD_4) was done with Becton Dickinson FACSCount® (BD Biosciences, San Jose, CA 95131 USA). The fluoridated anticoagulated blood was centrifuged (Zentrifugen, D-78532, Tuttlingen, Germany) at 3000 rpm for 5 minutes to separate the plasma from the deposit. The plasma was used to estimate the fasting blood glucose(FBS) by enzymatic method using the automated Selectra Junior.

Normal value range of measured parameters in Kumasi Laboratory include (FBS 3.3 6.4 mmol/l ,TC;3.1-6.5 mmol/l, TRIG 0.3-1.7mmol/l, HDL 0.75-1.88 mmol/l, LDL. 3.88-4.91 mmol/l) [17]were used to determine the lower and higher parameters levels.

Statistical analysis

Data were entered into Microsoft Office Excel version 11.0 (Microsoft Corporation, USA), and further analyzed using Graph Pad Prism (version 5.0). The unpaired t-test was done for the mean ±SD with the 95% confidence interval. Statistical significance was set at p-valuesd < 0.05 for the various parameters in the study. A linear regression and multivariate regression analyses, was done considering sex and the measures of fat distribution to find predictors of glucose level from the various parameters.

Results

Height, body weight, waist circumference, Waist-to-Hip ratio, bicep skin fold, systolic and diastolic blood pressure were all significantly higher ($p<0.0001$) in the HIV-infected HAART experienced patients than the control. There were no significant differences between the subjects and the control for BMI, subscapular skinfold. A similar trend was observed for the female and male subjects in comparison to the general population. Even though these parameters were significantly higher in the subjects than the controls all these parameters were within the physiological control levels.

Table 1: Anthropometric parameters of the Study population

Variables	Control (N=86:F, 55:M)	Case (N=164)	P-value	Female cases (N=122)	P-value	Male cases (N=42)	P-value
Age(years)	38.81±0.76	38.18±0.65	0.5290	37.33±0.77	0.5616	40.64±1.16	0.2914
Height(m)	1.52±0.01	1.60± 0.01	<0.0001	1.57±0.01	<0.0001	1.67±0.02	<0.0001
BW(kg)	54.87±0.90	60.37±0.73	<0.0001	59.54±0.89	0.0002	62.79±1.14	0.0005
BMI(Kg/m2)	23.98±0.44	24.07±0.33	0.8729	24.47±0.39	0.8842	22.90±0.67	0.5956
WC(cm)	77.35±0.68	83.77±0.67	<0.0001	84.25±0.82	<0.0001	82.40±1.08	0.0050
HC(cm)	91.16±0.62	95.21±0.70	<0.0001	96.02±0.85	<0.0001	92.86±1.10	0.2952
WHR	0.85±0.00	0.88±0.01	<0.0001	0.88±0.01	0.0001	0.89±0.01	0.0005
Biceps(mm)	4.18±0.22	5.78±0.24	<0.0001	6.25± 0.29	0.0002	4.40±0.27	0.0089
Triceps(mm)	8.90±0.47	10.41±0.46	0.0232	12.02±0.54	0.0393	5.71±0.31	0.1114
SC(mm)	11.79±0.45	12.92±0.48	0.0869	14.24±0.56	0.0399	9.10±0.60	0.1009
SI(mm)	8.57±0.34	9.11± 0.37	0.2912	9.89±0.41	0.2935	6.86±0.77	0.4205
SBP(mmHg)	103.62±1.26	116.34 ±1.35	<0.0001	115.49±1.58	<0.0001	118.81±2.55	<0.0001
DBP(mmHg)	67.80±0.84	75.37±1.01	<0.0001	75.08±1.19	0.0001	76.19±1.93	<0.0001

BW: Body weight; BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist to hip ratio; SC: Subscapular skin fold; SI: Suprailiac skin fold; SBP: Systolic blood pressure; DBP: Diastolic blood pressure and S.E: Standard error of the mean.

Table 2: Biochemical parameters of the Study population

Variables	Control (N=86:F, 55:M)	Case (N=164)	P-value	Female cases (N=122)	P-value	Male cases (N=42)	P-value
Hb(g/dl)	10.43±0.14	11.77±0.12	<0.0001	11.69±0.14	<0.0001	12.01±0.22	<0.0001
CD4(cells/ul)	233.35±16.69	358.71±17.29	<0.0001	370.85±20.89	0.0005	323.45±29.29	0.0003
FBS(mmol/l)	3.81±0.08	4.48±0.17	0.0005	4.59±0.21	0.0015	4.16±0.24	0.1904
TC(mmol/l)	3.65±0.08	4.54±0.08	<0.0001	4.69±0.09	<0.0001	4.09±0.15	0.0015
TRIG(mmol/l)	1.37±0.07	1.37±0.07	0.9967	1.38±0.08	0.8093	1.34±0.13	0.7174
HDL-C(mmol/l)	0.85±0.04	0.97±0.03	0.0122	1.01±0.04	0.1645	0.86±0.06	0.0962
LDL-C(mmol/l)	2.24±0.07	2.87±0.07	<0.0001	2.98±0.09	<0.0001	2.53±0.09	0.0086

