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Differences in body fat distribution assessed by ultrasonography in patients receiving antiretroviral drugs

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Summary

Objective: This study aimed to evaluate the body fat content of HIV patients according to the duration of antiretroviral therapy use (DURARV), < 1 year and ≥ 1 year. **Methods:** Multiple linear regression was used to investigate the association between ultrasonographic variables of body fat compartments (BFCs) of the face, arm, subcutaneous and visceral abdomen, and the following explanatory variables: gender, age, BMI, and DURARV. **Results:** Of all patients (187), 102 of them with DURARV ≥ 1 year were suffering from HIV-related lipodystrophy (HIV-LD), diagnosed through clinical questionnaires. Those with DURARV < 1 year (n = 85, ≈ 46%) did not have HIV-LD. Regarding the visceral compartment, the difference between those with DURARV ≥ 1 year and < 1 year was 11 mm of additional fat content in those with DURARV ≥ 1 year. Women had more fat than men in all peripheral BFCs, while men had 7.2 mm more visceral fat than women, on average. **Conclusion:** Ultrasonography is a method capable of measuring the thickness of BFCs and is applicable to clinical practice to diagnose HIV-LD.

Keywords: HIV-related lipodystrophy syndrome; highly active anti-retroviral therapy; cross-sectional studies; HIV infection.

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Introduction

The advent of highly active antiretroviral therapy (HAART) resulted in a substantial increase in survival and improved quality of life for patients living with AIDS[1,2]. However, these patients started to present chronic complications such as, for example, lipodystrophy and diverse metabolism alterations[3,4].

HIV-related lipodystrophy (HIV-LD) involves disorders of lipid metabolism and glucose and body fat redistribution. A typical pattern of body fat redistribution is the loss of subcutaneous fat in the face, limbs, and buttocks, called lipoatrophy. Another commonly observed pattern is dorsocervical and trunk fat accumulation, as well as increased abdominal visceral fat, called lipohypertrophy. The combination of the two patterns is called mixed lipodystrophy[3,5].

The diagnosis of lipodystrophy in HIV patients is usually subjective, whether it is carried out by patient self-assessment or clinical evaluation by the physician[6,7]. In order to meet the needs for an objective method capable of performing this assessment accurately and easily, several imaging methods have been suggested. Computed tomography (CT), magnetic resonance imaging (MRI), and dual energy X-ray absorptiometry (DEXA) are the imaging methods considered to be the gold standard[8]. However, their use increases the already high cost of treating the patient with HIV-LD[8-10]. In this context, ultrasound is a promising method, with lower cost and good patient acceptance, besides being an easily accessible, simple, and noninvasive method[11].

This article analyzed the differences in the amount of fat in body fat compartments (face, arms, subcutaneous and visceral abdomen) analyzed through ultrasonography in HIV patients on antiretroviral therapy (HAART).

Methods

The study sample consisted of patients with HIV on antiretroviral regimen using HAART[12], in accordance with the guidelines of the Brazilian Ministry of Health, who did or did not present HIV-related lipodystrophy (HIV-LD). Eligible patients included those with recent use of HAART (<1 year) and who did not have HIV-LD, and those under treatment for a period of ≥ 1 year, with HIV-LD. All patients were older than 18 years and were recruited during their visits to the outpatient clinic of a public hospital in the city of Rio de Janeiro, between November 2006 and October 2009.

The selected patients completed a form that included their demographic, clinical, and therapeutic characteristics. The information of interest were: age (in years), gender, presence or absence of signs/symptoms associated with HIV/AIDS and lipodystrophy; ongoing or prior treatments, which enabled the later establishment of the presence of AIDS-defining diseases in the previous 30 days, according to the criteria of the Centers for Disease Control and Prevention (CDC)[13]; the presence or absence of HIV-LD according to the criteria of Lichtenstein et al.[6]; and the duration of antiretroviral therapy use (DURARV) (continuous variable).

The variable DURARV was further categorized into ≥ 1 year and < 1 year of antiretroviral therapy use. Weight (kg) and height (m) were measured, and the body mass index (BMI) (kg/m^2) was calculated. The clinical and therapeutic data provided by the patients were carefully verified in their medical records. In case of discrepancy between the information provided by the patient and that in the medical records, the information in the latter was chosen as the reference information.

