What should we know about metabolic syndrome and lipodystrophy in AIDS?

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SUMMARY

Objective: Prevalence of chronic complications of HIV infection is increasing and early recognition and treatment of the components of metabolic syndrome (MS) are essential to prevent cardiovascular and metabolic complications. Considering this, we performed a cross-sectional study on the prevalence and risk-factors for MS among HIV-infected subjects. Methods: A total of 819 patients followed at a large outpatient HIV unit were assessed by an interviewer-administered questionnaire that recorded several demographic, epidemiologic, clinical, laboratory, and social variables. Lipodystrophy diagnosis relied on agreement between patient’s self-report and physician’s observation of altered body-fat deposits. The presence of three or more of the following characteristics identified MS: increased waist circumference, hypertriglyceridemia, low HDL cholesterol level, hypertension, and hyperglycemia. We used logistic regression analyses to study variables independently associated with MS. Results: The prevalence of MS was 20.6% and that of lipodystrophy was 38.5%. 61 (36.1%) out of 169 patients with MS had also lipodystrophy. Patients with metabolic syndrome were significantly more likely to be older (OR = 1.08), had higher CD4 counts (OR = 1.001), had an increased body mass index (OR = 1.27) and had longer exposure to antiretroviral therapy (OR = 1.01) than those without metabolic syndrome. Conclusion: Both traditional risk factors for cardiovascular disease and factors associated with HIV infection itself, such as an increased CD4 cell count and a longer exposure to antiretroviral therapy, seem to be associated with metabolic syndrome in the present study population.

Keywords: Metabolic syndrome X; antiretroviral therapy, highly active; HIV-associated lipodystrophy syndrome; HIV; risk factors; cross-sectional studies

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INTRODUCTION

Increased survival experienced by HIV-infected patients after the advent of highly active antiretroviral therapy (HAART) has been followed by the frequent occurrence of chronic metabolic abnormalities, such as dyslipidemia, the metabolic syndrome (MS), and HIV-related lipodystrophy (LD-HIV).  

MS is defined as the presence of abdominal obesity, insulin resistance, hypertension, and dyslipidemia. It is highly prevalent in both general and HIV-infected populations. MS is strongly associated with the development of type 2 diabetes mellitus and coronary atherosclerosis. MS is associated with the current obesity epidemic – more than 1 billion adults are overweight and at least 300 million of them are clinically obese. Data from the World Health Organization show that in Brazil 54% of males and 60% of females over 15 years are overweight or obese. These figures reflect the profound changes in alimentary and in behavioral patterns over recent decades, with increased consumption of more energy-dense, nutrient-poor foods with high levels of sugar and saturated fats, combined with reduced physical activity.

LD-HIV can be disfiguring cosmetically, and the physical findings may stigmatize the individual as one living with HIV infection, a worrisome complication due to its negative psychological impact on mood, self-esteem and, possibly, on adherence to treatment. LD-HIV is composed of three patterns of an altered body fat redistribution as follows: lipoatrophy, lipohyperthrophy, and simultaneous development of lipoatrophy and lipohyperthrophy. These syndromes of fat redistribution may or may not be associated with dyslipidemia and insulin resistance. Its onset may be related to the progression of HIV infection itself, to host-related factors and to the exposure to different antiretroviral agents.

MS pathogenesis emerges from fat deposition, especially in the visceral-abdominal region. Its pathogenesis is more comprehensive considering the concept of ectopic fat deposition, especially in liver and muscle, with consequent reduction in insulin sensitivity. Fat deposit in organs like liver and muscle has an important role in determining insulin resistance. The lack of peripheral fat tissue, as occurs in lipodystrophy, would lead to excessive fat storage in liver and muscle. As the prevalence of chronic metabolic disorders is increasing on HIV-infected population, and since the early recognition and treatment of MS are essential to the prevention of its complications, we performed a cross-sectional study on the prevalence and risk-factors for MS, and its association with LD-HIV, among HIV-infected patients followed at a large outpatient HIV unit in Rio de Janeiro, Brazil.

METHODS

All HIV-infected patients enrolled in the study were sequentially recruited between January and May 2005, as part of their scheduled visit to the Immunology Laboratory at Hospital Universitário Gaffrée & Guinle to perform routine CD4 cell count and plasma HIV viral load measurements, as requested by their attending physicians. Patients were eligible if they were aged ≥ 18 years and were under regular follow-up in the outpatient unit. Exclusion criteria were: pregnancy, lower extremity edema, ascites and psychiatric disorder which hinder the patients’ self-assessment of the body shape. Patients were invited to participate in the study after an oral explanation of its objectives and methods and those willing to take part were asked to provide a signed informed consent. The study protocol was reviewed and approved by the Ethics Review Board at Hospital Universitário Gaffrée & Guinle and there were no external funding sources for this study.

