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ORIGINAL ARTICLE / *ARTIGO ORIGINAL*

Body fat redistribution and changes in lipid and glucose metabolism in people living with HIV/AIDS

Redistribuição de gordura corporal e alterações no metabolismo de lipídeos e glicose em pessoas vivendo com HIV/AIDS

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ABSTRACT: ***Introduction:*** The HIV lipodystrophy syndrome is characterized by changes in metabolism, and body composition that increase cardiovascular risk of people living with HIV/AIDS (PLWHA) using highly active antiretroviral therapy (HAART). ***Objective:*** To assess the prevalence of lipodystrophy and changes in lipid and glucose metabolism in PLWHA in use of HAART. ***Methods:*** For the anthropometric evaluation we measured weight, height and abdominal circumference (AC). For the lipodystrophy evaluation we conducted physical examination (subjective) and the (objective) examination of absorptiometry with X-ray dual energy (DEXA) by fat mass ratio (FMR). We also conducted lipid profile tests and fasting glucose and used the criteria suggested by The National Cholesterol Education Program III for metabolic disorders classification. ***Results:*** The final sample consisted of 262 patients with a mean age of 44.3 ± 10.2 years. Lipodystrophy, according to the physical examination, was present in 47.7% (95%CI 41.7 – 53.8) of patients, while the prevalence using FMR (DEXA) was 40.8% (95%CI 33.1 – 48.5). Most (53.0%; 95%CI 47.0 – 59.1) of the patients showed increased abdominal adiposity according to AC. The most prevalent metabolic alterations were reduced HDL (67.6%; 95%CI 61.9 – 73.2) and hypertriglyceridemia (55.7%; 95%CI 49.7 – 61.7). ***Conclusion:*** The high prevalence of lipodystrophy and changes in lipid and glucose metabolism show the importance of early intervention in this group of patients to prevent cardiovascular complications.

Keywords: Prevalence. Lipodystrophy. Metabolic diseases. Body fat. HIV. Dyslipidemia.

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RESUMO: ***Introdução:*** A síndrome da lipodistrofia do HIV é caracterizada por alterações no metabolismo e na composição corporal, que aumentam o risco cardiovascular de pessoas vivendo com HIV/AIDS (PVHA) em uso da terapia antirretroviral de alta potência (TARV). ***Objetivo*:** Avaliar a prevalência de lipodistrofia e de alterações do metabolismo de lipídios e glicose em PVHA em uso da TARV. ***Métodos:*** Para avaliação antropométrica foram aferidos peso, estatura e circunferência abdominal (CA). Para avaliação da lipodistrofia foi realizado o exame físico (subjetivo) e o exame (objetivo) de absortometria com raios X de dupla energia (DEXA) por meio da razão de massa gorda (RMG). Foram também realizados exames de lipidograma e glicemia de jejum e utilizados os critérios sugeridos pelo *The National Cholesterol Education Program* III para classificação de alterações metabólicas. ***Resultados:*** A amostra final consistiu em 262 pacientes com idade média de 44,3 ± 10,2 anos. A lipodistrofia, de acordo com o exame físico, esteve presente em 47,7% (IC95% 41,7 – 53,8) dos pacientes, enquanto pela RMG (DEXA) sua prevalência foi de 40,8% (IC95% 33,1 – 48,5). A maioria (53,0%; IC95% 47,0 – 59,1) dos pacientes apresentou aumento de adiposidade abdominal segundo a CA. As alterações metabólicas mais presentes foram o HDL reduzido (67,6%; IC95% 61,9 – 73,2) e a hipertrigliceridemia (55,7%; IC95% 49,7 – 61,7). ***Conclusões:*** A alta prevalência de lipodistrofia e alterações do metabolismo de lipídios e glicose evidenciam a importância da intervenção precoce nesse grupo de pacientes para prevenir complicações cardiovasculares.

Palavras-chave: Prevalência. Lipodistrofia. Doenças metabólicas. Tecido adiposo. HIV. Dislipidemias.

INTRODUCTION

The number of people living with HIV/AIDS (PLWHA) increases each year, all over the world. Worldwide estimates indicate that by the end of 2014, approximately 36.9 million people lived with HIV[1].

