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Lipodystrophic syndrome of HIV and associated factors: a study in a university hospital

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Abstract *The use of antiretroviral drugs has increased the survival of HIV patients, but may have side effects, such as lipodystrophic syndrome. This article aims to identify the frequency of the lipodystrophic syndrome and its associated factors in patients with HIV using antiretroviral therapy. It involved a cross-sectional study with HIV patients, monitored on an outpatient basis. The syndrome was evaluated by the association of two parameters: peripheral weight loss through the lipodystrophy severity scale and central fat accumulation, measured by the hip waist ratio. Poisson regression analysis was performed to identify the associated variables. Of the 104 patients evaluated, 27.9% presented the syndrome. After adjustment, the female sex ($PR_{adjusted}$ = 2.16 $CI_{95\%}$ 1.43-3.39), being overweight ($PR_{adjusted}$ = 2.23 $CI_{95\%}$ 1.35-2.65) and a longer period of use of antiretrovirals ($PR_{adjusted}$ = 1.64 $CI_{95\%}$ 1.16-2.78), remained positively associated with the syndrome. On the other hand, a negative association with CD4 count £ 350 ($PR_{adjusted}$ = 0.39 $CI_{95\%}$ 0.10-0.97) was observed The high prevalence of the syndrome and its association with specific groups reinforce the need for adequate follow-up and early identification to intervene in modifiable factors.*

Key words *Lipodystrophy, AIDS, Anthropometry, Antiretroviral therapy*

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Introduction

Treatment for infection by the human immunodeficiency virus (HIV) involves antiretroviral therapy (ART), which inhibits the replication of the virus and is a benchmark in therapy for acquired immunodeficiency syndrome (AIDS), increasing the life expectancy of affected individuals[1]. In Brazil, the public healthcare system offers these medications, which has enabled an increasing number of individuals living with HIV HIV) to obtain treatment, as a 53.2% increase in cases was recorded between 2009 and 2014[2].

However, the living conditions of these patients is a major concern of the *World Health Organization* (WHO). Despite the longer survival, the use of ART has numerous side effects, including HIV-associated lipodystrophy. This outcome is associated with greater cardiovascular risk, morbidity and mortality and also alters body esthetics, which can compromise one's self-esteem, leading to a reduction in adherence to therapy[3,4].

Lipodystrophy is defined as a combination of the loss of peripheral fat (lipoatrophy) and the accumulation of central fat (lipohypertrophy). It was first denominated a syndrome in 1998 and includes metabolic disorders[5,6].

The prevalence of HIV-associated lipodystrophy ranges from 10 to 80%. This broad range is related to geographic, age, genetic and lifestyle factors as well as the different methods employed for the diagnosis[7-10]. Indeed, there is no consensus on the diagnostic method for HIV-associated lipodystrophy and several methodological approaches have been used[11-14]. The administration of questionnaires that use self-reported information to complement the examination of a health professional could facilitate the early identification of body changes. After this clinical assessment, anthropometry is generally performed to determine the occurrence of changes in the distribution of fat for the subsequent diagnosis of lipodystrophy[15,16].

Although there is no reliable parameter that reflects changes in fat distribution specific to HIV-associated lipodystrophy, some authors have used the waist-to-hip ratio (WHR)[17], which is correlated with total abdominal fat determined by computed tomography and offers the advantage of not requiring sophisticated equipment[18].

The pathogenesis of lipodystrophy in individuals living with HIV is multifactorial and has not yet been fully clarified. Although initially related to the type of ART and duration of use, other factors have also been investigated, such as HIV infection itself, genetic factors, lifestyle factors, the severity of markers of the disease, the T-CD4+ lymphocyte count and viral load. These factors can lead to metabolic disorders, such as dyslipidemia, and a change in the metabolism of glucose, resulting in cardiovascular complications[17,19-22].

It is therefore relevant to identify lipodystrophy syndrome and its frequency to enable interventions targeting modifiable associated factors to improve the health management of individuals with HIV in treatment with ART. Thus, the aim of the present study was to identify the frequency of lipodystrophy syndrome and associated factors in individuals living with HIV in treatment with antiretroviral therapy.

Methods

A cross-sectional study was conducted with individuals in outpatient care at the Infectious-Parasitic Diseases Clinic of the hospital of the *Universidade Federal de Pernambuco* between March and July 2017. The sample was composed of all patients who met the eligibility criteria for the study in this period. Male and female patients ≥ 20 years of age in treatment with ART for at least six months were included. Individuals unable to answer the questionnaires due to dementia or a low level of consciousness, those unable to undergo the anthropometric examination, those with edema and/or ascites and pregnant women were excluded from the study.

