Lipodystrophy and metabolic parameters of people living with HIV

Lipodistrofia e parâmetros metabólicos de pessoas vivendo com HIV

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ABSTRACT

Introduction: Since the earliest reported cases in the United States, Acquired Immunodeficiency Syndrome (AIDS) remains one of the major challenges to global health. **Objective:** To evaluate the metabolic parameters and clinical manifestations of lipodystrophy in patients with lipodystrophy syndrome associated with the use of antiretroviral therapy. **Methods:** A cross-analytical study carried out from December 2015 to June 2016, in a public reference hospital for the care of HIV patients, in the city of Belém, state of Pará, Brazil. The sample consisted of HIV positive serology patients in treatment with antiretrovirals and lipodystrophy. Interviews were conducted and a research protocol plus laboratory analysis applied. **Results:** A total of 54 patients was included, 68.5% male and 31.5% female, aged 26–72 years, average of 53.07 years (standard deviation — SD±10.41). Among the clinical forms of lipodystrophy, the mixed one was the most prevalent (72.2%). As for dyslipidemia, 30.8% of the patients presented isolated hypertriglyceridemia, 26.9% mixed dyslipidemia, 19.2% low high-density lipoprotein (HDL-c) and 17.3% without dyslipidemia. Regarding the glycemic profile, 28.3% of the patients were diabetic, 28.3% had altered fasting glycaemia and 5.6% had altered fasting glycaemia and glucose intolerance. **Conclusion:** The clinical form of mixed lipodystrophy was the most prevalent. In this study, there was no association between the lipid profile and the clinical forms of lipodystrophy. However, follow-up of these patients is necessary to avoid possible complications and risks of cardiovascular events.

Keywords: HIV; lipodystrophy; antiretroviral therapy, highly active.

RESUMO

Introdução: Desde os primeiros casos relatados nos Estados Unidos, a *Acquired Immunodeficiency Syndrome* (AIDS) ainda continua sendo um dos grandes desafios para a saúde global. **Objetivo:** Avaliar os parâmetros metabólicos e as manifestações clínicas da lipodistrofia em pacientes com síndrome lipodistrófica do HIV, associada ao uso de terapia antirretroviral. **Métodos:** Estudo transversal analítico realizado de dezembro de 2015 a junho de 2016 em hospital público de referência no atendimento de pacientes HIV, em Belém, Pará, Brasil. A amostra foi composta de pacientes com sorologia positiva para o HIV em tratamento com antirretrovirais e lipodistrofia. Foram realizadas entrevistas e foi aplicado um protocolo de pesquisa mais análise laboratorial. **Resultados:** Foram incluídos 54 pacientes, 68,5% masculinos e 31,5% femininos, com idade entre 26 e 72 anos e média de 53,07 anos (desvio padrão — DP±10,41). Entre as formas clínicas da lipodistrofia, a mista foi a de maior prevalência (72,2%). Quanto à dislipidemia, verificou-se que 30,8% dos pacientes apresentaram hipertrigliceridemia isolada, 26,9% dislipidemia mista, 19,2% lipoproteína de alta densidade (HDL-c) baixo e 17,3% sem dislipidemia. Quanto ao perfil glicêmico, 28,3% dos pacientes são diabéticos, 28,3% apresentaram glicemia de jejum alterada e 5,6% glicemia de jejum alterada e intolerância à glicose. **Conclusão:** A forma clínica da lipodistrofia mista foi a mais prevalente. Nesta pesquisa, não houve associação entre o perfil lipídico e as formas clínicas de lipodistrofia, contudo faz-se necessário o seguimento desses pacientes, para evitar possíveis complicações e riscos de eventos cardiovasculares.

Palavras-chave: HIV; lipodistrofia; terapia antirretroviral.

INTRODUCTION

After more than 30 years since the first reported cases in the United States, the Acquired Immunodeficiency Syndrome (AIDS) is still one of the major challenges for the global health[1]. According to data from the World Health Organization, there are about 36.7 million people living with HIV in the world, 3.3 million of them in the Americas. Despite it reflects the increase of new HIV infections, there is also a significant expansion of access to antiretroviral treatment, which has helped to reduce AIDS-related deaths, especially in recent years[2].

