ORIGINAL ARTICLE

Lipoatrophy among patients on antiretroviral therapy in Lagos, Nigeria: Prevalence, pattern and association with cardiovascular risk factors

SO Iwuala, OA Lesi, MA Olamoyegun[1], AA Sabir[2], OA Fasanmade

Department of Medicine, College of Medicine, University of Lagos, Idi-Araba, Lagos, Lagos State, [1]Department of Medicine, LAUTECH Teaching Hospital, College of Health Sciences, Ladoke Akintola University of Technology, Ogbomosho, Oyo State, [2]Department of Medicine, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria

Abstract

Context: Antiretroviral therapy (ART) is linked with morphologic abnormalities such as lipoatrophy (LA), which may accompany metabolic alterations (dysglycemias, dyslipidemia and insulin resistance) that increase cardiovascular disease risk. LA and its association with metabolic alterations have been infrequently studied amongst Nigerians on ART.
Aims: To determine the prevalence, pattern and association of LA with metabolic abnormalities and hypertension among patients on ART attending an ambulatory human immunodeficiency virus clinic in Lagos, Nigeria.
Subjects and Methods: A cross-sectional study was carried out among patients on ART using a structured interviewer administered questionnaire. Data obtained included patients and physician's assessment of body fat changes, drug history, blood pressure, body composition assessment using bioelectrical impedance analysis and biochemical evaluation (glucose, lipids). LA was defined clinically. Data were analyzed using IBM SPSS statistical software version 21.
Results: A total of 48 (33.1%) of the 145 patients had LA. The face was the most frequently affected body region. Patients with LA with lower body circumferences, skin-fold thickness and body fat ($P < 0.05$). The frequencies of lipid abnormalities were: Reduced high density lipoprotein–cholesterol (47.1%), elevated total cholesterol (35.6%), reduced low density lipoprotein-cholesterol (19.2%), elevated triglycerides (14.4%). Fasting plasma glucose (FPG)≥6.1 mmol/l and hypertension were present among 9.6% and 40.7% respectively. LA was not significantly associated with the presence of glucose intolerance, dyslipidemia or hypertension ($P > 0.05$).
Conclusions: Lipoatrophy, though commonly encountered in patients on ART in Nigeria was not associated with the presence of dyslipidemia, abnormal FPG or hypertension. Regular monitoring by the physician and increased patients awareness are necessary to reduce its prevalence and impact.

Key words: Antiretroviral therapy, cardiovascular, lipoatrophy, metabolic, Nigeria

Date of Acceptance: 16-Jan-2015

Introduction

The effective use of antiretroviral therapy (ART) has led to increased survival amongst patients with the human immunodeficiency virus (HIV) infection. However, adverse effects have been associated with ART. These include the HIV lipodystrophy syndrome comprised of morphologic and metabolic alterations: Fat redistribution or lipodystrophy, dysglycemia and dyslipidemia.[1-3] Lipodystrophy can present as lipoatrophy (LA) (peripheral fat wasting), lipohypertrophy (central fat accumulation) or a combination of both.[3,4] While lipohypertrophy can present independently of HIV

Address for correspondence:
Dr. SO Iwuala,
Department of Medicine, College of Medicine, University of Lagos, Idi-Araba, P.M.B. 12003, Lagos, Nigeria.
E-mail: sandraerhuanga@yahoo.com

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/1119-3077.154208

PMID: 26096241

infection and ART, LA has been linked with ART, especially with nucleoside reverse transcriptase inhibitors (NRTIs), which often form the backbone of ART in resource-poor settings.[3,5]

Lipoatrophy affects cosmetic appearance, thus contributing to stigma and potentially influencing long-term adherence to ART.[6,7] It is damaging to self-image and can reduce the quality of life of affected persons.[8] As part of the lipodystrophy syndrome, It may also be associated with metabolic complications such as dyslipidemia, glucose intolerance and insulin resistance, which contribute to HIV-related morbidity and mortality through increased cardiovascular and cerebrovascular disease.[9,10] The reported prevalence of LA varies widely, ranging from 13.3% to 52.9%,[11-14] possibly due to the difference in tests used in its assessment, population studied, the duration and type of ART regimens used in the various studies.

