Original Article

Prevalence of lipodystrophy and risk factors for dyslipidemia in HIV-infected children in Brazil

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ABSTRACT

The aim of present study was to describe the frequency of lipodystrophy syndrome associated with HIV (LSHIV) and factors associated with dyslipidemia in Brazilian HIV infected children.

HIV infected children on antiretroviral treatment were evaluated (nutritional assessment, physical examination, and laboratory tests) in this cross-sectional study. Univariate analysis was performed using Mann–Whitney test or Fisher’s exact test followed by logistic regression analysis. Presence of dyslipidemia (fasting cholesterol >200 mg/dl or triglycerides >130 mg/dl) was the dependent variable.

90 children were enrolled. The mean age was 10.6 years (3–16 years), and 52 (58%) were female. LSHIV was detected in 46 children (51%). Factors independently associated with dyslipidemia were: low intake of vegetables/fruits (OR = 3.47, 95%CI = 1.04–11.55), current use of lopinavir/ritonavir (OR = 2.91, 95%CI = 1.11–7.67). In conclusion, LSHIV was frequently observed; inadequate dietary intake of sugars and fats, as well as current use of lopinavir/ritonavir was associated with dyslipidemia.

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Introduction

Antiretroviral therapy (ART) has changed human immuno-deficiency virus (HIV) infection from a near-uniformly fatal disease into a chronic, manageable illness. Before the availability of highly active antiretroviral therapy (HAART), 5–10% of infected children survived for more than three years after their serologic diagnosis. Presently, the mortality rate has decreased 70%.† Children who survived HIV disease and AIDS are a new challenge to HIV/AIDS care standards, since this is the first generation of children who had the chance to use HAART.‡ One important challenge are the adverse events associated with HAART, as they are described in adults as
well as in children. The lipodystrophy syndrome (LSHV), the redistribution of body fat (increased of centripetal fat – lipo-
hypertrophy and/or reduction of peripheral fat – lipatropathy) and/or metabolic changes related to lipids profile (dyslipide-
ia), and glucose intolerance, is one example of these adverse events. Another important issue is that HIV infected chil-
dren and their caregivers must also deal with other challenges, related to the prevailing socioeconomic conditions in develop-
ing countries, such as nutrition deprivation, poor nutritional quality, or lack of regular physical activities.

The aim of this study was to describe the prevalence of LSHIV and assess factors associated with dyslipidemia in HIV
infected children treated with ARV, in a developing country setting, considering their nutrition routine.

**Materials and methods**

This is a cross-sectional study conducted at the HIV clinic of Instituto de Puercicultura e Pediatria Martagão Gesteira, a
tertiary university pediatric hospital affiliated to the Universidade Federal do Rio de Janeiro (IPFMG–UFRJ), from October
2007 to January 2009. Children were included if they were two or more years old, HIV infected (confirmed by two different
serological tests after 18 months of age), and on continuous ARV for at least the last three months prior to the interview.

Children were excluded if they had at the time of assessment any of the following: severe infection, opportunistic
or bacterial infections, neoplastic disease, severe encephalo-
pathy, wasting syndrome, or other metabolic disorders (such as diabetes and inborn errors of metabolism).

The LSHIV was defined as redistribution of body fat through
peripheral lipoatrophy, centripetal lipo hypertrophy or mixed form – presence of the two types of redistribution, and/or
also the presence of laboratory abnormalities (dyslipidemia),
based on the criteria defined by the European Pediatric Group lipodystrophy. Dyslipidemia was defined as serum choles-
terol ≥200 mg/dl and serum triglyceride ≥130 mg/dl, after 12 h
fasting. Data were collected during the interview and same
pediatrician (LP) did all physical examinations. Height, weight,
triceps, subscapular, and brachial skin folds, as well as waist
circumference were measured. Waist and arm circumference
were measured with ordinary tape measure. Sub-scapular
and arm skin folds were measured with Langer adipometer,
properly calibrated. All measures were taken three times, and
a mean of them was used. Collected data were com-
pared with the National Center for Health Statistics standard
growth curve and transformed into z-scores using the for-
mula: z-score = (observed value – mean)/standard deviation.
Anthropometric data were compared with the tables suitable
for age. Based on this anthropometric data, patients were
classified as presenting peripheral lipoatrophy, centripetal
lipo hypertrophy or mixed form of LSHIV. Patients were classi-
ﬁed according to Tanner curve, by the pediatrician (LP).

Laboratory data on fasting cholesterol, triglycerides, glu-
cose, CD4+ T lymphocytes and viral load were also collected.
A food assessment survey was conducted assessing the 48-
h food recall. Results were analyzed according to quality and
quantity of each food group. It was considered inadequate if
food intake was excessive and of poor quality and/or when it
was below the recommended for each particular food group.

