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DIFFERENT NUTRITIONAL-STATE INDICATORS OF HIV-POSITIVE INDIVIDUALS UNDERGOING ANTIRETROVIRAL THERAPY

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ABSTRACT: This study aimed at learning about the nutritional profile of HIV-positive individuals undergoing antiretroviral therapy and at comparing the performance of nutritional-state indicators. A transversal study was performed on 94 patients attending the Tropical Diseases Outpatient Hospital of Botucatu Medical School (FMB) - UNESP. The body mass index (BMI) and the classification by Papini-Berto (PB) were used to evaluate nutritional state, aiming at detecting malnutrition and obesity. The waist-to-hips ratio (W/HR) and waist circumference (WC) were adopted for identification of abdominal obesity and lipodystrophy. According to BMI, most of the individuals were eutrophic, followed by 30.9% overweight and 6.4% malnourished. By using the PB classification, the frequency of malnourished increased (22.3%). The analysis of the PB classification in relation to BMI indicated that the former presented high sensitivity and good specificity for malnutrition diagnosis, namely 100% and 83%, respectively. The prevalence of abdominal obesity was 7.44% according to WC, and a higher prevalence (38.3%) was observed when taking W/HR into account. There was significant positive association between nutritional diagnosis according to PB and T $CD4^+$ lymphocyte. The results support the use of PB classification for malnutrition detection as well as that of BMI and W/HR for overweight and fat redistribution.

KEY WORDS: HIV/AIDS, antiretroviral therapy, nutritional indicators.

CONFLICTS OF INTEREST: There is no conflict.

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INTRODUCTION

The United Nations World Organization estimates that approximately 44 million people are infected with the Human Immunodeficiency Virus (HIV) whether still in the asymptomatic state or already suffering from the clinical conditions resulting from the infection. In Brazil, the incidence rate is of 113 reported cases for every 100,000 inhabitants (39). AIDS is a chronic disease that causes the progressive destruction of the immune system, thus leading to recurring opportunistic infections, changes in body composition, adverse nutritional impact, evolutive debilitation and even death (4).

In 1996, the large-scale use of a new class of antiretroviral drugs, the so-called protease inhibitors, was included in AIDS treatment. Such medication provided a new boost in the treatment of the disease, since it enabled the introduction of highly active antiretroviral therapy (HAART) and, consequently, a drastic reduction in the numbers of deaths resulting from AIDS (13). At the same time, the nutritional aspects of HIV infection changed with the advent of such therapy: body depletion, particularly that of lean mass, fat redistribution by the lipodystrophy syndrome, increase in blood lipid concentration, insulin resistance, obesity and increased risk for chronic diseases (6, 7, 37, 38).

However, AIDS-associated malnutrition still occurs in uncontrolled phases of the disease, and its complications make the patient even more susceptible to opportunistic infections, reduction of the efficacy and tolerance to medication, and higher death risk (1, 37). Various authors have reported that the nutritional state is a strong predictive factor for survival and functional conditions during the course of HIV infection (9, 17, 25, 26, 33-35, 41).

According to the American Public Health Association, nutritional state is “an individual’s health condition that is influenced by the consumption and use of nutrients, identified by the sum of information obtained on his physical, biochemical, clinical and dietetic parameters” (45).

To ensure that the detection and monitoring of nutritional disorders and body composition are effective, measurements, indexes, indicators and classifications used to evaluate nutrition and body composition must be valid, which means that they should be accurate, reproducible, sensitive and specific for the defined purposes. Ideal methods for nutritional and body composition evaluation must also be low-cost and, non-invasive and capable of being performed by trained professionals without the need of high capacitation or qualification (2).

Since there is no ideal nutritional-state indicator which can isolatedly enable an adequate evaluation of the individual's global condition or the classification of the nature and severity of occasional nutritional disorders, healthcare professionals face a problem of difficult solution. The choice about which nutritional-state indicators to use in hospital and outpatient care to HIV and AIDS patients depends, among other elements, on patients' profiles and the operational availability of the service (24, 27). The "ideal" nutritional evaluation method for HIV/AIDS patients is still unknown.