Metabolic abnormalities among patients on ART in Nigeria have been well documented. Conversely, LA and its association with metabolic abnormalities have been infrequently studied in Nigeria, a country with one of the largest numbers of PLWHA and up to 32% of eligible PLWHA on ART.[15] The impact of ethnicity on disease manifestations and heterogeneity in response to medications warrants that LA, as well as its association with metabolic abnormalities, be clearly elucidated. The current study aimed to study the association of clinical LA with metabolic abnormalities and hypertension amongst patients on ART attending the HIV clinic of a tertiary health care facility in Lagos, Nigeria.

Subjects and Methods

Setting and design

This cross-sectional study was carried out among patients on ART attending the HIV outpatient clinic of a tertiary health care center where ART is provided at no cost to the patients. Approval for the study was obtained from the Health Research and Ethics Committee of the hospital. A written informed consent was obtained from the study participants.

Sample size determination

The sample size was determined using the Fisher's statistical formula for sample size i.e. $N = Z^2pq/D^2$, where N = minimum sample size, Z = standard deviation set at 1.96 which corresponds to a 95% confidence interval, P = prevalence of LA (9.8%) among Rwandan patients on ART,[16] $q = 1 - p$, D = margin of unacceptable error or measure of precision (0.05). The calculated sample size was 135. One hundred and forty five persons on ART were recruited to participate in the study.

Subjects

Ambulant consecutively consenting HIV positive patients on ART meeting the inclusion criteria were recruited into the study. Patients were included into the study if they were confirmed to have HIV infection (by western blot technique), were aged between 15 and 70 years, had been on ART for at least 6 months, were not on drugs affecting carbohydrate and fat metabolism or inducing lipodystrophy e.g. statins, corticosteroids, metformin, thiazolidinediones and were not known patients with diabetes mellitus or tuberculosis. They were excluded if they were moribund, acutely ill, pregnant or lactating.

Study protocol

A pretested structured interview questionnaire was administered to all the study participants. Information regarding the patients' sociodemographic characteristics, disease history and drug history was obtained. Patients self-report of body fat changes, as well as the severity, graded using the HIV Outpatient Study (HOPS) scale,[17] in six body regions (face, arms, legs, buttocks, abdomen, neck) were also obtained. A targeted physical examination for body fat changes in the same body regions was performed by a single physician. The case notes of the patients were also reviewed for the treatment history. Anthropometric indices - height, weight, waist, hip and mid-upper arm circumferences, skin fold thicknesses (SFT) (performed by a single physician) and blood pressure measurement were measured by standard methods. SFT was assessed at four sites with three measurements at each site using slim guide skin fold calipers and the mean at each site determined. Body composition was assessed with bioimpedance analysis (BIA) using the Omron body composition monitor with scale (HBF-500).

Fasting (at least 8 h of overnight fast) venous blood was collected from 104 randomly selected study subjects into appropriate specimen bottles for plasma glucose and lipid profile. Plasma glucose and lipid profile were determined using the glucose oxidase method of Trinder and the commercial kits by Biolabo S.A, France respectively. Patients CD4 count (done by flow cytometry [PARTEC cmbH Germany] and viral load [by Polymerase Chain Reaction using (AMPLICOR HIV-1 MONITOR Test, version 1.5, Roche Molecular Systems Inc, U.S.A) were also done.