LD-HIV diagnosis relied on agreement between the patient’s self-report questionnaire and physician’s examination of the following altered body areas: the presence of peripheral fat wasting with loss of subcutaneous tissue in either the face (temporal and maxillary wasting), arms, legs and/or buttocks, classified as lipoatrophy; the presence of either enlargement of dorsocervical fat pad (“buffalo hump”), circumferential expansion of the neck, breast enlargement or abdominal visceral fat accumulation, classified as lipohyperthrophy; or a combination of both lipoatrophy and lipohyperthrophy features, classified as mixed lipodystrophy.

The diagnosis of LD-HIV relied on the presence of at least one readily noticeable sign in tandem with another mild sign of the altered body fat compartment as mentioned before, the agreement between physician’s and participants’ self-report evaluations concerning the body fat compartments examined, and the absence of any signs of AIDS defining illnesses in the 30 days before their appointments. Increased abdominal girth was considered as a valid sign of altered body fat compartment.

MS was identified according to National Cholesterol Education Program-Adult Treatment Panel III (NCEP) criteria by the presence of three or more of the following: waist circumference greater than 102 cm in men and 88 cm in women; triglycerides ≤ 150 mg/dL; HDL cholesterol < 40 mg/dL (men) and < 50 g/dL (women); arterial blood tension ≥ 130/85 mmHg and fasting glucose ≥ 110 mg/dL.

Differences between categorical and continuous expressed as mean ± standard deviation (SD) variables were compared by applying the chi-square (χ^2) test and Student’s t-test, respectively. Statistical significance was
determined as a p-value of < 0.05. A logistic regression analysis was also used to identify variables independently associated with MS. Age, sex, body mass index (BMI), smoking, alcohol consumption, CD4 cell count, exposure and duration of antiretroviral therapy, use of a protease inhibitor, plasma HIV viral load, and lipodystrophy were used as explanatory variables. Those found to have a p-value < 0.20 were included in the multivariate model. Hosmer-Lemeshow tests were performed to assess the goodness-of-fit of the logistic regression model. Odds ratio (OR) and 95% confidence intervals (95% CI) were reported along with p-values. The null hypothesis was rejected in each statistical test when p-value was < 0.05. Statistical analyses were performed by using the free software R, version 2.9.113.

Results

A total of 819 patients were included in the study. Among these, 447 (54.6%) were male and 372 (45.4%) were female, with a mean (± SD) age of 41 (± 11) years (range 18-75) and a mean BMI of 24 (± 4.4) kg/m² (range 14-49). The vast majority (n = 767, 93.6%) of patients attributed the acquisition of HIV infection to unprotected sexual intercourse. The remaining patients imputed HIV infection to blood transfusion or blood products (n = 35, 4.3%) and to intravenous drug use (n = 10, 1.2%). Seven (0.9%) patients considered that the infection route was indeterminate. Table 1 shows the distribution of demographic, epidemiological, clinical and social variables.

More than two-thirds (n = 623, 76.1%) of the patients were receiving HAART, with a mean duration of therapy of 54 (± 36) months (range 1-158). Patients on treatment were currently receiving two nucleoside reverse transcriptase inhibitors as a treatment backbone in combination with either one or two protease inhibitors (n = 226, 27.6%) or one non-nucleoside reverse transcriptase inhibitor (n = 397, 48.5%). Most of the treated patients (n = 487, 90%) reported a good compliance to the HAART regimen (Table 1).

However, a total of 198 (24.2%) patients on more than 12 months of treatment had a plasma HIV viral load above 100 copies/mL. Patients with longer treatment histories were more likely to have a viral load above detection limits. A quarter (n = 215, 26.2%) of these patients also presented comorbidities such as hypertension (16.7%), other cardiovascular diseases (5.6%), and diabetes mellitus (3.9%). A family history of diabetes and cardiovascular disease was recorded from 38% and 55%, respectively.

The prevalence of MS was 20.6% (n = 169) and that of LD-HIV was 38.5% (n = 280 out of 721). Sixty-one patients were found to have both MS and LD-HIV. A total of 704 out of 819 (86%) patients had at least one component of MS. A low HDL-cholesterol level (91%) was the most prevalent component of diagnostic criteria for MS followed by hypertriglyceridemia (87.1%), increased blood pressure (78.8%), increased waist circumference (42.2%) and hyperglycemia (31.8%).

In a subgroup of 623 patients receiving HAART, patients with MS were more likely to be older, fatter, had a longer exposure to antiretroviral therapy and had greater CD4 cell counts than those without MS. There was no difference in the mean BMI (both groups = 24 kg/m², t-test = 0.66, p-value = 0.51) and plasma HIV viral load (t-test = 0.86, p-value = 0.40) between these groups. Nonetheless, patients with MS were less likely to be adherent to the treatment (chi-square = 3.98, p < 0.05) (Table 2).