At present, the early detection of both malnutrition and obesity as well of lipodystrophy is fundamental. Additionally, it is necessary to classify occasional nutritional compromising in terms of severity (slight, moderate, severe) and monitor positive and negative alterations in a short period of time in order to evaluate interventions. There is also the need for methods that will allow the priorization of patients for specialized nutritional care by identifying those with the highest risks for adverse outcomes, complications, long hospitalization periods, worsening in quality of life and death.

In face of these facts, it has become increasingly important to learn about the short-term and long-term impact of the disease and its treatment on the nutritional state of HIV-infected individuals as well as to define methodologies for sensitive and low-cost evaluation in order to adopt preventive measures aiming at improving patients' nutritional state and quality of life by decreasing the number, duration and cost of hospitalizations (1).

In this sense, this study aimed at describing the nutritional profile of HIV-positive individuals undergoing HAART by using different nutritional indicators and comparing the performance of such indicators and nutritional-state classifications for the detection of malnutrition, abdominal obesity and lipodystrophy.

INDIVIDUALS AND METHODS

A transversal study was carried out from 2003 to 2004. It included 94 adult male and female individuals with confirmed HIV diagnosis by the ELISA (enzyme-linked immunosorbent assay) method. Such patients were undergoing HAART and had been attending the Nutrition and Tropical Diseases Outpatient Hospital (ANDT) of the Botucatu Medical School – São Paulo State University (FMB - UNESP). The study was approved by the Research Ethics Committee of FMB - UNESP, and all participants signed an informed consent and agreement form.

All the studied individuals were evaluated by means of a pre-established and previously tested protocol that was applied at a single moment of the evaluation and involved epidemiological, clinical, anthropometric, biochemical, hematimetric and immunologic aspects. Other data, such as age, sex, skin color, medication used, smoking and drinking habits, were also collected for patient characterization.

As for anthropometric data, the following were measured: weight (kg), by using a digital anthropometric scale (Toledo) with gram precision while the individual was barefoot and wearing minimum clothes; height (m), by using the scale's movable height meter (16, 42). The body mass index (BMI) was obtained through the ratio between the patient's weight in kilograms and the square of the individual's height in meters (20), which was applied according to recommendation by the World Health Organization (WHO) (45).

Measurements of the tricipital cutaneous fold (TCF), bicipital cutaneous fold (BCF), subscapular cutaneous fold (SSCF), suprailiac cutaneous fold (SICF), arm circumference (AC), waist circumference (WC) and hips circumference (HC) were also made, and the arm muscular circumference (AMC) was obtained by the formula [AMC = AC – (0.314XTCF)] (20). All measurements were made on the individuals' non-dominant side, and AC was obtained on the arm's middle point, between the acromion and the olecranon, by using an inextensible cellulose millimeter measuring tape (20); TCF and BCF were measured on the same point on the triceps and biceps muscles, respectively, by using an adipometer (LANGE CALIPER – Cambridge Scientific, USA, with constant pressure of $10g/mm^3$). SSCF was obtained on the point located one centimeter below the scapular angle by observing the skin's natural strength lines while SICF was measured one centimeter above the iliac crest by folding the skin and subcutaneous tissue on the midaxillary line. All cutaneous folds (CF) were measured three times by taking into account the means of the obtained values (20, 42). From the sum of the four CF measurements (ΣCF), the body fat percentage was obtained (%G) by applying the Durnin and Womersley (12) formula.

The waist-to-hips ratio (W/HR) was obtained by calculating the ratio between the measurement of the waist and hips in centimeters. WC was measured by an inextensible cellulose millimeter tape by adopting the technique standardized by

WHO (44). HC was measured by using the same previously cited tape around the maximum gluteal extension (20). Abdominal obesity cases were defined on basis of increased risk for cardiovascular diseases resulting from fat deposition on the abdomen as WC ≥ 102cm for men and WC ≥ 88cm for women (44). Waist-to-hips ratio > 0.95 for men and > 0.85 for women also defined abdominal obesity (44).