Lipoatrophy was defined as self-report of loss of fat from the face, arms, legs, buttocks supported by targeted physical examination or fat wasting from the face, arms, legs or buttocks detected on physical examination.[18,19] Normal glucose tolerance was defined as fasting plasma glucose (FPG) <6.1 mmol/l (110 mg/dl).[20] Dyslipidemia was defined according to National Cholesterol Education Panel guidelines for desirable lipid levels: Total cholesterol (TC) <200 mg/dl, high-density lipoprotein-cholesterol (HDL-C)

>50 mg/dl in females and >40 mg/dl in males, low-density lipoprotein-cholesterol (LDL-C) <130 mg/dl, triglycerides (TGs) <150 mg/dl.[21]

Hypertension was defined as systolic blood pressure >140 mmHg or mean diastolic BP >90 mmHg or a prior clinical diagnosis of hypertension.[22] Staging of HIV infection was done by the CDC categorization of HIV infection.[23]

Statistical analysis

Data were entered into excel worksheet for cleaning before being imported to IBM for social sciences (SPSS) version 21 statistical software for analysis. Continuous variables were expressed as means and standard deviation when the data was normally distributed as determined by the Kolmogorov–Smirnov test. Variables with a skewed distribution were expressed as median and interquartile range (IQR). Categorical variables were expressed as frequencies with accompanying percentages in paracentesis. Differences between groups were compared using the Chi-square for categorical data. The unpaired independent *t*-test was used to compare means of normally distributed data between groups whereas the Mann–Whitney U-test was used for variables with skewed distribution. A $p < 0.05$ was accepted as significant.

Results

The clinical characteristics of the study population are shown in Table 1. There were 84 (57.9%) females and 61 (42.1%) males. Eighty-seven (60%) patients were married, 29 (20%) had no/primary school education, 76 (52.4%) had secondary school education and 40 (27.6%) had tertiary level education.

Table 1: Clinical characteristics of the study population and comparison of the study participants according to gender

Variable	Total (*n*=145)	Females (*n*=84)	Males (*n*=61)	*P*
Age (years)	40.3 (8.9)	38.4 (8.3)	41.0 (8.6)	0.002*
BMI (kg/m^2)	24.8 (4.0)	25.0 (4.0)	24.5 (3.9)	0.497
WC (cm)	85.3 (10.0)	84.2 (9.4)	86.8 (10.8)	0.135
HC (cm)	98.6 (9.0)	99.7 (9.6)	97.1 (8.0)	0.099
Waist-to-hip ratio	0.86 (0.07)	0.85 (0.06)	0.89 (0.07)	<0.001*
MUAC (cm)	29.3 (3.9)	28.8 (4.1)	30.6 (3.5)	0.006*
TSF (cm)	11 (6-21)	16.5 (10.7-25.2)	6.0 (4.0-10.7)	<0.001*
SSF (cm)	37.0 (28.0-65.0)	50.8 (33.5-75.7)	30.0 (22.7-37.0)	<0.001*
Percentage of BF	28.1 (11.2)	34.7 (8.3)	18.8 (7.4)	<0.001*
Percentage of skeletal muscle mass	32.2 (6.6)	27.7 (3.8)	38.3 (4.3)	<0.001*
Duration of ART (months)	29.0 (16-40.0)	27.50 (16.0-38.5)	30.0 (15.0-41.0)	0.829

Values are mean (SD) or median (IQR); *Statistically significant. BMI=Body mass index; WC=Waist circumference; HC=Hip circumference; MUAC=Mid-upper arm circumference; TSF=Triceps skin fold thickness; SSF=Sum of skin fold thickness; ART=Antiretroviral therapy; BF=Body fat

Table 2: Demographic, anthropometric, BIA and HIV related characteristics of patients with or without LA according to gender in the study participants