In Brazil, since the identification of the first case, in 1980, until June 2015, 798,366 PLWHA were registered, and over 290 thousand deaths were identified with AIDS as the primary cause[2].

In the 1990s, with the advent of combined highly active antiretroviral therapy (HAART), it was possible to reduce the mortality and morbidity of AIDS and allows for a better quality of life for those with HIV[3]. Despite their benefits and efficacy, the interaction between HAART with the infection itself and inflammation caused by HIV is associated with severe adverse effects, such as metabolic alterations and abnormal redistribution of body fat. These changes are called HIV lipodystrophy syndrome (HIVLS)[4].

The abnormal redistribution of body fat (lipodystrophy) in PLWHA using HAART is characterized by loss of subcutaneous fat, mainly on the face, gluteal region and limbs (lipoatrophy), as well as by accumulation of fat on the back of the cervix, breasts and visceral region (lipohypertrophy). Lipodystrophy is the focal point of HIVLS and may occur alone or associated with insulin resistance, type II diabetes, dyslipidemia, hypertension, endothelial dysfunction and altered production of cytokines and adipokines[5]. These alterations are similar to the ones occurred in the metabolic syndrome and characterize an atherogenic metabolic profile, increasing the risk for cardiovascular diseases in these patients[6].

The diagnosis of lipodystrophy may be done through method such as clinal exams, self-report, electrical bio impedance (BIA) or techniques that provide quantitative data about adipose tissue such as dual energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI) and computed tomography (CT)[7]. The imaging methods have high operational cost, limited availability and, in the case of DEXA and CT, involve ionizing exposure, making it rather difficult to be used in clinical practice. Thus, the evaluation by subjective method, which includes the patient's reports on the alterations in the distribution of body fat, associated to the confirmation of those alterations by the inspection of the evaluator has been the currently most used one[8].

DEXA is a reference technique in the evaluation of body composition[9]. In a French study from 2005, Bonnet et al. proposed, for the first time, an objective index obtained by DEXA to identify lipodystrophy, the fat mass ratio (FMR), which seems to allow for ta accurate and early diagnosis[10]. FMR is defined as a percentage of torso fat divided by the percentage of fat in the lower limbs. More recently, Beraldo et al. proposed a cutoff point of 1.26 to identify lipodystrophy in the Brazilian population[11].

There is still no consensus as for what is the best way to diagnose this disorder. Thus, due to the different methods and criteria used in these studies, the prevalence has been ranging between 1 and 84%[12]. A research carried out in Brazil, by Diehl et al., evaluated 180 HIV carriers older than 18 years of age through subjective method and found a prevalence of 55% of HIVLS. However, the authors observed, through clinical data, that 73% of those assessed had some kind of body fat, though only 76% of these individuals reported such alteration[13].

Due to the fact that alterations in body fat distribution and lipid and glucose metabolism significantly increase morbidity and mortality of PLWHA in HAART, it is essential to early identify the risk for cardiovascular diseases development. Thus, the objective of the present study was to evaluate the prevalence of lipodystrophy and lipid and glucose metabolism alterations in PLWHA using HAART.

METHODS

It is a cross-sectional study carried out in the University Hospital of the School of Medicine of Ribeirão Preto (*Hospital Universitário da Faculdade de Medicina de Ribeirão Preto* – HC/FMRP). The PLWHA were selected in outpatient units belonging to the Specialized Unit for Infectious Diseases Treatment (*Unidade Especializada para Tratamento de Doenças Infectocontagiosas* – UETDI). The UETDI is a specialized reference unit which assists people living with HIV/AIDS across the country, which, currently, serves approximately 1,800 people.

The study was approved by the Research Ethics Committee of the institution (HCRP protocol No. 17484/2013). The patients in outpatient units who met the selection criteria were invited to participate in the research Project and all volunteers who accepted it singed the Informed Consent.

Inclusion criteria were: HIV positive patients, being on HAART and having stable weight (oscillations below 10% during the previous year).

Exclusion criteria were: edema, thyroid diseases, chronic renal failure, lung disease, liver alterations, signs and symptoms of opportunistic infections and presence of a pacemaker or metal prosthesis.

