

Lipid Accumulation Product Index to Predict Metabolic Syndrome in People Living with HIV

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The Research Ethics Committee of the Federal University of Minas Gerais approved the present study, under the protocol number 0251.0.203.000-11, and all participants gave written informed consent.

ABSTRACT

Background: Dyslipidemia and central obesity are the main components of metabolic syndrome (MS), which represent important risk factors for cardiovascular diseases in people living with HIV. The lipid accumulation product (LAP) index has been shown in studies as an efficient marker of MS in general adult population and its applicability in HIV-infected population is not discussed. We aimed to assess the accuracy of the LAP index to identify MS in people living with HIV.

Methods: It is a cross-sectional study with 141 HIV-infected patients on antiretroviral therapy, conducted in a reference centre of infectious diseases in southeast Brazil. Evaluations included LAP index, anthropometric measurements and clinical and laboratorial variables. MS was defined by International Diabetes Federation (IDF) criteria.

Results: The prevalence of MS in our sample was 10.6%. A positive and significant correlation was found between the MS and LAP ($r=0.401$; $p<0.01$), MS and body mass index ($r=0.361$; $p<0.01$) and MS and waist circumference ($r=0.427$; $p<0.01$) in our sample. The analysis of the receiver-operating characteristic (ROC) curve revealed that the best cut-off value for LAP index to define MS was 59.4 (sensitivity 80%, specificity 79% and area under the curve (AUC) of 0.875. In female and male, analysis of the ROC curve revealed that the best cut-off value for LAP index to define MS was 56.3 (sensitivity 100%, specificity 82% and AUC of 0.929) and 52.0 (sensitivity 78%, specificity 74% and AUC of 0.838), respectively.

Conclusion: Despite the low prevalence of MS in our sample, the ROC curves analyzes demonstrated a good diagnostic accuracy as an additional screening tool of MS according to the IDF.

Keywords: HIV; Metabolic syndrome; Lipid accumulation product

BACKGROUND

Globally, cardiovascular diseases represent about 30% of deaths every year and it is the leading cause of morbidity and mortality worldwide.¹ Compared with the overall population, people living with HIV (PLWH) have higher cardiovascular risk.² Shah *et al.* (2018)³ reported, in their systematic review of longitudinal studies, that the relative risk of cardiovascular diseases in PLWH is 2.16 higher than uninfected population.³

Despite the considerable increase of the survival of PLWH due to the success of antiretroviral therapy (ART), long-term ART has been associated with metabolic and cardiovascular complications as it has become an important challenge in the clinical management of HIV infection.^{4,5} Dyslipidemia and central obesity are the main components of metabolic syndrome (MS), which represent important risk factors for cardiovascular diseases.⁶

There are several criteria for diagnoses of MS. The International Diabetes Federation (IDF) criteria which is focused on the presence of central obesity, evaluated by waist circumference (WC) adapted to anthropometric profile of the various populations.⁶

Among the anthropometric parameters to estimate body fat [Body mass index (BMI)] and measurement of adiposity (WC, waist-to-height and conicity index), the lipid accumulation product (LAP) index had been proposed as an easier and useful tool to predict lipid accumulation.^{7,8}

Described for the first time by Kahn *et al.* (2005),⁷ the LAP index is calculated by the combination of waist circumference (cm) and fasting triglycerides (TG) levels (mmol/L). The LAP index has been shown in studies as an efficient marker of MS in adult populations^{8,9,10} and it is mainly discussed in studies with women with polycystic ovary syndrome, which metabolic abnormalities are common as well.^{11,12}

The great variety of diagnostic methods for the detection of MS makes it difficult to compare the results of the studies that evaluate this comorbidity in PLWH. In view of the simplicity of execution and standardization of the measures that are part of the LAP index, this study aims to analyze the LAP index's ability to identify PLWH with MS according to IDF criteria after beginning of ART.

METHODS

Study Design and Participants

It is a cross-sectional study with 141 PLWH in use of antiretroviral, conducted in a Reference Centre of Infectious Diseases in southeast Brazil. All the participants of this study have had medical indication for the beginning of ART.