Variable	All LA (*n*=48)	Females			Males		
		LA present (*n*=17)	LA absent (*n*=67)	*P*	LA present (*n*=31)	LA absent (*n*=30)	*P*
Age (years)	42.2 (9.0)	38.9 (6.8)	38.2 (8.7)	0.773	44.0 (9.6)	42.0 (8.4)	0.398
BMI (kg/m^2)	22.6 (3.1)	21.8 (2.0)	25.8 (4.0)	<0.001*	23.0 (3.5)	26.0 (3.7)	0.002*
WC (cm)	81.0 (8.1)	78.8 (5.7)	85.6 (9.7)	0.007*	82.2 (9.1)	91.7 (10.4)	<0.001*
HC (cm)	92.6 (5.8)	92.0 (5.7)	101.6 (9.5)	<0.001*	92.9 (5.9)	101.7 (7.5)	<0.001*
MUAC (cm)	28.2 (3.4)	26.3 (2.8)	29.4 (4.1)	0.004*	29.2 (3.3)	32.1 (3.2)	<0.001*
Sum SFT (mm)	26.0 (22.0-33.2)	30.7 (24.7-39.3)	58.0 (37-80.0)	<0.001*	23.7 (19.7-31.7)	35.0 (28.0-50.3)	<0.001*
Percentage of BF	18.8 (8.1)	26.0 (7.5)	36.9 (7.0)	<0.001*	14.7 (5.0)	22.9 (7.3)	<0.001*
Percentage of skeletal muscle mass	37.1 (5.6)	31.7 (4.5)	26.7 (2.8)	<0.001*	40.1 (3.7)	36.4 (4.1)	<0.001*
Duration ART (months)	32.0 (14.5-49.0)	34.0 (22.0-39.0)	27.0 (16.0-38.0)	0.466	30.0 (12.0-51.0)	24.5 (16.0-38.0)	0.382
CD4 count (cells/mm^3)	335 (230-420)	347 (238-416)	414 (271-648)	0.058	335 (230-525)	285 (203-472)	0.446
ART regimen							
Stavudine based	22 (45.8)	6 (35.3)	17 (25.4)	0.394	16 (51.6)	9 (30.0)	0.161
Zidovudine based	19 (39.6)	9 (52.9)	32 (47.8)		10 (32.3)	11 (36.7)	
Tenofovir based	7 (14.6)	2 (11.8)	18 (26.9)		5 (16.1)	10 (33.3)	

BMI=Body mass index; WC=Waist circumference; HC=Hip circumference; MUAC=Mid-upper arm circumference; TSF=Triceps skin fold; SSF=Sum of SFT; BIA=Bioelectrical impedance analysis; LA=Lipoatrophy; SFT=Skin fold thickness; BF=Body fat; ART=Antiretroviral therapy; HIV=Human immunodeficiency virus

Table 3: Association of metabolic parameters and hypertension with LA in the study participants

	LA	No LA	*P*
FPG (mmol/l)*			
<6.1	32 (34.0)	62 (66.0)	0.303
≥6.1	2 (20/0)	8 (80.0)	
TC (mmol/l)*			
<5.17	23 (34.3)	44 (65.7)	0.795
≥5.17	11 (29.7)	26 (70.3)	
TG (mmol/l)*			
<1.67	30 (33.7)	59 (66.3)	0.415
≥1.67	4 (26.7)	11 (73.3)	
HDL male (mmol/l)*			
<1.03	8 (57.1)	6 (42.9)	0.461
≥1.03	13 (50.0)	13 (50.0)	
HDL female (mmol/l)*			
<1.29	6 (17.1)	29 (82.9)	0.351
≥1.29	7 (31.8)	22 (75.9)	
LDL (mmol/l)*			
<3.36	28 (33.3)	56 (66.7)	0.500
≥3.36	6 (30.0)	14 (70.0)	
Hypertension			
No	26 (69.8)	60 (30.2)	0.479
Yes	22 (37.3)	37 (62.7)	
Mean SBP (mmHg)	129.7 (24.7)	127.6 (19.0)	0.562
Mean DBP	82.4 (15.1)	81.0 (12.7)	0.577

*Based on 104 study participants. LA=Lipoatrophy; FPG=Fasting plasma glucose; TC=Total cholesterol; TG=Triglyceride; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; DBP=Diastolic blood pressure; SBP=Systolic blood pressure

All the patients had nucleoside and/or nucleotide analogs in their ART regimen. These three drugs were mutually exclusive in the study population, and so ART regimen were referred to as stavudine based, zidovudine based or tenofovir based. One hundred and thirty-five patients (93.1%) were on nonnucleoside reverse transcriptase inhibitors, comprised of 100 on nevirapine and 35 on efavirenz. Only 9 (6.2%) patients were on protease inhibitors (PI). The median duration, since HIV was diagnosed, was 34.5 months (19–55).