Using the questionnaires for the assessment of body fat compartments (BFCs), all patients performed a self-assessment of their BFCs, followed by a medical evaluation of these same compartments by a single physician blinded to the results of the patient self-assessment.The purpose was to differentiate body shape alterations in these assessments, such as loss of subcutaneous fat in the face, limbs and buttocks, and fat increase in the trunk and abdomen[6].

The diagnosis of HIV-LD followed the validated diagnostic criteria proposed by Lichtenstein et al.[6], which rely on the presence of at least one immediately perceptible sign associated with a discrete sign (detected only by careful examination) of alteration in the previously described body compartment; on the agreement between the medical assessment and that performed by the patients on the assessed BFCs; and on the absence of any sign of AIDS-defining illness for at least 30 days prior to the consultation. Abdominal obesity was not considered a defining sign of HIV-LD.

The patients, at the end of clinical and ultrasonographic assessments, were then divided in two groups: those with DURARV ≥ 1 year and presence of HIV-LD, and those with DURARV < 1 year and no HIV-LD.

The documents that summarized the physicians' and the participants' assessments were kept in a safe storage by the lead investigator and compared only after all the ultrasound measurements had been completed.

Ultrasonography

The ultrasonographic measures (SA-8000 EX equipment, Medison CO. Ltd.) were performed by a single, experienced operator. The ultrasonographist was blinded to the medical information of the assessed patients. Each of the body fat compartments studied (face, arm, abdominal subcutaneous and visceral) was measured twice, and the mean value of these measurements was recorded in the data form of each patient. The calibration of the ultrasound equipment had the following characteristics: frame average = 2, edge enhanced = 0, dynamic range = 105%, reject level = 2, view area = wide, tissue = normal, trapezoid = off, apex = up, frame rate = fast, and power = 80. The mean time between the interview/clinical assessment and ultrasonographic measurements was three days.

The measurements of fat thickness were performed using a high-frequency linear probe (10 MHz) lightly positioned transversely at a perpendicular angle to the body surface with the patient lying on the table in the supine position without a pillow. The probe was positioned on three anatomical landmarks, according to the description of the study by Martinez et al.[11]. On the malar region, the positioning was on the most prominent point of the zygomatic bone (cheekbone). Facial fat thickness was measured from the inner layer of the skin to the external fascia of the superficial facial muscle, at the point of junction of the zygomatic and maxillary bones (Figure 1).

In the brachial region, the mid-third of the right arm was placed in pronation and aligned with the body. Once the images of the humerus and the muscle had been displayed together on the screen, the image was frozen and the measurement of fat thickness was taken from the inner layer of skin to the external fascia of the biceps. In the umbilical region, just above the umbilicus, fat thickness was measured from the inner layer of the skin to the upper surface of the rectus abdominis, in the middle of the linea alba, with the patient holding the breath (Figure 2). Visceral fat thickness was measured in the umbilical area with a low-frequency probe (3.5 MHz) positioned perpendicularly and transversely to the body surface. Visceral fat measurement was performed from the inner surface (posterior) of the rectus abdominis muscles to the posterior wall of the abdominal aorta, just above its bifurcation, in accordance with the study by Radominski et al.[14].

The study protocol was approved by the hospital ethics committee and all patients signed the informed consent for the ultrasonographic and clinical-epidemiological evaluation.

Statistical analysis

Multiple linear regression was used to investigate the association between the variables of the BFCs (face, arm, subcutaneous and visceral abdominal fat), measured by ultrasonography, and the following explanatory variables: gender, age, BMI, and time on antiretroviral therapy (DURARV ≥ 1 year and < 1 year). The assumptions of linear regression models were analyzed graphically and through statistical tests[15]. The normality and homoscedasticity test results of the residues of each model are shown in Table 1. Statistical analysis was performed using the open source statistical package R, release 2.11.1[16].