Brazil has registered an average of 40 thousand new cases of AIDS in the past five years. The proportional distribution of the identified cases shows concentration in the Southeast and South, corresponding to 52.3 and 20.1% of the total cases, respectively — the Northeast, North and Midwest correspond to 15.4, 6.1 and 6.0% of the total cases, respectively[2]. The social organization of the space and the economic and cultural inequalities in the structure of the Brazilian society are the main factors that have determined and conditioned the receptiveness and vulnerability to the maintenance and dissemination of the epidemic of various transmitted diseases in the country[3].

Many of these diseases have hit large geographic isolation areas, as in the Amazon region[3], since in the past five years (2012 to 2016) the Northern region reported the average of 4,200 cases per year, noted that from 2007 to 2017 there were 14,275 new cases notifications[2].

This scenario demonstrates that the inequalities of the Brazilian society favors spreading the human immunodeficiency virus infection in the country, revealing an epidemic of multiple dimensions that over time showed significant transformations in the virus epidemiological profile[4]. With the arrival of antiretroviral therapy (HAART), also known as strongly active antiretroviral therapy in the 90s, there was deep impact on the natural history of HIV infection, as it significantly reduced morbidity and mortality by opportunistic infections and neoplastic diseases, but started a set of modifications known as HIV Lipodystrophy Syndrome (HIVLS)[5-7]. This clinical event consists of complex metabolic endocrine changes that can be associated

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with a significant increase in cardiovascular risk[8]. The antiretroviral drugs used in the treatment of HIV infection now totalize 21, and can be currently divided into five classes for clinical use: nucleoside analogue reverse transcriptase inhibitor (NARTI), non-nucleoside analogue reverse transcriptase inhibitor (NNRTI), protease inhibitors (PI), fusion inhibitors (FISH) and integrase inhibitors (II)[9].

Studies have been showing that the drugs used in HAART tend to raise levels of lipids, redistribute body fat and show insulin resistance. The use of HAART is considered the main cause for dyslipidemia, because with its introduction there is a change in the dyslipidemia profile with the aggravation of hypertriglyceridemia and an increase of total cholesterol and fractions, except high-density lipoprotein (HDL-c) and the state of insulin resistance[10].

The HIVLS is a side effect of the use of HAART, characterized by the redistribution of body fat. The clinic lipodystrophy was defined as a peripheral lipodystrophy, with or without central fat accumulation, evaluated by patients and doctors, showing three distinct forms, according to the distribution pattern of the body fat: lipoatrophy, lipohypertrophy and mixed form (simultaneous development of lipoatrophy and lipohypertrophy)[11-13].

OBJECTIVE

To evaluate the metabolic parameters according to the clinical forms of lipodystrophy in patients with HIV lipodystrophy syndrome associated with the use of HAART in outpatients of a reference public hospital in the state of Pará, Brazil.

METHODS

The study population consists of patients living with lipodystrophy syndrome associated with HIV, from the city of Belém and countryside of the state of Pará, assisted at Hospital Universitário João de Barros Barreto (HUJBB), in Belém, Pará, Brazil. The study occurred in the period from December 2015 to June 2016, and was approved by the Ethics Committee of the Center for Tropical Medicine (NMT) at the Universidade Federal do Pará, under Protocol no. 1,438,726.

Participants were included in the study after elucidation of the procedures and goals of the research and the proper signature of a free term of consent. This population consists of people of both sexes, over 18 years old, in treatment with HAART, for more than one year in a row, not inmates, non-pregnant women and functionally independent for their daily life activities, excluding those without positive serology for HIV/AIDS and those who were not within the research criteria. A cross-sectional analytical study was performed in a specific time period.

The research's participants were divided into three groups:

- patients with lipoatrophy: fat loss in the face, legs and limbs (associated or not with prominence of subcutaneous veins);
- patients with lipohypertrophy: accumulation of fat in neck, known as *hump* or *buffalo hump*, breast or abdomen;
- patients with mixed syndrome: association between fat loss and fat accumulation.