Among the 104 study participants who had biochemical evaluation done, low HDL-C was the most frequently (49 [47.1%]) encountered metabolic abnormality, followed in descending frequencies by elevated TC 37 (35.6%), elevated LDL-C 20 (19.2%), elevated TG 15 (14.4%) and elevated FPG 10 (9.6%).

Prevalence of lipoatrophy in the study population

The prevalence of LA was 48 (33.1%, confidence interval [CI] - 25.5–41.4%), made up of 17 (35.4%) females and 31 (64.6%) males. Males were 4 times more likely to have LA compared to females ($\chi^2 = 13.47$, odds ratio [OR] = 4.07 [1.85–9.07], $P < 0.001$).

Self-report of body fat changes

Out of 48 patients with LA in the study population, only 12 (25.0%) reported body fat changes. These comprised of 5 (41.7%) females and 7 (58.3%) males. There was no significant difference of self-report of body fat changes according to gender ($\chi^2 = 0.27$, OR = 0.70 [CI - 0.18–2.68], $P = 0.60$).

Pattern and severity of lipoatrophy in the study population

Of the body regions evaluated for LA, the face was the most common region affected. Thirty (62.5%) of the 48 patients had facial LA. Facial LA was followed in descending frequencies by LA in the upper limbs 24 (50%), lower limbs 13 (27.1%) and gluteal region 11 (22.9%).

Demographic, anthropometric, body composition (BIA) and HIV related characteristics of persons with LA in the study population

The comparison of the demographic, anthropometric, body composition (BIA), HIV related characteristics of persons with LA compared to those without according to gender is as shown in Table 2. The subjects with LA had a significantly lower body mass index, waist circumference, hip circumference, mid-upper arm circumference, triceps skin fold, subscapular skinfold thickness, % body fat, compared to the HIV patients without LA ($P < 0.001$). However, the % skeletal muscle mass was significantly higher in persons with LA compared to those without ($P < 0.001$ in males and females respectively).

There was no significant difference in the ART duration, CD4 count and drug regimen in patients with or without LA in the study participants (all $P > 0.05$), as shown in Table 2. None of the patients on PIs were diagnosed with LA.

Association of lipoatrophy with metabolic abnormalities

Table 3 examines the association between metabolic parameters and LA in the study participants. LA was not significantly associated with glucose intolerance, dyslipidemia or hypertension ($P < 0.05$).

Discussion

The aim of this study was to determine the prevalence of LA as well as its association with metabolic abnormalities amongst HIV positive patients on ART in Nigeria. There have been several reports of the prevalence and factors associated with LA from other sub-Saharan countries such as Senegal, Benin, Rwanda and South Africa,[13,16,24,25] but none from Nigeria. This study findings demonstrate that LA is commonly encountered amongst patents on ART in Nigerian patients as LA was present in 33.1% of the patients in this study. Lower prevalence (13.1-29.3%) of LA among patients on ART in developing countries have been reported.[13,16,19,25] In the developed world, while some workers reported a lower prevalence of 14-16%,[17,26] others found higher prevalence of 38.3 to 52.9% compared with

that obtained in this study.[11,12,14,27] The differences in these prevalence may be explained by the following reasons: Differences in duration and type of ART used, definition/assessment of LA, study design and patient factors. For instance, the higher prevalence rate of LA found in this study compared to that found by other studies[13,16] could be attributed to the longer duration of ART in this study. In a study in which ART duration was longer (13.3 years) than in our study, a prevalence of 52.9% of LA was reported. The pathogenic mechanisms inducing LA would be present for longer with longer duration of therapy.