Another body fat distribution index used was the ratio of the trunk folds (SSCF +SICF) / arm (TCF + BCF), which has been recently utilized in the study by Hartman *et al*. (19) as an attempt to express body fat redistribution. A possible relationship of such index with HAART duration was investigated.

The classification proposed by Papini-Berto (PB) was used (36). Such classification involves anthropometric (BMI, TCF and AMC) and laboratory (serum levels of lymphocytes and albumin) parameters for definition of malnutrition levels. The anthropometric measurements were situated, in relation to reference distributions, in percentiles, according to Cronk and Roche (11) and Frisancho (16). The same occurred to laboratory tests, and values under the 5th percentile of the reference for a healthy population were considered to be indicative of depletion. As regards albumin serum levels, figures under 3.5g/dl were taken into account, and in relation to total lymphocyte count, those under 1500/mm^3 were considered (29).

With such parameters and the cutting points described above, the nutritional state is classified by PB in 3 malnutrition levels, malnutrition risk and without nutritional risk, as follows: severe malnutrition for those who presented three of the five parameters below the 5th percentile; moderate malnutrition when there were two parameters below the 5th percentile, of which two could be anthropometric or one could be anthropometric and associated with a laboratory parameter; mild malnutrition when the two laboratory parameters were below the 5th percentile; nutritional risk for those who exhibited one anthropometric parameter between the 5th and the 10th percentiles associated with a laboratory parameter below the 5th percentile or two anthropometric parameters between the 5th and 10th percentiles; and without nutritional risk for those who were not included in any of the previously cited situations (36).

As for their global nutritional state, all the individuals were classified according to these two methods: the classification proposed by PB and BMI according to WHO.

The nutritional state classification proposed by Papini-Berto was later modified. One of the tested forms was the division of the individuals into only two strata –

malnutrition of any level and absence of malnutrition – so as to compare to BMI also in two strata, namely malnutrition of any level and absence of malnutrition. Another stratification of the Papini-Berto classification was used when the relationship between nutritional state and T $CD4^+$ lymphocyte levels was studied. Since only the moderate and severe malnutrition forms were related to AIDS severity indicator, two groups were separated: second and third-level malnourished individuals and others.

Total T $CD4^+$ lymphocyte count was obtained from each patient's medical chart. Biochemical and hematimetric tests were performed at the clinical laboratory of FMB - UNESP while immunologic tests were conducted in the same Institution's Blood Bank.

The association between abdominal obesity indicators (W/HR and WC) with BMI and HAART duration was also investigated.

The data were analyzed by using software SPSS 12.0.1 for Windows. Descriptive analysis was made by presenting the frequency distribution (absolute and relative) of the individuals and the central tendency and dispersion (mean and standard deviation) measurements, whenever relevant, in relation to the nutritional indicators and classifications. The analysis of performance for the classification proposed by Papini-Berto versus BMI was conducted according to Fletchen and Fletchen (14) by calculating sensitivity, specificity, and the percentages of correct and incorrect classifications. The association between indicators for fat location and HAART duration was studied through linear regression analysis by adopting $p<0.05$ as the level of significance. The comparison between mean T $CD4^+$ lymphocyte values according to the nutritional state, in two categories, was made by Student's t test after transforming into square root values, thus making data distribution symmetrical.

RESULTS

Of the 94 individuals under study, 51 (54.3%) were male and 43 (45.7%) were female; 95.7% were white and 4.3% black skinned. Their mean age was 38.52±9.29 years. Smoking habits and the ingestion of alcohol were present in 34.04% and 3.2%, respectively.