We were able to screen a total of 721 patients for physical signs of LD-HIV and found a prevalence of 38.5% (280). LD-HIV and MS were not statistically associated in this study (chi-square test = 0.94; p-value = 0.33),
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Among patients receiving HAART; 58 (23.3%) out of 249 patients with LD-HIV also had MS, while a half of 116 patients with MS had concomitant LD-HIV diagnosis. Isolated lipoatrophy (45%) was the most frequent pattern observed among patients with LD-HIV, followed by a mixed pattern (42.9%) and isolated lipohyper trophy (12.1%).

The multiple logistic regression model included CD4 cell count, duration of antiretroviral therapy, age, and BMI as explanatory variables (Table 3). For every 10 years increase in age and every 100 cells/mm$^3$ increment in CD4 cell count, the risk for a diagnosis of MS increases by 80% and 10%, respectively. The risk of MS increased 1% for every 10 months increase during antiretroviral exposure. Likewise, the risk of having a diagnosis of MS increased 27% for every gain of 1 kg/m$^2$ in BMI.

**DISCUSSION**

We found a high prevalence of MS (20.6%) in the present study population of HIV-infected patients followed at a large outpatient unit in Rio de Janeiro. This figure is similar to the prevalence of MS found in a study that enrolled patients under HAART from seven Latin American countries (20.2%)$^{14}$, in a large cross-sectional Italian study performed by Bonfanti et al. (20.6%)$^{15}$ and to the data reported by Mondy et al. (25.5%). In a Brazilian cohort from Paraná, a study carried out by Diehl et al., the prevalences of LD-HIV and MS were found to be 55% and 36%, respectively. These higher prevalences, when compared to the present study, are probably due to their higher proportion of patients receiving HAART (87%) and their longer exposure to antiretroviral therapy (77 months). Both these factors have been broadly recognized as associated with LD-HIV$^{9,17}$. There is, however, controversy in the literature concerning the importance of HIV treatment-associated factors in the development of MS. Some studies$^{14,18,19}$, including the present one, have found that the duration of antiretroviral exposure is significantly associated with MS, while others found no such an association$^{15,16}$. We believe that these conflicting results are due to population heterogeneity regarding genetic factors as well as different behavior characteristics, such as diet, physical activity, alcohol consumption and smoking.

Few studies on the prevalence of MS in the general Brazilian population are available. Our age estimate risk for MS is very similar to that reported from a large and longitudinal Latin American multicenter study (OR: 1.05 per year)$^{10}$. A population-based study con-

### Table 2 – Differences between HIV-infected patients receiving antiretrovirals with and without metabolic syndrome

<table>
<thead>
<tr>
<th>Variables</th>
<th>No (n = 650)</th>
<th>Yes (n = 169)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>40 (± 10)</td>
<td>46 (± 10)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI*</td>
<td>23 (± 3.7)</td>
<td>27 (± 5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of antiretroviral therapy (mo)*</td>
<td>52 (± 37)</td>
<td>63 (± 39)</td>
<td>0.003</td>
</tr>
<tr>
<td>Receiving PI</td>
<td>184 (28%)</td>
<td>40 (24%)</td>
<td>NS</td>
</tr>
<tr>
<td>Adherence to antiretroviral therapy</td>
<td>379 (88%)$^1$</td>
<td>108 (95%)$^1$</td>
<td>0.05</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm$^3$)*</td>
<td>370 (± 216)</td>
<td>455 (± 284)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Viral load (log/mL)*</td>
<td>3.2 (± 1.3)</td>
<td>3 (± 1.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Lipodystrophy**(n = 721)</td>
<td>219 (38%)$^4$</td>
<td>61 (42.4%)$^£$</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Mean (±SD); mo, month; $^t$-test p-value; $^*$Adherence, corresponding to taking ≥ 95% of the total pill burden prescribed in the previous week; $^i$out of 429 patients; $^j$out of 114 patients; $^k$out of 577 patients; $^l$out of 144 patients; **(n = 721), 721 patients were screened for lipodystrophy.

### Table 3 – Risk factors for metabolic syndrome

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Age$^a$</td>
<td>1.07 (1.04, 1.09)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CD4 cell count$^b$</td>
<td>1.001 (1.001, 1.002)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI$^b$</td>
<td>1.22 (1.2, 1.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of ARV$^b$</td>
<td>1.008 (1.003, 1.014)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

$^a$Continuous variable; $^b$month; BMI, body mass index, OR, odds ratio; 95%CI, 95% confidence interval; ARV, antiretroviral therapy. Hosmer and Lemeshow Test = 2.963, p value = 0.94
ducted in Vitória found a prevalence of MS of 29.8% in general population. Prevalence increased from the youngest (26-34 years) to the oldest (55-64 years) age groups (15.8% and 48.3%, respectively). The BMI is a traditional risk factor for MS, and our results corroborate to this assertive, because the prevalence of MS augmented among overweight (≥ 25 kg/m²) patients as it was also observed in other Brazilian studies and elsewhere.