The lipoatrophy was identified by the spontaneous report of patient before the presence of relevant morphological changes to the face (loss of Bichat and/or preauricular fat cushion), arms, legs, and abdominal subcutaneous tissue. The lipohypertrophy was defined as the progressive increase in waist circumference, breasts size or back or cervical fatty cushions, or supraclavicular fat accumulation. Later on, a questionnaire containing demographic data, medical history, personal habits, family history and anthropometric measurements was applied.

All patients were examined by the physician in charge, as well as the standardized measures of weight (kg), height (m), and blood pressure (mmHg), measured and weighed without shoes and wearing light clothes. Laboratory fasting procedures for analysis of serum levels of total cholesterol (mg/dL), HDL-c (mg/dL), low-density lipoprotein (LDL-c) (mg/dL), triglycerides (mg/dL), glucose (mg/dL) and insulin (μ IU/mL) were performed in the HUJBB laboratory, since they are already part of the routine of patients' follow-up in the lipodystrophy ambulatory.

The cut-off points for normality of the biochemical tests were established according to the Brazilian Society of Cardiology: total cholesterol <200 mg/dL, triglycerides <150 mg/dL, HDL-c >60 mg/dL and LDL-c <160 md/dL[14]. The values regarding glycemic indexes have been established by the Brazilian Society of Diabetes: blood glucose normal <100 mg/dL, fasting blood glucose altered >100 and <127 mg/dL, oral glucose intolerance ≥140 and <200 mg/dL after overload[15].

The statistical analysis of the results was performed by the BioStat 5.0 and Epi Info 3.5.2 software, through the G-nonparametric test, qualitative variable. The quantitative variables were analyzed by parametric tests (ANOVA) or nonparametric (Kruskal-Wallis), according to the distribution of the variables with normal or nonparametric distribution. Values $p<0.05$ were considered significant.

RESULTS

We included 54 patients, 68.5% male. In relation to the distribution by age, we included patients between 26 and 72 years old, the average of 53.07 years old (standard deviation — SD±10.41). Regarding the distribution of body fat associated with the lipodystrophy syndrome, the clinical form of mixed lipodystrophy was the most prevalent in ambulatory, reaching 72.2%, the lipoatrophy, 24.1%, and the lipohypertrophy, 3.7%.

When we related lipodystrophy to sex (**Table 1**), the most frequent clinic form was the mixed one in both genders (67.6%

Table 1 – Lipodystrophy classification according to sex of patients undergoing antiretroviral therapy*, Belém (PA), Brazil, 2016.

	Male		Female	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Lipoatrophic	11	29.7	2	11.8
Lipohypertrophic	1	2.7	1	5.9
Mixed	25	67.6	14	82.3
Total	37	100.0	17	100.0

*Test G (p=0.3580).

males, and 82.4% female). In this study, there was no association of sex (p=0.3580) with the lipodystrophy form. The standard therapeutic scheme in studied cases shows that 22.2% made use of nucleoside reverse transcriptase inhibitor (NRTI)+PI; 18.5% NRTI+NRTI+PI; and 18.5% NRTI+NNRTI, in which the NRTI (96.3%) and PI (64.8%) were the most used antiretroviral drugs in the therapeutic scheme of patients of this study (**Table 2**). The time of HAART use was of at least two years and the highest 21 years, with the average of 12.9 years (SD±4.6). As for the distribution of patients, it occurred according to the dyslipidemia classification (**Figure 1**).

There was higher prevalence of hypertriglyceridemia (30.8%), followed by mixed dyslipidemia (26.9%), low HDL-c (19.2%), without dyslipidemia (17.3%) and 5.8% isolated hypercholesterolaemia, being the latter the less frequent class.

By analyzing the lipid profile (**Table 3**), total cholesterol (TC) showed value from 115 to 629, HDL-c (mg/dL) from 21 to 156, LDL-c (mg/dL) from 41 to 241 and triglycerides (mg/dL) 64 and 3,555, minimum and maximum values, respectively. There was no association in the relationship of the lipid profile with the clinical forms of lipodystrophy (**Table 4**).