The distribution of individuals as regards the use of HAART resulted in 42.6% of patients with an association of nucleoside analog transcriptase inhibitors with non-nucleoside analog transcriptase inhibitors (NRTI + NNRTI), 41.5% receiving an association of protease inhibitor with nucleoside analog transcriptase inhibitor (PI +

NRTI), and 15.9% using NRTI. The mean AR therapy duration was of 23.37±23.71 months.

Table 1 characterizes the nutritional profile of the studied individuals according to the nutritional classification by BMI/WHO: most of the individuals were eutrophic (E), which was followed by 30.9% with pre-obesity (PO) and level-I obesity (OB I). Malnourished or low weight accounted for 6.4% of the individuals. By using the Papini-Berto nutritional classification, the frequency of malnourished individuals (22%) was higher, and most of them were level II (MN II). The mean percentage of body fat for men and women was of 21.73±5.84 and 29.51±5.38, respectively. The prevalence of abdominal obesity was 7.44% when taking waist circumference measurement into account; nevertheless, such prevalence increased to 38.3% when considering the waist-to-hips ratio. As regards abdominal obesity, as evaluated by WC, there was significant difference according to sex (p=0.03): prevalence of 85.7% in women and 14.3% in men, which did not occur when taking W/HR into account. The trunk/arm index, a possible fat distribution indicator, showed higher mean values for men in relation to women.

When analyzing the performance of the nutritional classification proposed by Papini-Berto in relation to the BMI classification, it was possible to observe that PB presented high sensitivity and good specificity for malnutrition diagnoses, which were of 100% and 83%, respectively. The correct classification proportion was of 84%, pointing out that all individuals considered to be malnourished according to the BMI/WHO criteria were also considered to be so by the Papini-Berto classification (Table 2).

The analyses aiming at evaluating the behavior of indicators for location and relative distribution of body fat in view of the BMI/WHO classification are presented in Table 3. It was observed that 33.9% of the eutrophic individuals had a high waist-to-hips ratio, which indicated abdominal fat accumulation in relation to the gluteal region. Among those showing overweight (OB I + PO), 48.3% were in such condition. It is also noteworthy that 11.1% of the individuals with low weight/malnutrition according to the BMI/WHO criteria showed a high waist-to-hips ratio. When the waist measurement was adopted as an indicator, the frequencies of individuals classified as being at risk due to fat excess were lower, that is, 20.7% for those overweight (OB I + PO) and virtually zero for the others (E + MN I).

Table 4 presents the results of the analyses aiming to observe the existence of an association between the fat distribution indexes with HAART duration. A significant positive association between the waist-to-hips ratio and between waist circumference and therapy duration was observed. Such association was more significant for W/HR; nevertheless the trunk/arm index was not associated with therapy duration.

The means for T $CD4^+$ lymphocyte serum levels according to nutritional state are presented in Figure 1 as shown by the PB classification. There were no differences in T $CD4^+$ levels between patients with mild malnutrition and those without malnutrition, but the means for patients with moderate and severe malnutrition (MN II and MN III) were significantly lower than those for the others, $p<0.05$, Student's t test. When separated according to two BMI groups, patients with BMI < 18.5kg/m² (malnourished) and patients with a higher BMI than that value (not malnourished) did not show a significant difference in the means of T $CD4^+$ lymphocyte serum levels

Table 1. Nutritional profile of 94 HIV-positive patients undergoing HAART and assisted at the Nutrition and Tropical Diseases Outpatient Hospital, Botucatu Medical School – São Paulo State University (FMB - UNESP), 2003/04.