Hb: Hemoglobin concentration; CD4: Cluster of differentiation 4; FBS: Fasting blood glucose
TC: Total Cholesterol; TRG: Triglycerides; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol

CD4 count, FBS, Total cholesterol, HDL and LDL were significantly ($p<0.0001$) elevated in HIV-infected HAART experienced patients. However, there was no significant change in the triglycerides levels between the control population and the subject population. A similar trend was observed for the female and male subjects in comparison to the general population. Even though these parameters were significantly higher in the subject than the controls all these parameters were within the physiological control levels except for the CD4 count.

Table 3: Effect of HAART combination and gender on lipodystrophy

Fat distribution	d4T/3TC/NVP (n=68)		d4T/3TC/EFV (n=30)		AZT/3TC/NVP (n=36)		AZT/3TC/EFV (n=21)		Total
	F	M	F	M	F	M	F	M	
Lipoatrophy									
Face	17	1	5	6	3	3	2	2	39
Limbs	5	2	4	1	4	2	0	0	18
Lipohypertrophy									
Neck	19	5	7	3	14	2	1	1	52
Breast	12	1	2	0	10	2	0	0	27
Abdomen	13	5	8	2	7	5	7	1	48
Buttocks	8	3	3	1	5	2	0	0	22

F: Female, M: Male

Table3.Shows fat distribution, in association with HAART used and gender across the study population

24% HAART experienced participants had facial fat depletion. Of this figure, 18 were using d4T/3TC/NVP combination therapy, 11, 6 and 4 were using d4T/3TC/EFV, AZT/3TC/NVP and AZT/3TC/EFV respectively. Participants on AZT/3TC/EFV combination therapy had no changes in appearance in terms of fat depletion on the limbs as well as fat accumulation in the breast and buttocks. 18, 10, 12, 8 had truncal obesity after using d4T/3TC/NVP, d4T/3TC/EFV, AZT/3TC/NVP and AZT/3TC/EFV combination therapy respectively.

When the result of fasting glucose was compared to duration of antiretroviral therapy (table 4.), 4.3% HAART experienced participants developed type II diabetes between 6-18 months on the therapy. Also, 0.6% and 1.8% HAART experienced participants developed type II diabetes between19-31 and after 31 months on therapy respectively. Of the 4.3% HAART experienced participants who developed IFG, 1.2% developed IFG between 6-18 months. 2.4% developed IFG between 19-31 months and 0.6% developed IFG after 31 months on therapy (table 4).

Family history of hypertension and type II diabetes are important risk factors of cardiovascular disease and diabetes. In this study, participants with a family history of type II diabetes had 7 times the chance of developing type II diabetes among the HAART experienced group: X^2(P), 8.6(0.0034).

Further analysis of the data suggest that HAART experienced subjects were 5 times more likely to develop type 2 diabetes, and raised CD4 count, four times likely to develop hypercholesterolemia and a significantly reduced chances of raised HDL and LDL, and a non-significanttriglyceride change (table 5).

Table 4: Duration of HAART in association with the development of dysglycaemia

Duration	Normal			IFG			Diabetes		
(Months)	Total	Female	Male	Total	Female	Male	Total	Female	Male
6-18	98	67	31	2	2	0	7	5	2
19-31	30	26	4	4	4	0	1	1	0
31+	18	13	5	1	1	0	3	3	0
Total	146	106	40	7	7	0	11	9	2

IFG: impaired fasting glucose; Duration: Duration of HAART in months

Table 5: Assessment of biochemical parameters as risk factors of development of diabetes and CVD