Information were obtained about the use of lipid-lowering and hypoglycemic agents, currently used antiretrovirals and biochemical tests (viral load and CD4 T cells).

All anthropometric measures were performed in the meeting by trained personnel. Before starting the evaluation, patients should remove all metal accessories and wear light clothing. They were questioned about bladder emptying, practice of physical activity within the last 12 hours and consumption of alcohol within 24 hours prior to the evaluation.

CLINICAL TESTING FOR LIPODYSTROPHY CLASSIFICATION

For the classification of lipodystrophy, individuals should report peripheral lipoatrophy confirmed by clinical examination, accompanied or not by lipohypertrophy[9].

All assessments were carried out by the same investigators.

DEXA FOR LIPODYSTROPHY CLASSIFICATION

DEXA testing was carried out using a model of Hologic instrument (Discovery Wi, QDR® series, Waltham, MA, USA) operated by a trained technician, strictly following standard procedures.

The FMR was calculated as the percentage of fat in the torso divided by the one of lower limbs, obtained by DEXA. The cutoff point for lipodystrophy classification was 1.26[11].

ANTHROPOMETRY FOR THE ASSESSMENT OF BODY FAT DISTRIBUTION

The body weight, in kilograms, was measured with an electronic Filizola platform scale, with a maximum capacity of 300 kg and precision of 0.1 kg. The height was measured with a stadiometer with an accuracy of 0.1 cm.

The body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Circumference measures were taken using a metal measuring tape, Sanny with accuracy of 0.1 cm and maximum length of 2 m. The assessment of abdominal circumference (AC) was performed at the midpoint between the last rib and the iliac crest in a horizontal plane. The hip circumference (HC) was taken in the region of the largest circumference between abdomen and thigh[14]. The waist-hip ration (WHR) was calculated by the division

of AC (cm) by HC (cm). The reference values for metabolic alterations risk by the World Health Organization (WHO) were considered[15].

BIOCHEMICAL ANALYSIS

Serum lipid concentrations (total cholesterol = TC, triglycerides = TG and high-density lipoprotein = HDL) were measured by enzymatic colorimetric method using the COBAS INTEGRA 400 instrument (Roche Diagnostics, Indianapolis, IN, EUA). The low-density lipoprotein (LDL) was calculated the Friedewald's formula [LDL = TC - (TGs / 5 + HDL)]. Plasmatic glucose was determined in an automatic analyzer (2300 STAT, Yellow Springs Instruments Inc., Yellow Springs, OH, EUA).

Alterations were considered: TC ≥ 220 mg/dL, TG ≥ 150 mg/dL, HDL ≤ 40 mg/dL, LDL ≥ 130 mg/dL or in dyslipidemia treatment; fasting blood glucose ≥ 100 mg/dL or in treatment[16].

SAMPLE CALCULATION AND STATISTICAL ANALYSIS

A sample calculation was performed for the study. Considering a sample of 50% lipodystrophy, a population of 800 follow-up patients in the unit (within the age range of the study) and a tolerable absolute error of 5%. The sample size necessary for a real lipodystrophy prevalence estimate would be 260 individuals.

All continuous variables were presented in means and standard deviations and the categorical variables in frequencies and percentages accompanied by their confidence intervals of 95% (95%CI). The comparison between groups used the unpaired Student's *t*-test and χ^2 test, considering a normal distribution (Kolmogorov-Smirnov test). A significance level of 5% was considered. The analyses used the Bioestat 5.3 software.

RESULTS

In the period from January 2011 to December 2013, 262 PLWHA were assessed (56.8% males) with mean age of 44.3 ± 10.1 years. The mean values found for CD4+ T were under control, and the majority of patients was undetectable viral load (< 50 copies/mL). The female subgroup had a significantly longer time of HAART use than the male one (Table 1).

As for the HAART regimen, 54.5% of patients used the combination of two nucleoside reverse-transcriptase inhibitors (NRTI) in addition to a non-nucleoside reverse-transcriptase inhibitor (NNRTI); 37.7% used the combination of two NRTI in addition to a protease inhibitor (PI); 6.1% used a combination of NRTI in addition to a NNRTI and a PI; and 1.5% used the combination with integrase inhibitor (II).