As for the glucose tolerance profile, 28.3% of the patients are diabetics, 28.3% presented fasting glucose altered, 5.6% presented fasting glucose altered and glucose intolerance, and 37.7% showed no change in glycemic profile (normoglycemia). As regards the use of lipid-lowering, 57.4% made use of lipid-lowering (fibrate and/or statin).

DISCUSSION

In this study, all participants were patients with lipodystrophy syndrome and made use of HAART, most male (68.5%). Similar studies in patients with lipodystrophy also identified high prevalence in males (67.0 and 60.8%, respectively)[8,16]. The average age of patients was of 53.07 years old ±10.41; in other studies, results similar to 44.11 years old ±9.84 and 44.2 years old ±9.4[17,18]. The prevalence of lipodystrophy evaluated in several studies ranged from 32.4 to 65% in HIV-infected patients in ambulatory follow-up and positively related to the use of antiretrovirals[16,19].

Table 2 – Therapeutic scheme pattern in the studied cases, Belém (PA), Brazil, 2016.

Class of antiretroviral	Frequency	Percentage (%)
INNTR + PI	2	3.7
INTR + INNTR	10	18.5
INTR + INNTR + PI	3	5.5
INTR + INTR + INNTR	9	16.7
INTR + INTR + INNTR + PI	1	1.9
INTR + INTR + PI	10	18.5
INTR + INTR + PI + II	1	1.9
INTR + INTR + PI + PI	2	3.7
INTR + INTR + PI + PI + II	2	3.7
INTR + PI	12	22.2
INTR + PI + PI	2	3.7
Total	54	100.0

INNTR: non-nucleoside reverse transcriptase inhibitors; PI: protease inhibitors; INTR: nucleoside reverse transcriptase inhibitors; II: integrase inhibitors.

Differences in the prevalence rates can be attributed to age, gender, type or time of anti-retroviral therapy. Lipodystrophy syndrome is defined by the redistribution of body fat according to the patient's own report and confirmed in clinical examination.

Among the clinical forms, the mixed lipodystrophy was the most prevalent in this study, 72.2%. Similar data, 52.0 and 49.9%, respectively, were found with mixed lipodystrophy[17,18]. When morphological changes are correlated to sex, both male and female, the mixed lipodystrophy was the most prevalent (67.6 and 82.4%, respectively). In the present study, there was no association of sex (p=0.3580) with the form of lipodystrophy (**Table 1**). In another study conducted in the Southeast region of Brazil, in the Centre of Testing and Monitoring