Parameters		Control	Case	OR(95% CI)	Chi²	P-Value
FBS(mmol/l)	Low	83(58.9)	86(52.4)	0.9(0.6-1.5)	0.08	0.7780
	*Normal	55(39.0)	61(37.2)	1		
	High	3(2.1)	17(10.4)	5.1(1.3-28.4)	7.33	0.0068
TC(mmol/l)	Low	45(31.9)	15(9.2)	0.2(0.1-0.4)	23.68	0.0000
	*Normal	95(76.4)	143(87.2)	1		
	High	1(0.7)	6(3.7)	4.0(0.5-185.2)	1.87	0.1710
TRIG(mmol/l)	Low	0(0)	1(0.6)	------	0.87	0.3502
	*Normal	113(80.1)	129(78.7)	1		
	High	28(19.9)	34(20.7)	1.1(0.6-1.9)	0.05	0.8290
HDLC(mmol/l)	Low	84(59.6)	71(43.3)	0.4(0.3-0.8)	10.44	0.0012
	*Normal	48(34.0)	88(53.7)	1		
	High	9(6.4)	5(3.1)	0.3(0.1-1.1)	4.53	0.0333
LDLC(mmol/l)	Low	138(97.9)	143(87.2)	0.1(0.0-0.6)	8.98	0.0027
	*Normal	2(1.4)	15(9.2)	1		
	High	1(0.7)	6(3.7)	0.8(0.0-55.0)	0.03	0.8652
CD_4(cells/ul)	*Low	52(36.9)	18(11.0)	1		
	Normal	89(63.1)	146(89.0)	4.7(2.5-9.1)	28.77	0.0000

FBS: Fasting blood glucose; TC: Total cholesterol; TRIG: Triglycerides; HDLC: High density lipoprotein cholesterol; LDLC: Low density lipoprotein cholesterol; CD_4: Cluster of differentiation 4. OR; Odd Ratio (crude), CI, Confidence Interval.

Table 5 presents the analysis for co morbidity for type II diabetes and CVD. Total cholesterol was higher in the cases than the control and the difference was statistically significant (P=0.0068). Also, LDL in the cases were nonsignificantly higher than in the controls (P=0.8652)

Table 6: Assessment of family history as risk factor of development of diabetes and CVD

Parameters		Control	Case	OR(95% CI)	Chi²	P-Value
FH Diabetes	*No	139(98.6)	149(90.9)	1		
	yes	2(1.4)	15(9.2)	7.0(1.6-63.8)	8.60	0.0034
FH Hypertension	*No	136(96.5)	146(89.0)	1		
	yes	5(3.6)	18(11.0)	3.4(1.2-11.8)	6.00	0.0143

FH: Family history, OR: Odd Ratio

Discussion

The use of HAART has significantly decreased morbidity and mortality in HIV infected patients leading to an increase in life expectancy. However, the benefits of antiretroviral combination therapy are associated with a wide spectrum of side effects with some clinical manifestations[18,19]. Lipodystrophy, hyperlipidaemias, insulin resistance, hyperglycaemia and even overt diabetes has been reported in subjects treated with protease inhibitors (PIs) and nucleoside-reverse transcriptases inhibitors (NRTIs)[20]. Aclassification of morphological and metabolic abnormalities following HAART administration is summarized in Table.1.Suprailiac skinfold and BMI were not significantly changed between the subject and control. BMI has been shown in several studies not to give a good reflection of body fat distribution but fat to muscle mass ratio (obesity)[21]. Indeed waist circumference, hip circumference and hip-to-waist

ratios which have been shown to be better reflectors of body fat distribution, were significantly elevated in the HIV-infected patients on HAART. Dyslipidaemia in the HIV–infected, is characterized by hypertriglyceridaemia, and low HDL levels[22]. This is mostly attributed HAART treatment.The prolonged surge of pro inflammatory cytokines such as TNF-alpha, IL-1, IL-6 IFN-alpha observed following the chronic state of HIV infection have been shown to contribute to lipid dysrgulation[23]. Cytokines such as TNF-alpha, IL-1, IL-6 IFN-alpha have also been reported to increase lipogenesis, decrease clearance of circulating LDL and inhibit hepatic lipase activity[24, 25]. This probably partly account for the observed slightly increase in serum LDL levels in this study.

Dyslipidaemia has also been observed in HAART-naive HIV-infected patients, suggesting that HIV-infection itself has a metabolic deleterious effect[10,11.] It is not however certain whether these complications are exclusively due to the viral load or associated with HAART recommended by the WHO[5,26]. The changes in the lipid profile in this study were similar in the male and female cases suggesting that the fat distribution were not exclusively due to gender effect[27]. In several studies in Ghana, women have been shown to have higher waist circumference, hip circumference and hip-to-waist ratios[28] as opposed to what is typically reported in the Western World. It therefore implies that HAART is the main cause of lipid redistribution in this study since these anthropometric parameters were raised in both male and female alike. HIV-infected patients did not show dyslipidaemia despite having been on HAART for well over six months (table 2). Lipid changes were all within the physiological range. However, Total cholesterol, HDL and LDL were significantly ($p<0.0001$) elevated in the HAART-experienced patients while triglycerides were not significantly changed. The elevated HDL contradictsthe effect of NRTI treatment which has been shown to lower HDL levels[10,11,19.]