Regarding anthropometric variables, 51.9% of individuals were overweight, according to their BMI, and 53% had AC alteration (Table 2). The female subgroup had higher BMI values and fat mass, however, WHR, FMR and lean mass values were significantly lower in relation to the male subgroup (Table 3). Higher prevalence of alterations in BMI, AC and WHR was found in the female subgroup.

Table 1. Clinical characteristics of people living with HIV/AIDS.

		All	Female	Male
		(262)	(113)	(149)
Age		44.3 ± 10.1	44.3 ± 10.7	44.4 ± 9.8
Time with HIV (months)		113.8 ± 79.5	125.9 ± 82.2	104.5 ± 76.4
Time of HAART use (months)		96.7 ± 147.8	110.0* ± 211.8	86.5* ± 63.4
CD4+ T cell count (mm^2)		556.8 ± 324.7	583.8 ± 326.0	535.5 ± 317.8
Viral load n(%)	< 50 copies/mL	229 (90.5%)	96 (85.7%)	133 (94.3%)
	> 50 copies/mL	24 (9.5%)	16 (14.3%)	8 (5.7%)

Values expressed in mean ± SD (standard deviation); HAART: highly active antiretroviral therapy; *p < 0.05.

Table 2. Prevalence of metabolic alterations and fat redistribution.

	All		Female		Male	
	(262)		(113)		(149)	
	%	95%CI	%	95%CI	%	95%CI
Lipodystrophy clinical exam	47.7	41.7 – 53.8	56.5	37.3 – 55.6	48.6	40.6 – 56.7
Lipodystrophy DEXA (n = 157)	40.8	33.1 – 48.5	15.8	4.2 – 27.4	48.8*	39.8 – 57.7
BMI	51.9	45.9 – 58.0	60.5	51.6 – 69.9	45.3*	37.3 – 53.3
AC	53	47.0 – 59.1	77.2	69.5 – 84.9	34.5*	26.8 – 42.1
WHR	50.4	44.3 – 56.4	68.4	59.9 – 77.0	36.5*	28.7 – 44.2
Glycemia	24.8	19.6 – 30.0	28.1	19.8 – 36.3	22.3	15.6 – 29.0
Triglycerides	55.7	49.7 – 61.7	48.2	39.1 – 57.4	61.5*	53.6 – 69.3
Total cholesterol	31.7	26.0 – 37.3	32.5	39.1 – 57.4	31.1	23.6 – 38.5
LDL-C	32.4	26.8 – 38.1	39.5	30.5 – 48.4	27*	19.9 – 34.2
HDL-C	67.6	61.9 – 73.2	76.3	68.5 – 84.1	60.8*	52.9 – 68.7

95%CI: confidence interval of 95%; DEXA: dual-energy X-ray absorptiometry; BMI: body mass index, reference value > 24.9 kg/m^2; AC: abdominal circumference, female reference value ≥ 80 cm and male ≥ 94 cm; WHR: waist-hip ratio, female reference value ≥ 0.85 and male ≥ 1; glycemia, reference value ≥ 100 mg/dL; triglycerides, reference value ≥ 150 mg/dL; total cholesterol, reference value ≥ 220 mg/dL; LDL-C, reference value ≥ 130 mg/dL; HDL-C female reference value ≤ 50 mg/dL and male ≤ 40 mg/dL; *p < 0.05 comparison between male and female.

Biochemical analysis indicated that most individuals evaluated had alterations in their triglyceride and HDL concentrations, and the male subgroup had higher prevalence of hypertriglyceridemia, while the female subgroup had higher prevalence of low HDL-C concentrations. As for glucose metabolism, approximately 25% of those evaluated had elevated plasma glucose (Table 2).

Data show that 47.7% of those assessed had lipodystrophy according to the subjective evaluation method, with no significant difference between genders. On the other hand, the male subgroup had higher prevalence of lipodystrophy by FMR score. It is important to note that, due to the elevated costs of the procedure, only 157 (60.7%) of the individuals were submitted to DEXA evaluation, 75.8% were males. Among all the ones evaluated by DEXA, 40.8% were diagnosed with lipodystrophy according to the FMR score.