A standardized form was used for the collection of socio-demographic, clinical, biochemical, anthropometric and lifestyle data. Interviews and the nutritional assessment were performed in accordance with the availability of the individual and conducted by a nutritionist. The researcher did not at any time intervene or express an opinion that could interfere with the answers or results of the study.

The diagnosis of HIV-associated lipodystrophy was determined by two parameters: peripheral fat loss, evaluated using the Lipodystrophy Severity Scale, and the accumulation of central fat, measured by the WHR. Patients with both these criteria were identified as having lipodystrophy syndrome.

The Lipodystrophy Severity Scale was adapted from Carr et al.[23] for the evaluation of the presence/absence of peripheral fat loss (upper and lower limbs). For such, the patients classified the degree of fat loss as none (score: 0), mild

(score: 1), moderate (score: 2) or severe (score: 3). Peripheral fat loss was recorded when a patient attributed a score of 1 to 3 in both regions (arms and legs). For the determination of the accumulation of central fat, the WHR was used considering the classification proposed by the Brazilian Health Ministry[17], which establishes a cutoff point of ≥ 1.0 for males and ≥ 0.85 for females.

Sociodemographic variables were classified as follows: sex (female; male); age (20 to 44; ≥ 45 years), schooling (£ nine; > 9 years of study); income (< R$ 1000; ≥ R$ 1000) and ethnicity/skin color (white; non-white).

Nutritional status was defined using the body mass index (BMI). Weight and height were determined using the methods recommended by Lohman et al.[24]. The BMI was then calculated and classified using the recommendations of the WHO[25], with ≥ 25 kg/m² considered indicative of excess weight.

The following clinical and laboratory variables were considered: CD4+ count, viral load, lipid profile, fasting glucose, time since diagnosis, class of ART and duration of treatment with ART. The CD4+ count was categorized as > 350 or £ 350 cells/mm³; viral load was categorized as > 40 or £ 40 copies/ml; lipid profile was determined based on the 5th Brazilian Guidelines for Dyslipidemia and the Prevention of Atherosclerosis[26]; fasting glucose was considered altered when ≥ 100 mg/dL and unaltered when < 100 mg/dL. Time since diagnosis and duration of treatment with ART were categorized as > 60 months and £ 60 months; class of ART was categorized as two types of nucleoside analog reverse-transcriptase inhibitor (NARTI) combined with a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or two types of NARTI combined with a protease inhibitor.

Regarding lifestyle variables, alcohol use was categorized as absent/present regardless of the quantity and quality of the beverages; smoking was categorized as smoker, ex-smoker and non-smoker; and physical activity was investigated using the short version of the International Physical Activity Questionnaire (IPAQ), with the classification of the individual as sedentary, insufficiently active, active or very active[27].

This study was conducted in accordance with the ethical norms for research involving human subjects stipulated in Resolution 466/12 of the Brazilian National Board of Health and received approval from the Human Research Ethics Committee of *Universidade Federal de Pernambuco*.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 13.0, and Stata, version 7.0. Poisson regression analysis with robust variance was performed to determine factors associated with HIV-associated lipodystrophy, calculating prevalence ratios (PR) and 95% confidence intervals (CI). All variables with a p-value < 0.20 in the unadjusted bivariate analysis, determined using either the chi-square test with Yates correction or the linear trend chi-square test, were incorporated into the multivariate analysis using the stepwise method. Only variables with a p-value < 0.05 after the adjustments remained in the final model.

Results

Among the 104 individuals living with HIV who participated in the present study, 68.3% were men, mean age was 41.11 ± 11.46 years and 27.9% (n = 29) had HIV-associated lipodystrophy (Table 1). Some missing data occurred for the following variables: income, schooling, ART, viral load, CD4+ count, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, excess weight and fasting glucose.

Among the sociodemographic and lifestyle variables, only the female sex had a greater probability of lipodystrophy (PR = 2.31, p = 0.013) in the bivariate analysis (Table 1). Among the clinical variables, patients with a CD4+ count £ 350 had a lower probability of lipodystrophy (PR = 0.26, p = 0.037). In contrast, patients with excess weight had a threefold greater chance of having lipodystrophy (PR = 3.20 p = 0.002) (Table 2). Other variables, such as age ³ 45 years, hypercholesterolemia, time since diagnosis > 60 months and duration of ART > 60 months, had a p-value < 0.20 in the unadjusted bivariate analysis and were therefore incorporated into the multivariate analysis.