Results

The study sample consisted of 187 patients, mean age (± standard error) of 42 (± 0.8) years, of which 137 (≈ 73%) were males. The time of treatment showed a

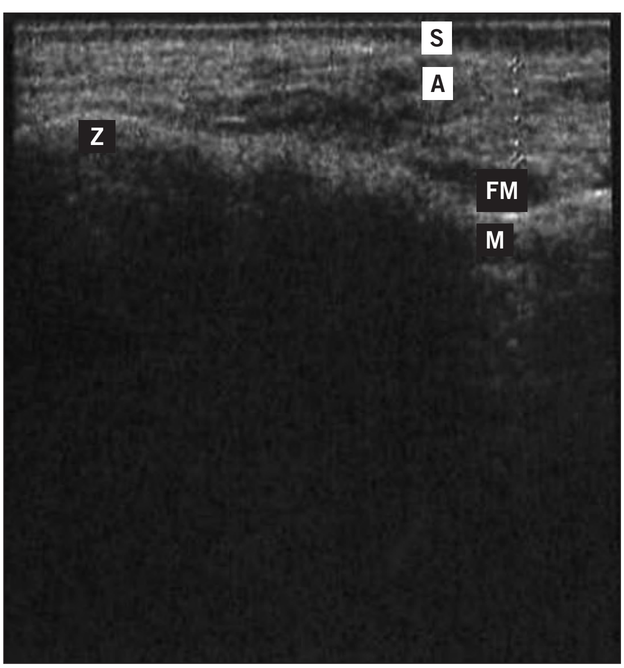

Figure 1 – Measurement of subcutaneous adipose thickness of the face. Cross-sectional plane (10MHz) of the most prominent part of the zygomatic bone, from the internal skin layer to the outer fascia of the facial musculature.
S, skin; A, subcutaneous adipose tissue; FM, facial muscle; Z, zygomatic bone; M, maxillary bone.

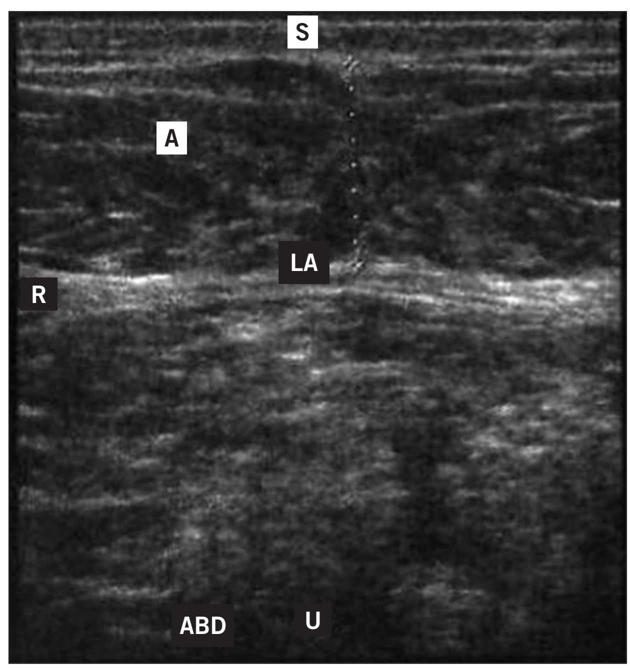

Figure 2 – Measurement of the subcutaneous adipose thickness of the abdomen. Cross-sectional view (10MHz), from the internal skin layer to the outer surface of the rectus abdominis muscles.
S, skin; A, adipose subcutaneous tissue; LA, linea alba; R, rectus abdominis; ABD, abdomen; U, above umbilicus.