On average, 120 PLWH receive ART per year in this reference centre of infectious diseases. Regarding the sample calculation, we worked with MS prevalence of 16.7% in PLWH according to the overall prevalence found in meta-analyses of Nguyen *et al.* (2016).¹³ The margin of error of this study is $\pm 5\%$ and 99.99% of confidence level. The minimum sample size calculated was 105 individuals.

Ethical Considerations

The Research Ethics Committee of the Federal University of Minas Gerais approved the present study, under the protocol number 0251.0.203.000-11, and all participants gave written informed consent.

Data Collection

The data were collected through anthropometric, clinical and laboratorial evaluations. Height and weight were collected using standardized procedures by the World Health Organization (WHO).¹⁴ In order to measure height, the stadiometer of the anthropometric scale of the brand “Filizzolla®” was used. Body weight was determined on an anthropometric scale of the Tanita brand with a capacity of 150 kg. WC was defined as the measurement at the midpoint between the lateral iliac crest and the lowest rib.¹⁵ BMI was calculated as weight (kg) divided by height (m²).

A modified WHO STEPS cardiovascular risk data surveillance questionnaire was administered to collect data about physical activity and lifestyle. The collected data was registered in specific forms.

Assays

Blood samples were taken after a 12-h overnight fast. Plasma glucose, total cholesterol (TC) and TG were determined enzymatically (Vitros Chemistry Products, Johnson & Johnson Clinical Diagnostics®, Rochester, USA). High density lipoproteins (HDL) was measured using an immuneinhibition assay (Labtest Diagnosis®, Lagoa Santa, Brazil), and insulin was measured by chemiluminescence (Diagnostic Products Corporation®, Los Angeles, CA, USA).

Low density lipoproteins (LDL) was calculated. LDL was not evaluated in patients with triglyceride levels above 400 mg/dl.

CD4+ T lymphocytes count were obtained by flow cytometry (FACSCalibur Becton & Dickinson, USA) using BD Multitest kits (Becton Dickinson, USA). Plasma viral load was determined by Real Time PCR (Abbott RealTime HIV-1 assay) (Abbott, USA).

Definitions

The IDF classifies patients with MS according to the presence of abdominal obesity (WC > 94cm for men and > 80cm for women), as a condition sine qua non, and two or more criteria, such as: TG > 150mg/dl; HDL < 40mg/dl for men and < 50mg/dl for women; systolic arterial pressure > 130mmHg or treatment for hypertension and diastolic arterial pressure > 85mmHg or treatment for hypertension; and raised fasting plasma glucose \geq 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes.⁶

LAP index is determined by the following equation for women: $(WC [cm] - 58) \times (TG [mmol/L])$ and for men: $[WC (cm) - 65] \times TG (mmol/L)$.

Statistical Analyses

All statistical analyses were performed using *SPSS*, version 20.0 for Windows (Chicago, IL, USA).

The data were described as measures of central tendency (mean or medians) and measures of dispersion [standard deviation (SD) or interquartile range (IQR)] for numerical

variables. To check data normality, the Shapiro-Wilk test was applied. A variable was considered as having a normal distribution if p -value < 0.05 and as asymmetrical distribution if p -value > 0.05 . Continuous variables were compared using the Mann–Whitney test.

The non-parametric Spearman rank correlation coefficient was used to assess agreements between MS and the continuous independent variables (BMI, WC and LAP index).

Variables with p -value < 0.1 related to the increase in MS by univariate analysis were considered candidates for the logistic regression model. Stepwise backward logistic regression was used in the construction of multivariate model. Calibration and discrimination of the models were determined by the Hosmer-Lemeshow test and the receiver-operating characteristic (ROC) curve analysis, respectively.

For all tests, they were considered as level of statistical significance a p -value < 0.05 .