Hence combination treatment with NNRTI and NRTI drugs may therefore be more beneficial than treatment with only one of the nucleosides, because elevated HDL has a positive effect in lipid metabolism as it increases reverse cholesterol transport effect and therefore anti-atherogenic and possibly partly accounting for the observed physiological level of the lipids. It is also possible that this observation could be explained by genetic influence and or the low diet fat in the Ghanaianas compared to the fat rich western diet, or due to the dietary restriction as part of treatment package. Indeed, HIV-infected patients require aggressive treatment including low-fat diets, avoidance of simple sugars, and elimination of alcohol intake[29]. The advert effect of high fat diet on health and fat distribution has been extensively studied[30,31]. Lipodystrophy characterized by peripheral loss of fat tissue and abnormal fat distribution including the enlargement of dorsocervical fatpad, lipomatosis, breast hypertrophy, and visceral abdominal fat accumulation have recently been reported in HIV-1 patients receiving HAART[6,32-3540.] In this study the combined use of NNRTI and NRTI resulted in 24% of the subjects experiencing facial fat depletion. However, participants on AZT/3TC/EFV combination therapy had no changes in appearance in terms of fat depletion on the limbs as well as fat accumulation in the breast and buttocks. About 29% had truncal obesity after using the various combinations of NRTI and NNRTI (table 3). The association between visceral obesity and NRTI therapy has been reported in several studies[32, 43].
The development of diabetes and or insulin resistance is not only due to hyperlipidaemia but also lipodystrophy[5,8]. Indeed increased visceral fat has been shown to be associated with the development of type2 diabetes whilst peripheral and subcutaneous fat levels, inversely correlates to the development of type 2 diabetes. Haffner, et al. [36]found that WHR was a better single screening measure for NIDDM than BMI and that upper body adiposity predicted diabetes even in leanmen and women. Ohlson,et al.[37] also found that WHR was positively and significantly associated with NIDDM even after BMI was considered among men.

Metabolic syndrome has been reported in HIV patients on HAART[38]. Hyperglycemia, and insulin resistancethe hallmark of metabolic syndrome mostly associated with HIV patients receiving protease inhibitors, have been implicated in patients on NRTIs alone[39.] The development of insulin resistance and diabetes with HAART is time dependent. In this study 4.3% HAART experienced participants developed type II diabetes between 6-18 months on therapy and 6.1% between19-31 and after 31 months, whilst 1.2% of the 4.3% developed IFG between 6-18 months. 3.0% developed IFG between 19-31 months and after 31 months on therapy (table 4). Several mechanisms have been proposed to explain this phenomenon. Among these, the animal and human models of diabetes

mellitus suggest that mitochondrial dysfunction is significantly related to the development of insulin resistance. Several studies have also shown that Nucleoside reverse transcriptase inhibitors (NRTIs) impair mitochondrial function in individuals infected with human immunodeficiency virus (HIV)[41 42]

Even though the fasting blood glucose was significantly higher in the subjects, the significance of the difference between the HAART-experienced and HAART-naïve groups as well as among the subgroups, was lost when the data was subjected to further statistical analyses to determine if this significance could correlate to the development of type 2 diabetesX^2(P): 0.4(0.7904) X2(P): 3.1(0.2136). However, the risk of developing type II diabetes among the HAART experienced group was 5 times higher than the HAART naive group: X^2(P), 7.3(0.0068) (table 5).

The distribution of fat also shows a tendency to the development of hypertension. Even though the systolic and diastolic blood pressures in both HAART-naïve and HAART- experience subjects were within the physiological range, the levels in the HAART-experienced were significantly elevated (table1).

Family history of hypertension and type II diabetes are important risk factors for the development of these diseases. In the study, the HAART experienced group,with a family history of type II diabetes were 7 times more likely to develop type II diabetes than the HAART -naive: data not shown (table 6).

Conclusion

Waist circumference, hip circumference and waist-to-hip ratio which are the key indices for assessing body fat distribution were significantly raised in HAART-experienced than HAART-naïve HIV-infected patients in Kumasi, implying that HAART could result to lipodystrophy. Even though the quantitative values of triglycerides, high density lipoprotein, low density lipoprotein and total cholesterol were all within the physiological range, total cholesterol, low density lipoproteins and high density lipoproteins were significantly raised ($p<0.0001$) in the HAART-experienced. The raised HDL level as a result of the combined use of NRTI's and NNRTI's in this study may therefore serve to improve reverse cholesterol transport and therefore bringing the lipoproteins to the physiological level and their use would be much recommendable.Also, though the fasting blood glucose levels were not significantly different between the control and the subjects, the tendency for the HAART patients to develop dysglycaemia was 5 times higher than the HAART-naive group.

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