In the multivariate Poisson regression analysis adjusted by the explanatory variables, the female sex ($PR_{adjusted}$ = 2.16, $CI_{95\%}$: 1.43 to 3.39), excess weight ($PR_{adjusted}$ = 2.23, $CI_{95\%}$: 1.35 to 2.65) and longer duration of ART ($PR_{adjusted}$ = 1.64, $CI_{95\%}$: 1.16 to 2.78) remained positively associated with lipodystrophy syndrome. In contrast, a negative association with CD4+ count £ 350 was found ($PR_{adjusted}$ = 0.39, $CI_{95\%}$: 0.10 to 0.97) (Table 3).

Table 1. Associations between lipodystrophy syndrome and sociodemographic and lifestyle variables in HIV+ patients at an outpatient clinic of a university hospital in the city of Recife, Brazil, 2017.

Variables	HIV-associated lipodystrophy syndrome								
	Yes		No		Total		†PR	$CI_{95\%}$	p
Sex	N	%	N	%	N	%			
Female	15	45.5	18	54.5	33	31.7	2.31	1.27-9.23	0.013[a]
Male	14	19.7	57	80.3	71	68.3	1.00		
Age (years)									
⩾45	15	37.5	25	62.5	40	38.5	1.71	0.93-3.16	0.133[a]
20-44	14	21.9	50	78.1	64	61.5	1.00		
Family income (Brazilian currency)									
⩽1000	16	30.8	36	69.2	52	51.0	1.59	0.85-2.97	0.216[a]
> 1000	12	24.0	38	76.0	50	49.0	1.00		
Schooling (years)									
⩽ 9	13	28.3	33	71.7	46	46	1.09	0.57-2.08	0.971[a]
> 10	14	25.9	40	74.1	54	54	1.00		
Alcohol intake**									
Yes	11	22.4	38	77.6	49	47.1	0.69	0.36-1.31	0.343[a]
No	18	32.7	37	67.3	55	52.9	1.00		
Smoking									
Smoker	04	20.0	16	80.0	20	19.2	0.74	0.23-1.95	0.491[b]
Ex-smoker	08	38.1	13	61.9	21	20.2	1.41	0.72-2.79	
Non-smoker	17	27.0	46	73.0	63	60.6	1.00		
Level of physical activity									
Sedentary/insufficiently active	08	25.0	24	75.0	32	30.8	0.94	0.33-2.63	0.967[b]
Active	17	29.8	40	70.2	57	54.8	1.12	0.44-2.83	
Very active	04	26.7	11	73.3	15	14.4	1.00		

*†PR – crude prevalence ratio, **intake independently of quantity or quality of beverage, IC – confidence interval, achi-square test with Yates correction, blinear trend chi-square test.*

Discussion

The major studies on metabolic complications of the use of ART have mainly been conducted in high-income countries. However, there has been an increase in studies evaluating the short-term and long-term effects of ART in middle-income and low-income countries[28].

Knowledge regarding the health status and the occurrence of complications in individuals living with HIV in the local population enables the identification of patients at risk and the guidance of prevention methods. Several complications, such as lipodystrophy, can predispose these individuals to cardiovascular risk, impacting their quality of life and adherence to treatment[29].

Thus, the purpose of the present study was to evaluate the occurrence of lipodystrophy syndrome in patients using ART. The prevalence of HIV-associated lipodystrophy (27.9%) was similar to the rate described by Della Justina[30] (32.4%) in a Brazilian cross-sectional study, also using a combination of subjective and objective methods for the diagnosis in outpatients in ART. In other Brazilian studies, the prevalence ranged from 32 to 68%, which is similar to the range found in other countries (30 to 62%). This broad range in the prevalence of HIV-associated lipodystrophy may be explained by the lack of consensus in the literature regarding the diagnosis of the syndrome[4,12,31,32].

Women had a 2.16-fold greater probability of having lipodystrophy. This association has also been reported in previous studies[11,33-35], with a probability 2.5-fold greater in the female sex[34-37]. Such an association may be attributed to physiological differences between the sexes. There is evidence of polymorphism of the estrogen receptor gene in adipose cells in women, suggesting a genetic predisposition to the development

Table 2. Associations between lipodystrophy syndrome and clinical and anthropometric variables in HIV+ patients at an outpatient clinic of a university hospital in the city of Recife, Brazil, 2017.