There were no differences in the prevalences of lipodystrophy between patients using PIs and the ones who were not, both by subjective and objective evaluations ($p = 0.68$ e $p = 0.46$; respectively).

Of the patients evaluated, 29.3% were smokers and 6.1% were formed smokers. Only eight (3.0%) were considered active, i.e., practiced physical activities for at least 150 minutes a week.

DISCUSSION

The present study presents as main results the high prevalence of metabolic alterations and the resdistribution of body fat if PLWHA in HAART.

Table 3. Anthropometric and biochemical characteristics of people living with HIV/AIDS.

	All (262)	Female (113)	Male (149)
Weight (kg)	70.2 ± 15.5	66.5* ± 16.2	73.0* ± 14.4
BMI (kg/m^2)	24.3 ± 4.97	26.3* ± 5.6	24.6* ± 4.2
AC (m)	90.8 ± 12.5	90.2 ± 14.2	91.3 ± 11.1
WHR	0.94 ± 0.09	0.90** ± 0.09	0.97** ± 0.07
Lean mass (kg) (n = 156)	48.4 ± 8.7	39.0** ± 5.8	51.4** ± 7.3
Fat mass (%) (n = 156)	26.9 ± 7.8	35.6** ± 6.24	24.1** ± 6.0
FMR (n = 156)	1.26 ± 0.56	0.91** ± 0.03	1.37** ± 0.56
Glucose (mg/dL)	99.2 ± 41.9	101.5 ± 51.8	87.3 ± 31.1
Triglycerides (mg/dL)	215.1 ± 145.2	182.1** ± 114.5	242.0** ± 161.5
Total cholesterol (mg/dL)	203.4 ± 72.9	195.4 ± 52.3	209.9 ± 85.6
LDL-C (mg/dL)	119.2 ± 41.4	122.6 ± 42.0	116.1 ± 40.9
HDL-C (mg/dL)	40.6 ± 28.1	41.5 ± 12.5	39.8 ± 36.4

Values expresses in mean ± SD. BMI: body mass index, reference value > 24.9 kg/m^2; *p < 0.01; **p < 0.001; AC: abdominal circumference; WHR: waist-hip ratio; FMR: fat mass ration; LDL-C, reference value ≥ 130 mg/dL; HDL-C female reference value ≤ 50 mg/dL and male ≤ 40 mg/dL.

The studied group consists of a population with long periods of positive HIV. The atherogenic lipid profile of the majority of patients assessed is in agreement with the standard risk for metabolic and cardiovascular diseases due to redistribution of body fat, in which there is central accumulation and peripheral loss. The data found are worrisome due to the elevated incidence of acute myocardial infarction and stroke in this population[17].

The adipose tissue remains as a major trigger of metabolic alterations and the development of chronic diseases and its redistribution is the focal point of lipodystrophy syndrome.

It is well known the abdominal adipose tissue synthesizes and secretes several mediators and cytokines which participate in the mechanisms leading to dyslipidemia, insulin resistance, hypertension and atherosclerosis[18,19]. Also known as adipocyte, according to their location, it presents different metabolic characteristics, visceral adiposity being the one high the greatest impact on the deterioration of insulin sensitivity. However, it seems that not only visceral fat has an unfavorable metabolic behavior, but also the abdominal subcutaneous fat, especially the one below the abdominal fascia[20]. On the other hand, the gluteo-femoral subcutaneous adipose tissue seems to have a protective role regarding insulin resistance[21]. Thus, in case of body fat redistribution, the two factors (lipoatrophy and lipohypertrophy) tend to contribute to a worsening of the metabolic profile.

The present study found more altered mean values of TC, TG, LDL and glycemia when compared to the ones of a national study carried out in Rio de Janeiro, which assessed 203 seropositive patients[22].

When comparing the presence of metabolic adverse effects in the studied patients, it is observed that the prevalences of hypercholesterolemia, hypertriglyceridemia, elevated LDL and altered fasting glycemia are slightly higher than the prevalences found in the study by Domingos and colleagues, whose objective was to evaluate the presence of metabolic abnormalities in 292 PLWHA in HAART[23]. There was a greater prevalence of reduced HDL, considering our study had a higher one (67.6 *versus* 42.8%). These data confirm the high prevalence of lipid and glucose metabolism associated with HIV/HAART.