RESULTS

The study included 141 PLWH with a median beginning of ART of 7.5 months [IQR 28] and median ART of 24 months [IQR 8]. The median age was 37 years [IQR 14]. Women were statistically older and there were no statistically significant differences between the sexes in relation to their schooling, current smoker, sedentary lifestyle, blood pressure, fasting glucose, BMI, WC, TG, TC, LAP index and MS. **Table 1** summarizes the demographic, lifestyle, clinical and laboratorial variables of the overall study sample and categorized by sex. It was

possible to observe that men had higher alcohol consumption, weight, LDL and lower HDL when compared with women.

A positive Spearman's rank correlation (r) was found between the MS and LAP (0.4007; p -value < 0.01), MS and BMI (0.3606; p -value < 0.01) and MS and WC in our population (0.4274; p -value < 0.01).

Overall, the analysis of the ROC curve revealed that the best cut-off value for LAP index to define MS was 59.4 (sensitivity 80%, specificity 79% and area under the curve (AUC) of 0.875). In female population, the analysis of the ROC curve revealed that the best cut-off value for LAP index to define MS was 56.3 (sensitivity 100%, specificity 82% and AUC of 0.929. In male, the ROC curve revealed the best cut-off value was 52.0 (sensitivity 78%, specificity 74% and AUC of 0.838 (**Figure 1**).

DISCUSSION

This is the first study to assess the LAP index to predict MS in PLWH. In Brazil, a cross-sectional epidemiological study conducted with 211 public employees in Belo Horizonte, the analysis of ROC curves showed that the LAP index was a significant discriminator for MS with sensitivity and specificity greater than 80% in the best cutoff identified in all diagnostic criteria analyzed (NCEP-ATP III updated, IDF, AHA/NHBLI and harmonized NCEP-ATP III/IDF).⁸

Guimarães *et al.* (2018)¹⁶ demonstrated in a cross-sectional analysis prior to this study that the LAP index was correlated with the homeostasis model assessment - insulin resistance (HOMA-IR) index, a useful surrogate index of insulin resistance, constituting an additional risk factor to cardiovascular diseases in male HIV-infected patients. Unlike our study, patients with metabolic disorders such as hyperlipidemia, diabetes mellitus and lipodystrophy prior to the diagnosis of HIV-infection was excluded. The authors suggested that the screening of LAP and HOMA-IR index as part of the clinical protocol of this population could be useful even before the beginning of the symptoms of cardiovascular diseases.¹⁶

The LAP index presented a good diagnostic accuracy of MS in our population according to the IDF criteria, as all the areas under the curve (AUC), overall and for both sexes, were above 0.80 (85%). Our findings are corroborated by studies that evaluated the LAP index to identify MS in the overall population.^{8,10,17} Ray *et al.* (2018)¹⁷ has shown that LAP index is a better predictor of MS compared to BMI and WC and has high sensitivity and specificity.

In our study, the LAP index presented a weak positive correlation with MS as well as the other anthropometrics markers evaluated. The low prevalence of MS in our sample may have affected the correlation analysis between the variables, yet the correlation between MS and LAP index was similar to the correlation between MS and BMI. BMI is the anthropometric markers most widely adopted in the clinical practice to evaluate alterations in body mass. Considering the LAP index, which is based on a combination of WC and fasting TG levels, may better reflect the combined anatomic and physiological changes associated with lipid over accumulation than the BMI.

The prevalence of MS in our study is lower than other similar studies in HIV-infected population on ART.¹⁸⁻²⁰ The regular medical care, nutritional support, psychological counseling and support groups available at the health service may be contributed with this low prevalence of MS in our sample. Besides that, the median age of our sample is lower when compared with these studies. The HIV infection is a chronic condition and the aging of this population increases the risk of non-infectious diseases and development of components of MS.²¹

The higher prevalence of metabolic disorders in PLWH and its relation to the development of cardiovascular diseases are described in the literature. Many studies were demonstrated that higher values of BMI, waist-hip ratio, diastolic arterial pressure, TG and low HDL at the beginning of ART can be significantly associated with the development of MS.²²⁻²⁴

This study has been shown that LAP index, as anthropometric marker for identifying individuals with MS, can be promisor and useful in the screening of the PLWH. However, the accuracy of the LAP index must be assessed in other studies to validate its real accuracy in this population.