Variables	
Nutritional classification - BMI [n (%)]	
Level-I malnutrition	06 (6.4)
Eutrophy	59 (62.8)
Pre-obesity	25 (26.6)
Level-I obesity	04 (4.3)
Nutritional classification – Papini-Berto [n (%)]	
Level-III malnutrition	03 (3.2)
Level-II malnutrition	16 (17)
Level-I malnutrition	02 (2.1)
Non-malnourished	73 (77.7)
% of body fat (mean±SD; 1st q; 3rd q)	
Males (n=51)	21.73±5.84; 17.7; 25.9
Females (n=43)	29.51±5.38; 25.9; 33.7
WC - cm (mean±SD)	
Males (n=51)	87.89±9.06
Females (n=43)	77.89±8.58
Abdominal obesity – WC classification [n (%)]	
Total	7 (7.45)
Males	1 (1.06)
Females	6 (6.39)
W/HR (mean ± SD)	
Males (n=51)	0.93±0.07
Females (n=43)	0.83±0.07
Abdominal obesity – W/HR classification [n (%)]	
Total	36 (38.3)
Males	19 (20.2)
Females	17 (18.1)
Trunk/arm index (mean±SD; 1st q; 3rd q)	
Males (n=51)	2.15 ± 0.75; 1.64; 2.45
Females (n=43)	1.75±0.64; 1.29; 2.38

SD = standard deviation

WC = waist circumference

W/HR = waist-to-hips ratio

q = quartile

Table 2. Performance of the nutritional classification by Papini-Berto in relation to the BMI classification and agreement indexes in 94 HIV-positive patients undergoing HAART and assisted at the Nutrition and Tropical Diseases Outpatient Hospital, Botucatu Medical School - São Paulo State University (FMB - UNESP), 2003/04.

	Classification - BMI					
	Malnourished		Non-malnourished		Total	
Classification - Papini-Berto	n	%	n	%	n	%
Malnourished	6	100	15	17.05	21	22.3
Non-malnourished	0	0	73	82.95	73	77.7
Total	6	100	88	100	94	100

Sensitivity for diagnosis of malnourished individuals = 100%

Specificity for diagnosis of malnourished individuals = 83%

Correct classification % = 84%

Table 3. Distribution of the 94 HIV-positive individuals undergoing HAART and attending the Nutrition and Tropical Diseases Outpatient Hospital, Botucatu Medical School – São Paulo State University (FMB - UNESP), according to waist-to-hips ratio (W/HR) and waist circumference (WC) in relation to BMI, 2003/04.

		Classification - IMC							
Fat distribution indexes		OB I		PO		E		MN I	
		n	%	n	%	n	%	n	%
W/HR	High	1	25	13	52	20	33.9	2	11.1
	Normal	3	75	12	48	39	66.1	16	88.9
WC	High	2	50	4	16	1	1.7	0	0
	Normal	2	50	21	84	58	98.3	6	100

OB I = level-I obesity
PO = pre-obesity
E = eutrophy
MN I = level-I malnourishment

Table 4. Results of the univariate linear regression analyses between treatment duration and body fat indexes of 94 HIV-positive individuals undergoing HAART and assisted at the Nutrition and Tropical Diseases Outpatient Hospital, Botucatu Medical School - São Paulo State University (FMB - UNESP), 2003/04.

Body fat distribution indexes	R^2	F	β	p
Trunk/arm index**	0.027	2.5	0.164	0.12
WC	0.041	3.963	0.203	0.049*
W/HR	0.09	9.072	0.3	0.03*