Variables	HIV-associated lipodystrophy syndrome								
	Yes		No		Total		†PR	$CI_{95\%}$	p
Time diagnosis (months)	N	%	N	%	N	%			
> 60	17	37	29	63	46	44.2	1.79	0.95-3.35	0.106
60	12	20.7	46	79.3	58	55.8	1.00		
Use of ART (months)									
> 60	16	38.1	26	61.9	42	40.4	1.82	0.98-3.37	0.091
60	13	21	49	79.0	62	59.6	1.00		
Type of ART									
2 NARTIs + 1 NNRTI	17	30.4	39	69.6	56	59.6	1.15	0.59-2.24	0.847
2 NARTIs + 1 PI	10	26.3	28	73.7	38	40.4	1.00		
Viral load (copies/ml)									
> 40	04	28.6	10	71.4	14	16.3	0.98	0.40-2.42	0.782
40	21	29.2	51	70.8	72	83.7	1.00		
CD4+ count (cells/mm³)									
350	02	9.1	20	90.9	22	25.3	0.26	0.07-1.00	0.037
>350	23	35.4	42	64.6	65	74.7	1.00		
Hypercholesterolemia (mg/dL)									
Yes	12	46.2	14	53.8	26	31.7	1.99	1.06-3.74	0.065
No	13	23.2	43	76.8	56	68.3	1.00		
Hypertriglyceridemia (mg/dL)									
Yes	09	25.0	27	75.0	36	42.9	0.80	0.40-1.62	0.701
No	15	31.3	33	68.8	48	57.1	1.00		
Low HDL (mg/dL)									
Yes	18	27.7	47	72.3	65	83.3	0.72	0.33-1.59	0.320
No	05	38.5	08	61.5	13	16.6	1.00		
High LDL (mg/dL)									
Yes	14	33.3	28	66.7	42	53.2	1.50	0.71-3.16	0.404
No	08	22.2	28	77.8	36	46.8	1.00		
Excess weight (≥ 25 kg/m²)									
Yes	22	43.1	29	56.9	51	49.5	3.20	1.50-6.84	0.002
No	07	13.5	45	86.5	52	50.5	1.00		
Altered fasting glucose (mg/dL)									
Yes	18	28.1	46	71.9	64	77.1	0.76	0.38-1.55	0.658
No	7	36.8	12	63.2	19	22.9	1.00		

†PR – crude prevalence ratio, IC – confidence interval, ART – antiretroviral therapy, NARTI – nucleoside analog reverse-transcriptase inhibitor, NNRTI – non-nucleoside reverse-transcriptase inhibitor, PI – protease inhibitor, HDL – high-density lipoprotein, LDL: low-density lipoprotein, achi-square test with Yates correction.

of lipoatrophy and/or the accumulation of body fat[21,38,39]. Thus, it is important to pay attention to this group, because women, especially those in underdeveloped countries, are less likely to receive healthcare, education and support during treatment, which exerts a further impact on the metabolic consequences[40,41].

The level of physical activity was not associated with lipodystrophy in the present study. However, the literature reports a high incidence of sedentarism among individuals with HIV-associated lipodystrophy[30,34,42], indicating that the practice of physical activity may be a protection factor regarding the occurrence of this syndrome[43]. The practice of physical activity combined with an adequate diet is known to reduce the progression of lipodystrophy and lower its impact on both health and quality of life. In previous studies, in-

Table 3. Poisson regression with crude and adjusted prevalence ratios of factors associated with lipodystrophy syndrome in HIV+ patients at an outpatient clinic of a university hospital in the city of Recife, Brazil, 2017.

Variables	HIV-associated lipodystrophy syndrome					
	Crude PR†	$CI_{95\%}$	p	Adjusted PR†	$CI_{95\%}$	p
Female sex	2.31	1.27-9.23	0.013	2.16	1.43-3.39	0.022
Age ≥ 45 years	1.71	0.93-3.16	0.133	1.14	0.88-3.04	0.413
Time diagnosis > 60 months	1.79	0.95-3.35	0.106	1.84	0.56-3.22	0.214
Duration ART > 60 months	1.82	0.98-3.37	0.091	1.64	1.16-2.78	0.042
CD4+ count ≤ 350	0.26	0.07-1.00	0.037	0.39	0.10-0.97	0.034
Excess weight	3.20	1.50-6.84	0.002	2.23	1.35-2.65	0.000
Hypercholesterolemia	1.99	1.06-3.74	0.065	1.43	0.53-3.24	0.112

†PR – prevalence ratio, IC – confidence interval, ART – antiretroviral therapy.

dividuals living with HIV and lipodystrophy presented improvements in cardiorespiratory and metabolic aspects as well as quality of life after a six-month exercise program compared to those who did not exercise[44,45].