The low prevalence of MS that may have overestimated the accuracy of the LAP index to identify MS in our sample would be one the limitations of this study. Our sample is representative of the population of a reference centre of infectious diseases in Southeast Brazil. Therefore, the results of this study may not be generalizable to other PLWH. In addition, the design of this study did not evaluate the validity of the LAP index for incident

cases of MS. The cross-sectional design does not allow determining how long the individuals diagnosed with MS have this clinical condition and whether this is due to or preceded by ART. Therefore, we suggest that longitudinal studies can better identify the application of the LAP index as a predictor of MS in PLWH.

CONCLUSION

Despite the low prevalence MS in our sample, the ROC curves analysis demonstrated a good diagnostic accuracy of the LAP index in order to predict MS according to the IDF criteria. These data reinforce the applicability of LAP as a tool for diagnostic screening.

The early detection of who are prone to develop MS will enable therapeutic interventions in order to reduce the development of cardiovascular diseases and provide a better quality of life to PLWH.

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Table 1. Clinical and metabolic features in PLWH after beginning of ART (n=141).

Variables	Overall (n=141)	Male (n=107)	Female (n=34)	P value
Age (years)	37 [14]	35 [14]	44.5 [7]	<0.001 ^ε
Schooling				
< 7 years	61 (43.3%)	43 (40.2%)	18 (52.9%)	0.13 ^{&}
≥ 7 years	80 (56.7%)	64 (59.8%)	16 (47.1%)	
Current smoker	28 (19.9%)	22 (20.6%)	6 (17.6%)	0.46 ^{&}
Alcohol consumption				
≥ 3 times per month	84 (59.6%)	70 (65.4%)	14 (41.2%)	0.01 ^{&}
< 3 times per month	57 (40.4%)	37 (34.6%)	20 (58.8%)	
Sedentary lifestyle	40 (60.6%)	21 (46.7%)	11 (50.0%)	0.81 ^{&}
Blood pressure (mmHg)				
Systolic	120 [20.0]	120 [20.0]	120 [20.0]	0.89 ^ε
Diastolic	80 [10.0]	80 [10.0]	80 [10.0]	0.96 ^ε
Fasting glucose (mg/dl)	88.0 [11.0]	89.0 [11.0]	87.0 [11.0]	0.38 ^ε
Weight (Kg)	72.6 [18.3]	75.0 [17.3]	65.0 [16.4]	<0.001 ^ε
BMI (Kg/m ²)	25.0 [5.8]	25.0 [5.3]	24.4 [7.0]	0.69 ^ε
WC (cm)	86.0 [18.0]	86.0 [17.5]	86.0 [20.4]	0.94 ^ε
TG (mg/dl)	111.0 [92.3]	108.0 [90.0]	118.0 [107.0]	0.16 ^ε
TC (mg/dl)	182.4 (±41.7)	176.0 (±41.4)	201.3 (±37.3)	0.50 ^ε
LDL (mg/dl)	131.0 [5245.0]	154.0 [7766,3]	114.0 [42.0]	0.007 ^ε
HDL (mg/dl)	44.0 [15.0]	42.0 [12.5]	54.0 [25.0]	0.005 ^ε
LAP index	34.4 [47.3]	34.1 [42.2]	36.1 [53.2]	0.70 ^ε
MS	15 (10.6%)	9 (8.4%)	6 (17.6%)	0.12 ^{&}

Note: BMI - Body mass index; HDL - High density lipoproteins; LAP index - Lipid accumulation product index; LDL - Low density lipoproteins; MS - Metabolic Syndrome; TC - Total Cholesterol; TG - triglycerides; WC - Waist circumference. ^εMann-Whitney test; [&]Chi-square Test; ^εT-test

Figure 1. ROC curve for lipid accumulation product index as a marker of metabolic syndrome.