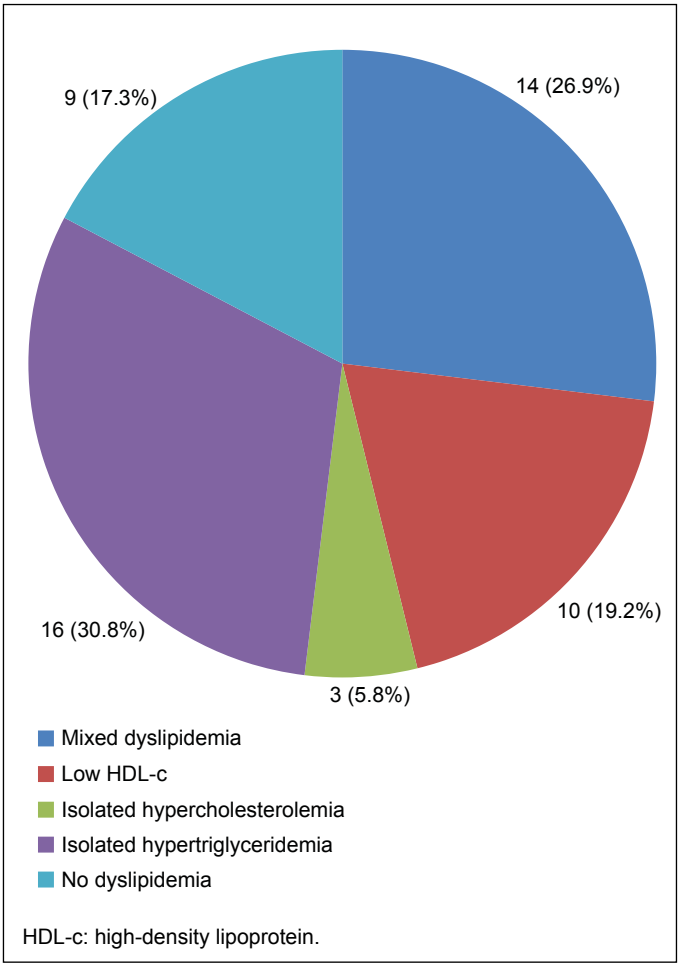

Figure 1 – Classification of dyslipidemia in lipodystrophy syndrome patients secondary to antiretroviral therapy, Belém (PA), Brazil, 2016.

Table 3 – Lipid profile of lipodystrophy syndrome patients secondary to antiretroviral therapy, Belém (PA), Brazil, 2016.

Lipid profile	Average and standard deviation	Minimum and maximum
Total Cholesterol (mg/dL)	213.78±73.27	115 and 629
HDL-c (mg/dL)	49.58±19.56	21 and 156
LDL-c (mg/dL)	115.17±37.35	41 and 214
Triglycerides (mg/dL)	283.88±477.52	64 and 3,555

HDL-c: high-density lipoprotein; LDL-c: low-density lipoprotein.

of Presidente Prudente, in São Paulo state, no significant statistical differences in the occurrence of lipodystrophy among categories of sex (p=0.140) and age group (p=0.964) were observed[20].

According to recommendation by the national coordination of Sexually Transmitted Diseases (STD)/AIDS, the initial recommended therapy consists of two NRTI associated to one NNRTI or PI. Initial schema changes may be necessary due to therapeutic failure, toxicity or intolerance to treatment. In relation to the use of drugs, 96.3% of participants of this study made use of NRTI and 64.8% of PI.

A similar result was found in Guimarães et al.[21], in which 98.5% of the patients made use of NRTI and 46.3% of PI, and in Diehl et al. [19], in which 99.9% were users of NRTI and 65.5% of PI. The time of HAART was of at least two years, and a maximum of 21 years, with average of 12.9 years (SD±4.6).

A similar study in the Northern region of Brazil, in the Centre of Attention on Acquired Infectious Diseases (Centro de Atenção à Saúde em Doenças Infecciosas Adquiridas — CASADIA) and in the Reference Unit Specialized in Special Infectious and Parasitic Diseases (Unidade de Referência Especializada em Doenças Infecciosas Parasitárias Especiais — UREDIPE), in Belém, Pará State, reported that all patients used HAART during the average time of 8.49 years (SD±4.31), using therapeutic schemes with two or more classes of antiretroviral drugs, and 69.6% was on treatment for more than seven years[18].

Another study in Southeastern Brazil, in the city of Ribeirão Preto, São Paulo state, observed that time of treatment with antiretrovirals was from 2 to 13 years, the average time of 7.5 years (SD±2.70)[9]. The group with increased use of HAART showed the highest proportion of individuals with lipodystrophy, a result that strengthens the relation of time of medicine use with the emergence of the syndrome[20].

In the association of antiretroviral use and dyslipidemia, a study in São Paulo with 319 HIV-patients divided into groups of those who made use of HAART and those who did not, showed that concentrations of total cholesterol, triglycerides and glucose were statistically higher among patients who used HAART[22].

These studies allow us to infer that the greater the use of HAART, the greater the repercussions related to lipodystrophy, dyslipidemia and fasting glucose.

The present investigation observed that most patients on antiretroviral therapy (82.6%) showed a change in the lipid profile (total cholesterol levels, LDL-c, triglycerides and low HDL-c), agreeing with studies in which the dyslipidemia associated with HIV infection is characterized by a significant increase of plasma levels of triglycerides, total cholesterol and reduced HDL-c in patients using HAART[15,17,23].

With the coming of HAART, especially with the use of PI, lipid profile change occurs with elevated triglycerides values, total cholesterol, lipoproteins of very low and low density (VLDL-c and LDL-c), leading to a decreased HDL-c, leaving these patients at risk of developing diabetes, hypertension and cardiovascular risk[20,24,25].