* $p < 0.05$

** Trunk/arm index = (SSCF+SICF)/(TCF+BCF)

WC = waist circumference

W/HR = waist-to-hips ratio

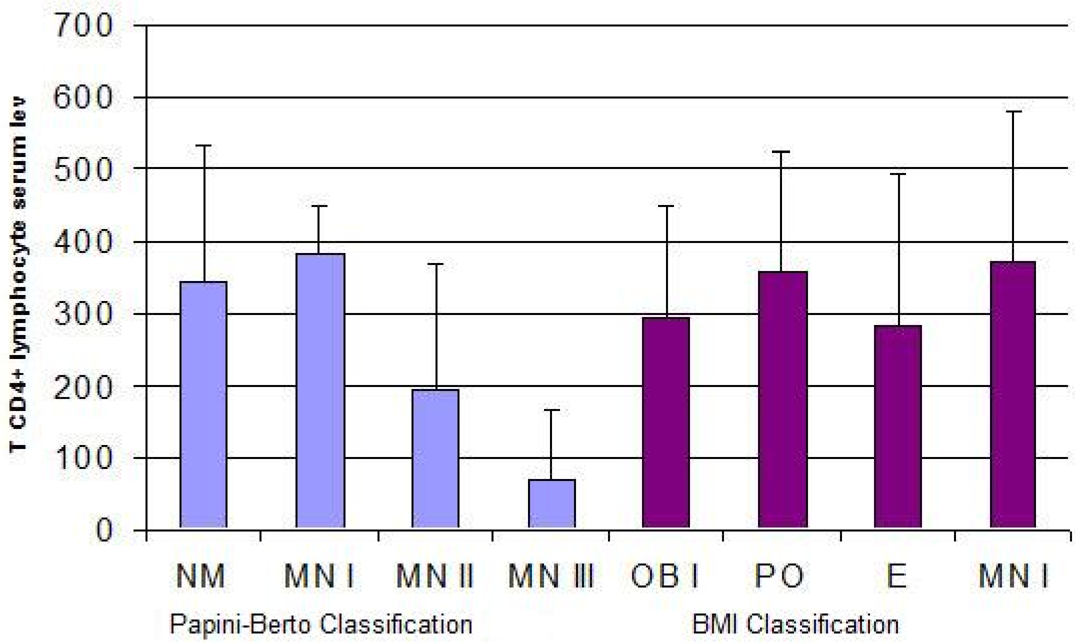

Figure 1. Association between serum T $CD4^+$ lymphocyte means and the Papini-Berto and BMI nutritional classifications of 94 HIV-positive individuals undergoing HAART and assisted at the Nutrition and Tropical Diseases Outpatient Hospital, Botucatu Medical School - São Paulo State University (FMB - UNESP), 2003/04. (NM = non-malnourished; MN I = mild malnourishment; MN II = moderate malnourishment; MN III = severe malnourishment; OB I = level-I obesity; PO = pre-obesity; E = eutrophy).

DISCUSSION

Different indicators and classifications were used for nutritional diagnosis with the purpose to characterize the profile of HIV-positive individuals, observe the performance of different classifications for malnutrition diagnosis and identify the association between fat distribution indicators and global nutritional state indicators and therapy duration. In summary, it was observed that, by using the BMI/WHO classification, malnutrition frequency was low (less than 10%), and more than one third of the individuals showed overweight. Nevertheless, when using the nutritional classification proposed by PB, which takes into account anthropometric and biochemical parameters, a much higher frequency was found, that is, more than three times as many malnourished individuals.

The results obtained with the BMI/WHO nutritional classification are in agreement with those from a British study in which the researchers found a 6% prevalence of low weight in individuals infected with HIV under HAART by using the same BMI/WHO criteria (21). Similarly, they agree with another Brazilian study which identified a 30.5% prevalence of overweight HIV-positive patients attending a healthcare facility in the city of São Paulo (22).

On the other hand, malnutrition prevalence according to the PB classification was similar to that obtained in studies performed in the pre-HAART era, such as that found by Niyongabo *et al.* (32) in Paris, in which a high prevalence of ponderal deficit (34.8%) was found (32). However, there is a cohort study from the HAART era in which 33.6% of the participants showed low weight or weight loss that were characteristic of cachexia (43).

Which indicator could then best express the prevalence of malnutrition in HIV-positive patients? In this study, the analysis of performance of the nutritional classification proposed by PB in relation to BMI showed that the former presented high sensitivity and good specificity for malnutrition diagnosis in relation to the BMI measurement. Its use could lead to the identification of many false positives (malnourished). Or are the individuals classified as malnourished by PB in fact so?