Table 1 – Linear models of body fat compartments

BFC	Face		Arms		Subcutaneous abdomen		Visceral abdomen	
Variables of interest	Univ.	Multivar.	Univ.	Multivar.	Univ.	Multivar.	Univ.	Multivar.
BMI	(0.16 ± 0.02)$^{\delta}$	(0.2 ± 0.03)$^{\delta}$	(0.22 ± 0.02)$^{\delta}$	(0.2 ± 0.02)$^{\delta}$	(1.2 ± 0.1)$^{\delta}$	(1.2 ± 0.1)$^{\delta}$	(1.9 ± 0.23)$^{\delta}$	(2.4 ± 0.2)$^{\delta}$
DURARV (< 1 year)*	(0.8 ± 0.2)$^{\delta}$	(0.7 ± 0.2)$^{\delta}$	(0.42 ± 0.2)$^{¥}$	(0.4 ± 0.16)$^{\delta}$	(4.6 ± 1.3)$^{\alpha}$	(4.4 ± 1.1)$^{\delta}$	(-8.5 ± 1.9)$^{\delta}$	(-11.2 ± 1.5)$^{\delta}$
Gender (F)§	(0.4 ± 0.2)$^{\alpha}$	(0.7 ± 0.2)$^{\delta}$	(1.7 ± 0.2)$^{\delta}$	(1.9 ± 0.18)$^{\delta}$	(6.4 ± 1.4)$^{\delta}$	(7.7 ± 1.2)$^{\delta}$	(-7.2 ± 2.2)$^{\alpha}$	(17.4 ± 9.8)$^{¥}$
BMI: gender§§	–	–	–	–	–	–	–	(-1.1 ± 0.4)$^{\delta}$
$r^{2\,//}$	–	0.25	–	0.56	–	0.41	–	0.5
Liberty grades	–	184	–	184	–	184	–	183
Normality test$^{\#}$	–	0.051	–	0.1	–	0.1	–	0.3
Homog. T. Var.**	–	0.06	–	0.2	–	0.1	–	0.7

BMI, body mass index (continuous variable); *duration of antiretroviral therapy use with exposure category < 1 year; §exposure category: female gender; §§interaction term between BMI and gender; $^{//}$quality adjustment of the linear model; $^{\#}$p-value of the Kolmogorov-Smirnov test for normality; **p-value of Bartlett test of homogeneity of variances; Univ., univariate estimation of the model; Multivar., multivariate estimation of the model ± standard deviation; BFC, body fat compartments; $^{\delta}$< 0.01; $^{\alpha}$< 0.05; $^{¥}$< 0.10.

bimodal distribution, and a cutoff was set at one year. In the group of patients with more than 1 year of treatment (n = 85, ≈ 46%) the mean time was 3,418 (± 139) days of treatment. All these patients had HIV-LD. In patients with < 1 year of antiretroviral drug use (n = 102), the average time of treatment was 73 (± 7.2) days and there were no cases of HIV-LD. The signiﬁcant difference in time between the treatment groups (t = 24, p < 0.0001) and the interval of 475 days between the extremes of the two groups justiﬁes the dichotomization of this variable used in the multivariate analysis.

The mean ultrasonographic measurements of the BFCs of face, arm, subcutaneous and visceral abdomen were respectively 3.43 (± 0.1) mm, 1.8 (± 0.13) mm, 13.4 (± 0.7), and 45.5 mm (± 1) mm for all patients. The univariate regression coeﬃcients of the variables of interest (age, BMI, DURARV, and gender) and their signiﬁcance values are shown in Table 1. The mean BMI of the study population was 24.4 kg/m^2 (± 0.28). There was no association between BMI and gender (males: 24.5 (± 0.30) kg/m^2); females: 24.1 (± 0.62) kg/m^2, t = 0.76, p = 0.5), or between BMI and treatment duration (group > 1 year: 24 (± 0.5) kg/m^2; group < 1 year: 25 (± 0.3) kg/m^2); t = -1.713, p = 0.9). On the other hand, patients with DURARV > 1 year were signiﬁcantly older (49 (± 1)) than those with DURARV < 1 year (age 37 (± 0.9), t = 8.8, p < 0.0001).

In multivariate analysis, the variables BMI, gender, and time of treatment were signiﬁcantly associated with all BFC measurements analyzed by ultrasound.

Females had 0.7 mm, 1.9 mm and 7.7 mm more fat, respectively, in the face, neck, and subcutaneous abdomen, on average, than the corresponding values of the respective male compartments. As for the male visceral compartment, there was an increase of 7.2 mm in fat compared to the same compartment in females. The increase of one unit of BMI was associated with increased fat in all BFCs studied, and ranged from 0.2 mm in the face and arm to 1.2 mm and 2.4 mm in the subcutaneous and visceral abdomen, respectively.