In this study, LA was defined clinically and was weighted on physician assessment of LA as have been done by other workers.[18,19] There was a low prevalence of self-report on questioning for body fat loss in the study population with LA. This finding of low rate of self-report of body fat changes in patients with LA has been reported in other studies done in developing countries.[18,19] This may be due to patients' lack of awareness of the morphological effects of ART. Furthermore, overall weight gain and well-being after commencement of ART may have precluded the observation of fat loss from certain body sites. Even in the HOPS study (USA), physician assessment of the severity of LA prevailed when there were differences between physician and patient's assessment.[17] Though an objective case definition for diagnosing lipodystrophy syndrome, in general, has been suggested, its reliability in the absence of tools like DEXA is low.[28] DEXA was not available at this study site, and many other centers and so could not be employed in this study for regional body composition. However, the clinical diagnosis of LA was supported by lower anthropometric indices, SFT and % body fat determined by BIA in persons with lipoatropophy compared to those without LA.

The factors associated with LA assessed for in this study include host, treatment and disease factors. Male gender was significantly associated with LA. A study from Burkina Faso also found male gender to be a factor in the development of LA.[29] Males physiologically have less body fat than females and thus may be more prone to the pathologic mechanisms inducing LA.[30-32] Other studies have found females to be more at greater risk for LA compared with males.[16,33] Age was not a factor associated with LA in this study population unlike what some researchers have reported.[17,34]

Evidence exists to show that NRTI associated adipose tissue mitochondrial toxicity plays an important role in the pathogenesis of LA.[30-32] Stavudine, among the NRTIs has been frequently implicated in the development of LA.[16,33,35-37] However, current drug regimen, including stavudine use was not significantly associated with LA in this study. This may be due to the use of a lower dose of stavudine in our study participants compared studies in which LA was linked to stavudine use. Furthermore, majority of the study participants were on NRTI based regimens.

In this study other diseases related factors such as ART duration and CD4 count were not also significantly associated with LA. Basal CD4 counts as well as nadir CD4 count are some of the disease related factors that have been associated with LA.[16,36,38] These data were not available for all the patients in this study and so were not analyzed.

Association of lipoatrophy with metabolic abnormalities and hypertension

In this study, the presence of LA was not significantly associated with glucose intolerance, dyslipidemia or hypertension. The lack of association of glucose intolerance or hyperlipidemia with LA is in keeping with other studies.[26,39] Conversely, low TGs reported to be associated with the presence of LA was not found in our study.[26,40]

While several workers have reported an association of lipodystrophy syndrome with hypertension,[41-43] only a few have examined the association of LA with hypertension.[44] In this study, the presence of LA was not significantly associated with hypertension, as some workers have reported.[45] The differences in the findings of the association of LA with metabolic abnormalities and hypertension may be due differences in the ART, heterogeneity in response to medication, HIV infection itself as well as other factors present in non-HIV infected populations such as genetic or environmental factors.

The strength of this study included the use of objective methods of assessing body fat such as anthropometric indices and % body fat using BIA. The cross-sectional study design is also a limitation of our study.

Conclusions

Lipoatropy is a not uncommonly encountered in patients on ART in Nigeria. The clinical diagnosis of LA was confirmed by lower anthropometric indices, SFT and % body fat in affected patients. Male gender was associated with LA. However, the presence of LA was not associated with metabolic abnormalities and hypertension, cardiovascular disease risk factors. Regular monitoring by the physician and increased patients awareness are necessary to reduce its prevalence and possible impact among patients on ART.

Acknowledgment

The authors wish to acknowledge the AIDS prevention initiative among Nigeria (APIN)/President's Emergency Plan for AIDS Relief (PEPFAR) staff at the study site for their administrative support during the study.

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How to cite this article: Iwuala SO, Lesi OA, Olamoyegun MA, Sabir AA, Fasanmade OA. Lipoatrophy among patients on antiretroviral therapy in Lagos, Nigeria: Prevalence, pattern and association with cardiovascular risk factors. Niger J Clin Pract 2015;18:626-32.

Source of Support: Nil, **Conflict of Interest:** None declared.