An attempt to answer such question would be the observation of the lower T $CD4^+$ lymphocyte count in these individuals, that is, the more severe the disease, the worse the nutritional state. This hypothesis was partly verified. By dividing the individuals into two groups based on the PB classification – level-II and level-III malnutrition and other situations – there was an inverse association with an immunologic indicator known as a disease severity marker. Hence, it seems to be more acceptable to consider that 20% of the patients (level-II and level-III malnourished individuals according to PB) and not 6% (malnutrition frequency according to BMI < 18.5kg/m²) were in fact malnourished. The findings in this study indicate that the classification adapted from PB seems to better detect malnutrition in patients with AIDS, whereas the use of BMI seems to underestimate it.

Based on these results, we propose a possible malnourishment classification in HIV patients: severe malnutrition, when the individual presents at least three of the five parameters (BMI, TCF, AMC, albumin and lymphocytes) below the 5^{th} percentile; moderate malnutrition or MN II, when the individual presents two of those five parameters below the 5^{th} percentile, two of which may be anthropometric parameters or one anthropometric associated with a laboratory parameter; non-malnourished, for those who do not present any of the previously cited conditions. The importance of some biochemical indicators for diagnosing the nutritional state of individuals with AIDS was proposed in a Spanish tudy carried out by Guerra *et al.* (18).

Concerning the identification of fat in the abdomen, as evaluated by WC, there was significant difference according to sex, and it was prevalent in females. These data are in agreement with the Brazilian study conducted in the city of São Paulo in which abdominal obesity detected by WC was significantly prevalent in women (22). Another study, a prospective cohort of HIV-positive patients in Spain who were followed in the mid-1990s and undergoing HAART, central obesity as evaluated by physical examination was also more frequent in women (28).

The prevalence of abdominal obesity evaluated by the waist-to-hips ratio did not differ between the sexes, contrarily to what was observed in another Brazilian study (23). Again, we face another question: What would the best abdominal indicator be?

There were individuals who were classified as presenting abdominal obesity by W/HR among those with BMI in the normal range or even with low weight, which was not expected. This result can be attributed to morphological alterations, such as the decrease in hips circumference and increase in waist circumference in HIV-positive patients undergoing HAART. This effect (body fat redistribution), more than the excessive accumulation of abdominal fat, may have been detected by the W/HR measurement, a fact that is of utmost importance at the present life of these individuals in face of the lipodystrophy syndrome. Other authors have pointed out the importance of the waist-to-hips ratio in lipodystrophy detection as well as the value of WC as a specific indicator of abdominal fat accumulation (10, 15, 40).

In this study, it was possible to observe that W/HR and WC were significantly associated with HAART duration, and such association was more significant in the case of W/HR. Various studies have related the use of HAART with the development of the lipodystrophy syndrome (3, 5, 8, 19, 30).

The trunk-arm index used in this study as a fat redistribution parameter, particularly of atrophy in upper limbs and abdominal accumulation, was higher in males, thus showing that men presented greater subcutaneous fat loss from their arms. A study by Muurahainen *et al.* (31) reported that men with AIDS have greater tendency to develop lipoatrophy of the limbs (31). However, this index was not associated with HAART duration, which does not support its use as a lipodystrophy marker in this population. Further studies are necessary in order to evaluate this index in patients with AIDS.

In summary, the findings in this study clearly indicate that, in AIDS patients undergoing HAART, the major nutritional problems are overweight, obesity and lipodystrophy. Nevertheless, even in the HAART era, the number of malnourished individuals is not small (20%), and the early detection of malnutrition is still a priority. According to the results found, an adapted classification of the proposal by PB based on anthropometric and biochemical measurements is suggested as a criterion for malnutrition detection in this group of individuals. BMI and W/HR are recommended for detection of overweight and body fat redistribution, respectively, while waist measurement would be useful for detection of abdominal obesity and risk for non-transmittable chronic diseases.

The use of nutritional evaluation protocols with standardized techniques, indicators and classifications is fundamental to prevent, detect, monitor and treat nutritional alterations presented by AIDS patients as well as to enable comparisons between studies and populations.

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