The thickness of body fat compartments was strongly associated with treatment time in both men and women. In those with DURARV < 1 year there was, respectively, an increase of fat of 0.4 mm and 0.7 mm, in the arm and face, and 4.4 mm in the subcutaneous abdominal compartment (Table 1). Conversely, in the visceral compartment, patients with DURARV ≥ 1 year had on average 11 mm more visceral fat than patients with shorter treatment time (Table 1).

Discussion

It has been estimated that by the end of 2009 there were approximately 35 million people living with HIV worldwide; of these, more than 95% were living in countries with low and middle incomes. In these countries there are now approximately 5.2 million people using antiretroviral medications, and 10 million people awaiting the expansion of antiretroviral therapy programs in order to start treatment[17].

The Ministry of Health reported 592,914 cases of AIDS (clinical syndrome) in Brazil, from 1980 until June 2010[18]; of these, 200,000 regularly receive antiretroviral treatment[19]. In spite of the substantial increases in the quality and length of survival of HIV patients since its first use in 1996, this type of therapy has significant adverse effects[20], in addition to the difficulties of treatment compliance in the long term, which, so far, corresponds to a period that encompasses the life of each patient with HIV/AIDS[21].

The prevalence of abnormal fat redistribution in different studies is closely associated with the duration of antiretroviral use, and other factors such as age, gender, body weight, and duration of HIV infection. Except for the last variable, of which information is inaccurate or unknown for most people with HIV, the others were studied in the present study, as well as in other international studies[3,7,8], by regression models of fat compartments of interest.

The gender of patients has a significant effect on changes in body composition of fat that occur during HIV infection; women, who usually have a higher proportion of fat mass when compared to men, lose disproportionately more fat, thus reducing the sexual differences in body composition of HIV patients over time[22]. Kotler et al.[22] also observed that the amounts of fat in subcutaneous compartments are higher among women, when compared to men. The opposite is observed with respect to the visceral compartment: there is a smaller amount of fat in women when compared to men, and these observations were corroborated by the present study.

Height and weight have a strong influence on the mass of body cells, in relation to both lean mass and fat mass[22]. As expected, a positive association between BMI and fat content of body compartments, particularly in the visceral compartment, was found. Conversely, there was no statistically significant association between BMI and length of use of antiretrovirals. This result suggests that the fat loss occurs in the same amounts in patients with different BMI values. In turn, the impact of this loss, when measured as loss relative to the initial weight, will be greater in those with lower BMI, as the loss of fat mass will be significantly higher in relation to the pre-existing fat mass.

The smaller amounts of fat measured in the peripheral compartments of patients with DURARV ≥ 1 year/HIV-LD compared with those with DURARV < 1 year/without HIV-LD, suggest a thinning of the arm and fat atrophy in the face and abdomen, possibly in response to treatment. In the latter (the stomach compartment compressible with the fingers), which is not normally measured by the clinical diagnostic methods of HIV-LD[5,23], there was a substantial reduction of fat associated with longer time of treatment.

Regarding the visceral compartment, there was a greater amount of fat in the group receiving prolonged treatment (> 1 year), compared to the group that had started treatment more recently (< 1). The visceral fat accumulation usually occurs in the clinical pictures of abnormal fat redistribution, but its presence alone does not define the diagnosis of HIV-LD, as there are other diseases or disorders that also course with visceral obesity, such as metabolic syndrome. Therefore, it is necessary to perform differential diagnosis before associating visceral obesity with HIV-LD.

In routine care, the diagnosis of HIV-LD is performed based on the self-assessment of patients and on the attending physician's assessment (subjective information), due to the considerable advantages, such as low cost and flexibility of the language used in the questionnaire, adjusted to the patient's language skills. This diagnostic method was validated by Lichtenstein[6], who, in a multicenter U.S. study, evaluated 1,077 patients with HIV submitted to self-assessment and evaluation by their physicians for signs of HIV-LD. Patients who had diagnostic concordance of HIV-LD in both evaluations were considered as having HIV-LD.