In our study, patients with MS were more likely to have greater CD4 cell counts. Similar findings were reported by an American study where mean CD4 cell count was significantly higher in patients with MS when compared to patients without MS (542 cells/mm³ vs. 417 cells/mm³).

We and others have found that a low HDL-cholesterol is the most common metabolic abnormality, followed by hypertriglyceridemia. Otherwise, a Brazilian population-based study conducted by Salaroli et al. found that the most frequent component of the MS in males was arterial hypertension, followed by hypertriglyceridemia, low HDL-cholesterol, hyperglycemia and increased waist circumference, whereas low HDL-cholesterol, increased waist circumference, hypertriglyceridemia and hyperglycemia were the most frequent in females. In contrast to our findings, another Brazilian study carried out in São Paulo found that the most prevalent components were, in order of frequency, hypertriglyceridemia, increased waist circumference, hyperglycemia, low HDL-cholesterol and hypertension.

As the HIV-infected population grows older, MS will likely become increasingly prevalent. Some authors found 81% and 88% of HIV-infected patients with at least one of the individual components of MS. These estimates were very consistent with our findings. Cardiovascular risk factors were highly prevalent in our study population. Our findings were very consonant with those of Silva et al., who found 27% and 18% prevalences of smoking and hypertension, respectively. The striking prevalence of familiar history of cardiovascular disease verified among our patients was also consistent with 40% and 31% previously reported in the literature.

It is also remarkable the difference on prevalences of MS observed between the studies of Diehl et al. and ours (36% vs. 20%). It might be explained by the higher proportion of patients with an isolated or combined hypertrophy pattern of LD-HIV observed in their study. Under these circumstances, the increased abdominal girth, visceral adiposity and its associated metabolic disturbances are more prevalent, and it could have added to the emergence of surplus cases of MS seen in their study.

Studies on MS among Brazilian HIV-infected patients are scarce as well as on its association with LD-HIV. In our research and in the study by Diehl et al., the patients with MS did not significantly meet consensus criteria for both metabolic syndrome and LD-HIV. In contrast, Carr et al. found a statistical association between MS and LD-HIV. Potential explanations for discrepant results observed between those studies could be the employment of a more accurate method for diagnosing LD-HIV developed by Carr et al., besides demographic differences verified between those study samples.

Concerning the association between MS and LD-HIV, we know that a loss of peripheral fat occurs in the latter syndrome that leads to a lessened ability for storing fat in peripheral adipocytes. In consequence, the dietary fat will be deposited in the abdominal adipocyte, but, due to their smaller capacity to store fat, fatty-acids released into intra-abdominal-visceral region return to circulation through portal vein and deposit first in liver (causing steatosis and insulin resistance) and also in muscle and pancreas. This is defined as ectopic fat deposition theory.

The MS has a multifactorial etiology; the emergence of this syndrome may not indicate a single underlying pathological process. Genetic background, HIV infection by itself, abnormal release of adipokines or antiretroviral-related effects may be partially responsible for some elements of this mixed syndrome. In our study, we observed an increased risk for MS in the sample patients as they increased their age, BMI, CD4 cell counts and exposure to antiretrovirals, corroborating with other studies. The BMI was the variable with greater OR in our MS regression model and together with CD4 cell counts represented the health return of these patients promoted by antiretroviral therapy. Antiretrovirals, in turn, administered over an extended period of time, play a vital role in prolonging the lifespan of HIV-infected patients. However, its chronic metabolic consequences on lipids became prevalent in the clinical practice and contributed for the development of MS in our study.

This panel demonstrates how physicians that care for HIV-infected patients are constantly facing new challenges. And in this changing scenario, physicians need to determine to what extent this represents a restoration of health or an increase in cardiovascular risk factors.

**Conclusion**

In conclusion, we found that traditional risk factors for cardiovascular disease, such as older age and increased body mass index, as well as factors inherently associated with HIV infection, such as an increased CD4 cell count and a longer exposure to antiretroviral therapy, seem to be associated with the metabolic syndrome in the present
study population. Furthermore, the current obesity, sedentary lifestyle, dyslipidemia, and hypertension “epidemics,” besides smoking, alcohol consumption and type 2 diabetes mellitus, also target the HIV-infected population.

As of regular medical appointments, physicians shall not lose the opportunity to encourage patients to change lifestyle and unhealthy social habits, choose individual antiretroviral regimens that combine the least toxic with greater antiviral activity, and decide if a hypolipemic agent is needed. The interdisciplinary assistance, including psychological, nutritional and other related-medical specialties, should be considered and may be of utmost importance.

REFERENCES