Studies estimate that the prevalence of dyslipidemia in HIV patients during HAART can range from 67.5 to 77.5% and can be influenced by several factors, including the type of study, the sample type and time of HAART[9,26,27]. It was observed prevalence of hypercholesterolemia from 31 to 47% and hypercholesterolemia from 47 to 71%[25].

A study with 268 HIV patients in a university hospital in Rio de Janeiro concluded that in male patients the prevalence of dyslipidemia is greater when compared to the female, and that family history of hyperlipidemia is directly related to both the occurrence of dyslipidemia and the time of use of HAART by patients[9].

The present research (**Table 3**) showed that the overall average of total cholesterol, LDL-c and triglycerides are high and HDL-c low, showing a lipid profile change. Studies show that metabolic abnormalities are characterized by a highly atherogenic lipid profile, with increase of total cholesterol and LDL-c, triglycerides and reduced HDL-c[28].

Evidences accumulate in the direction of pointing out that the HIV/AIDS infection itself plays the main role in the lower HDL-c rates[26,29,30]. When assessing the glucose tolerance profile, 62.7% of the patients have altered glycemic profile, in which 28.3% of them are diabetics and 33.9% have altered fasting glycaemia and glucose intolerance. Studies carried out in different regions of Brazil, as the Hospital de Clínicas da Universidade Estadual de Londrina, in 2008, where 8% are diabetics, found out that 15% showed fasting glucose >100 mg/dL and 23% had modified glucose. In the university hospitals of the states of Pernambuco and Santa Catarina, in which 5.7 and 8% are diabetics, respectively, the researchers revealed lower prevalence when compared to the present research[19,23,25].

Dyslipidemia in HIV carrier making use of HAART therapy is characterized by a high level of VLDL (the biggest transporter of triglycerides), LDL-c and reduced HDL-c level[3].

The authors even suggest that factors that would lead HIV patient to dyslipidemia are not yet elucidated. It is not exactly known if it occurs directly by the use of HAART or if it is the product of several factors, such as antiretroviral treatment, genetic predisposition, diet and exercise, or other factors, as the host's response to HIV infection[8,17,20].

The present study did not find association between lipid profile and clinical forms of lipodystrophy (**Table 4**), in spite of these

Table 4 – Lipid profile as to the Lipodystrophy Classification in Lipodystrophy Syndrome patients secondary to antiretroviral therapy. Belém-PA, 2016

Lipid profile	Lipodystrophy classification			p
	Lipoatrophic	Lipohypertrophic	Mixed	
Total Cholesterol (mg/dL)	183.78±55.67	221±38.18	215.73±80.80	0.4603*
HDL-c (mg/dL)	46.54±10.04	58±8.48	50.21±22.20	0.4744**
LDL-c (mg/dL)	127.12±42.28	132.5±55.86	110.83±35.15	0.3651*
Triglycerides (mg/dL)	230.27±177.88	152±48.08	311.07±550.44	0.4314**

*ANOVA; **Kruskal-Wallis; HDL-c: high-density lipoprotein; LDL-c: low-density lipoprotein.

parameters are changed at the time of the interview (p>0.005). According to the studies, the HIV infection itself and HAART promote these changes in the metabolic profile of these patients, leading to dyslipidemia in HIV carrier who makes use of HAART[5,21]. When checked the use of lipid-lowering, 57.4% make use of fibrate and/or statin. Diehl et al. observed that 13% made use of lipid-lowering and 70% of patients presented lipodystrophy[19]. The treatment of dyslipidemia in HIV-infected patients deserves special attention in the safety of the drug interaction between antiretrovirals and lipid-lowering drugs.

CONCLUSION

The clinical form of mixed lipodystrophy was the most prevalent in both sexes. In this research, there was no association between lipid profile and clinical forms of lipodystrophy. However, it is necessary to observe these patients to avoid possible complications and risk of cardiovascular events.

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Conflict of interests

The authors declare no conflict of interests.

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