In a study of objective definition of lipodystrophy, in which 10 clinical and metabolic variables were used, and the variables related to body compartments were measured by DEXA, the authors[24] showed a sensitivity of 79% and a specificity of 80% for the diagnosis of HIV-LD. However, this method is currently restricted to health facilities with better infrastructure, as it relies on sophisticated metabolic tests and DEXA, which are not on the list of routine examinations in most Brazilian hospitals. Ultrasound may represent an intermediate option between the high-tech methods, which have higher cost and lower availability in medical facilities, and methods based on subjective information only, which have lower cost and are widely available, but also generally show problems with accuracy, reliability, and validity[8].

Sectional studies with HIV patients, conducted in Spain[25,26], assessed the inter-exam reliability of ultrasound, CT, and DEXA, when evaluating fat compartments in the subcutaneous abdomen and arm in patients with lipoatrophy, and found statistically significant correlations[25,26]. In the arm, the Spearman's rank correlation coefficient varied from 0.64 to 0.84, whereas in the subcutaneous abdomen, these correlations, although weak, were statistically significant, and ranged from 0.34 (p-value < 0.05) to 0.40 (p = 0.001)[25,26]. Similarly, for the visceral fat, a good reproducibility of ultrasound measurements when compared with CT (r = 0.84) was observed[26].

In another study, which measured visceral fat thickness by ultrasound in patients with HIV receiving antiretroviral therapy *versus* those who had never received it, Guimarães et al.[27] also found differences in visceral adiposity that were significantly higher in the group of patients receiving antiretrovirals.

Most studies of inter-exam reliability that evaluated the ultrasonography for the face and clinical methods found a signiﬁcant correlation between them[11,28,29]. However, Carey et al.[30] found no signiﬁcant association between the malar region studied by ultrasound and other body regions studied by different methods of measurement, such as CT and DEXA. It can be postulated that it would not be possible to establish correlation between the measurements, as the method used in this study did not maintain similar observation conditions in the several procedures performed.

An additional advantage of ultrasonography is the low variability of its measurements of subcutaneous (< 5%)[11,27,31] and visceral (2.6%) fat thickness when performed by a single well-trained operator.

The multivariate model adjusted for ultrasonographic data of the face had the worst quality of ﬁt ($r^2 = 0.25$). Two possible explanations can be proposed. First, this result suggests the need to include in these evaluations additional variables that were not studied in the present study. However, no studies in the literature that used linear regression to study the differences in body fat compartments in this population were found, so it is not possible to compare the present results with those of other studies.

The fact that the measurement of facial fat has the highest degree of technical diﬃculty among the procedures used in this study is noteworthy. Anatomical variations and variability in facial shape and fat content of this body compartment require the ultrasonographist's skill to produce an image that includes the anatomical reference points (the junction of the zygomatic and maxillary bones in the lower right eye socket, and adjacent muscle and fat tissues) (Figure 1). Therefore, one possible explanation for the high variability observed in measurements of the face (and consequent low quality of ﬁt) would be the result of signiﬁcant differences in the form and content of the fat compartments of patients examined by ultrasound.

Simultaneously with the expansion of antiretroviral treatment provided to millions of HIV patients, there is ongoing development of new drugs with less toxic proﬁles, tending to replace ﬁrst and second-line antiretroviral drugs, which are relatively inexpensive, effective, and widely prescribed, but are often associated with metabolic disorders and HIV-LD. The economic impact of these substitutions in antiretroviral programs with free and universal access is likely to jeopardize the continued expansion of these programs for new patients and even the maintenance of those already being treated[32].

It is suggested that ultrasonography should be used to study the fat compartments, in parallel or in series with the clinical method of diagnosis of HIV-LD throughout outpatient-based treatment. This approach is similar to that which has been routinely used in relation to the monitoring of immunological and metabolic parameters of patients in follow-up care. It is expected that ultrasound can be used as an important tool in early diagnosis of abnormal fat redistribution, and can indicate patients for whom replacement of antiretroviral drugs closely associated with HIV-LD by others with less pronounced side effects is recommended.

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