PIs have been more often associated to the development of the lipodystrophy syndrome, although there was no difference in the prevalence of lipodystrophy between the groups using or not PI in the present study. It can be justified by the fact that all patients use NRTI, which is a drug class that has been named in studies as the main cause for lipodystrophy through the induction of adipocyte apoptosis due to mitochondrial toxicity[24].

Some recent researches conclude the use of HAART is not the only determinant of these changes in the nutritional profile (despite their direct association with adipose tissue and insulin resistance), but rather their sum with genetic, environmental and nutritional factors[25].

The prevalence of clinical dystrophy in this study was similar to the one found in another national study of similar size[23]. In an article by Soares et al.[26] with 227 PLWHA, the prevalence

of lipodystrophy found through subjective method was 40%, the highest prevalence was observed among women (44 *versus* 38.8%), as observed in our study (56.5 *versus* 48.6%). On the other hand, Diehl et al.[13] found a higher prevalence of lipodystrophy among men (68 *versus* 46%), as observed here by the FMR index.

The accuracy of clinical definition for lipodystrophy depends on the skills of the observer, which means specialist ones grant greater precision. Thus, this method is rather difficult be used by less experienced professionals in the area[27]. In addition, many patients may not report changes in their body composition, which may make diagnosis difficult and, thus, contribute to the differences found in prevalences between studies.

No other national study evaluated the prevalence of lipodystrophy using FMR (DEXA) as an instrument. DEXA presents great accuracy of results, however, their cos tis high, thus it is not widely available. In addition to the subjective method used in clinical practice, the objective method suggested by Carr et al.[28] uses many criteria which make this model complex and of limited use for the clinical practice.

In the male subgroup, lipodystrophy prevalences evaluated by both method (subjective and DEXA) were more concordant than the ones in the female subgroup, possibly due to the fact the cutoff point for FMR evaluation was previously standardized in men[11]. These results suggest future studies propose cutoff point in order to identify lipodystrophy by using FMR in females, once that DEXA method is more accurate to contribute in the assessment of prevalence of lipodystrophy in scientific studies.

The high prevalence of increased AC (specially in females, 77.2%) justified the atherogenic profile of these patients, considering a recent analysis found that this anthropometric measure is a good tool to indicate metabolic alterations in the seropositive population. The AC assesses the deposition of central fat in the abdominal region and abdominal obesity is a greater risk cardiovascular factor than overall obesity[29].

A study by Freitas and colleagues, the prevalence of abdominal lipodystrophy among women also reached the 80% range, double the prevalence of males, corroborating the present study[27].

In addition to HAART adverse effects (fat redistribution and metabolic alterations) and the chronic inflammation by the virus, traditional risk factors due to inadequate habits also contributed to the increase of coronary disease[30]. In this context, patients analyzed here were found under these inadequate habits, considering a considerable portion consists of smokers and sedentary people.

HAART has been initiated earlier and earlier, once despite their adverse effects, their benefits outweigh the clinical impact of lipodystrophy, reducing diseases related to AIDS and mortality[31]. The choice of ideal ART drugs combo should be individualized and have the primary objective of reducing viral load and improving immunological response, however, it should be the least likely possible to cause metabolic abnormalities. Thus, the evaluation of cardiovascular risk should be continuous in all HAART patients[32].

The present study had some limitations, in particular by being cross-sectional, which does not allow for long term outcome observation. However, clinical data obtained by

specialized professionals and the use of an accurate method for the quantitative evaluation of fat and lean mass ensure high confidence to the results.

CONCLUSION

Finally, the atherogenic metabolic profile of a large part of evaluated patients indicates the importance of early interventions. Thus, the encouragement of lifestyle changes with nutritional follow-up and orientation to regular physical exercise practice and, as a last resource, a change in the therapeutic regimen (considering the responses for each regimen are individual) may contribute to improve the metabolic profile and consequently reduce the cardiovascular risk of these patients.

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