Regarding clinical variables of HIV infection, patients with a CD4+ count ≤ 350 cells/mm³ had a lower chance of developing lipodystrophy in both the crude and adjusted analyses, which is in agreement with data described in the literature. Lichtenstein et al.[46] studied a cohort of 1077 patients with a mean age of 41 years (85% men) and Segatto et al.[42] evaluated 42 patients (55% men) and found an association between the higher levels of TCD4+ cells and lipodystrophy among individuals in treatment with ART. Therefore, this therapy tends to improve one's immune status, with a consequently slower progression of the disease and lower incidence of death, but is associated with the emergence of HIV-associated lipodystrophy[34,42,47-49].

In contrast, Silva[50] evaluated 219 patients who were not in regular use of antiretrovirals and found an association between a lower CD4+ count and higher BMI as well as higher percentage of body fat. These findings may be the result of the harmful effects of HIV infection itself, probably as a consequence of the activation of macrophages in adipose cells, which could increase both local and systemic inflammation[30,51].

A long time in ART was also associated with the development of lipodystrophy. In a cohort of 219 patients, Soares and Costa[52] also found that men and women with lipodystrophy had been using ART for a longer time (four to seven years). As these medications are made available in Brazil and contribute to improving immune status, we should bear in mind that individuals in treatment with ART can experience an increase in survival as well as the side effects of this therapy (redistribution of body fat and metabolic abnormalities), exposure to the physiological factors inherent to the aging process and external factors, such as a sedentary lifestyle and high calorie intake, which increase cardiovascular risk[2,17,34,53-55].

No association was found between the type of ART and lipodystrophy in the present study. In contrast, the literature reports that lipodystrophy is among the most prevalent and worrisome side effects of some types of ART[56]. The development of the syndrome was initially attributed to the use of the protease inhibitors[46,57]. However, with the introduction of other classes of antiretrovirals, NARTIs, particularly stavudine and zidovudine, were also found to be associated with the syndrome[17,58-60].

Excess weight has been found in 35 to 45% of the population with HIV-associated lipodystrophy[22,61,62], which is in agreement with the prevalence in the present study (43%; $p < 0.002$). In a study conducted in the city of Recife (northeastern Brazil) with a sample of 958 patients (61% men), Arruda Junior et al.[63] found that HIV-associated lipodystrophy was associated with overweight/obesity (52.7%) and these individuals had been in ART for a longer period (> 24 months). Moreover, overweight/obesity remained associated even after controlling for confounding factors. Mariz et al.[64] state that the increase in the prevalence of obesity in individuals living with HIV is associated with a significant reduction in the occurrence of opportunistic diseases and the chronicity of HIV as a consequence of the use of ART, which works directly against important steps in the replication of the virus[65]. Other studies have also demonstrated excess weight in

this population as a worrisome finding, since the use of ART combined with excess weight and the accumulation of fat predisposes these patients to the development of metabolic syndrome and cardiovascular disease[66].

We found no association between HIV-associated lipodystrophy and dyslipidemia or altered fasting glucose. However, previous studies have reported these associations[67-69]. In a cross-sectional study conducted in Thailand with 278 patients infected by HIV, 93% of those with lipodystrophy had at least one metabolic abnormality (dyslipidemia, glucose intolerance or insulin resistance)[70]. However, other studies with large databanks found no such association when the results were adjusted for traditional risk factors[67,68,71,72].

The present study has limitations that should be considered, such as the small sample size, the lack of a diagnostic consensus, the absence of data on adherence to ART and the fact that data collection was performed at a single reference center with unique characteristics inherent to the local reality, thereby limiting the external validity of the findings. However, the present results contribute knowledge on the health status of patients at this service, enabling better care and follow-up for the population. These findings can also be used in clinical practice for the comparison and assessment of individuals living with HIV.

The frequency of lipodystrophy syndrome in the present study was similar to rates described in the literature, demonstrating that anomalous body distribution may be identified in individuals living with HIV in treatment with ART. Moreover, an association was found between lipodystrophy syndrome and modifiable risk factors, such as overweight/obesity, revealing that this group is a greater risk of the development of other comorbidities, such as DM and hypertension.

This study proved that it is possible to diagnose HIV-associated lipodystrophy and identify the main associated factors with using simple methods that are applicable to clinical practice. Thus, it is possible to outline prevention and early intervention measures based on the situation of each individual or population. Such measures can contribute to improvements in the health status of these individuals, with a consequent increase in life expectancy and quality of life.

Collaborations

LLG Silva, development of the study and writing of the manuscript; Santos EM, data collection; LCP Nascimento, tabulation of data; M Cavalcanti, correction of the introduction and development of the manuscript; MCL Luz, co-adviser and final corrections; PC Cabral, guidance and statistics.

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