Antiretroviral therapy (ARV), but the zidovudine syrup used
for HIV vertical transmission prevention, was deﬁned as the
continuous use of any antiretroviral medication.

Food deprivation was considered when the patient was
starving and did not have food access enough his/her well-
being for a week or more during their lives (excluding dietary
recommendations).

The dependent variable was deﬁned as the presence or
absence of dyslipidemia in children. Independent variables
were gender, age, at HIV diagnosis, length of HAART use,
CD4+ T lymphocytes percent cells, and viral load at the time of
the interview. Socioeconomic status and nutritional variables
were also evaluated: number of minimum Brazilian wages
per capita, history of food deprivation (when the child had
no food shortages due to poverty), inadequate intake (over
lack thereof) of food groups, treatment compliance (deﬁned
as self-report adherence to at least 95% of prescribed doses
of ARV, three days prior the interview), physical activity (at
least 30 min per day, at least three times a week of any physical
activity).

Statistical analysis: the information obtained in the ques-
tionnaires were stored in a database using Access 2007®
software. Subsequently, the distribution of all continuous
variables was studied. The frequency of all the categorical
variables was described and univariate analysis of con-
tinuous variables was performed using Student’s t-test or
Mann–Whitney test if the variable did not have normal distri-
bution. Univariate analysis of categorical variables was per-
formed using the Fisher exact test followed by multivari-
ate logistic regression analysis. The independent variables
selected to be included in the ﬁnal model were those that in
univariate analysis presented with p-value <0.15. Statistical
analysis was performed using the statistical package STATA
version 9.0, Texas, USA.

Ethical considerations: this study was approved by IPFMG –
Ethical Committee.

**Results**

Ninety patients were enrolled. The mean age was 127.3
months, and 52 children were female. Among the female
group, 16 had history of menarche. The mean age of chil-
dren when they were ﬁrst diagnosed as HIV infected were 37
months.

Among the legal guardians of those children, 58 (64.4%) were illiterate or had less than eight years of education.

All children were using ARV for at least three months, 32
were in their ﬁrst ARV regimen, 27 were in second ARV regi-
imen, and 31 had experienced three or more ARV regimens.
Protease inhibitor (PI) based regimen was the current ARV regi-
men of 47 children (43 on lopinavir/ritonavir), whereas 33 were
on non-nucleoside reverse transcriptase inhibitors (NNRTI)
based regimens, and 10 patients were currently using nucleo-
side reverse transcriptase inhibitors (NRTI) based regimens.

According to the European Pediatric Group lipodystrophy
(4), 46 children presented lypodystrophy, as illustrated in Fig. 1.

Fig. 1. Representation of children’s physical profile. A) showing normal body mass index (BMI); B) showing excessive body
mass index (BMI); C) showing underweight (BMI); D) showing centripetal lipoatrophy; E) showing subscapular
lipodystrophy.
No children presented hyperglycemia. The mean cholesterol was 153.2 mg/dl and the mean triglyceride was 111.4 mg/dl.

Overall mean body mass index (BMI) was 16.6 (z-score −0.34), 17.1 for the group without LSHIV and 15.4 for the group with LSHIV (p = 0.01).

In Table 1 shows demographic, clinical, and laboratory characteristics according to the presence or absence of LSHIV Demographic characteristics (income), clinical presentation (category C event), laboratory data (nadir CD4+ lymphocytes), use of ARV (lopinavir/ritonavir), and nutritional history were associated with LSHIV.

CD4+ T lymphocytes varied from 45 to 2300 cells/mm³ (3–50%), and viral load at the moment of the interview varied from undetectable to 80,400 copies/mL. All variables with p-value <0.15 were included in the multivariate analysis, except BMI. Table 2 shows the result of the multivariate analysis.

**Discussion**

Among 90 children on ARV, 51% (46) were classified as having LSHIV; 22% presented lipoatrophy and 32% lipohipertrophy. The proportion of children affected by this syndrome ranged from 20 to 50%, according to studies that evaluated different populations. In studies of adult groups, the prevalence of LSHIV varied from 15 to 50%. An European study of 426 children found a 42% prevalence of clinical manifestations of LSHIV. In a study involving 364 Ugandan children, the prevalence was lower: 27% presented clinical manifestations and 34% laboratory abnormalities. Glucose metabolism abnormalities were not observed. Werner et al. in a study of 30 Brazilian children on ARV, found 88.3% with dyslipidemia (laboratory abnormality) and only 13.9% with abnormal body fat distribution.

Since all clinical diagnoses were prone to observer bias, i.e. even measuring circumferences and skin folds, the diagnosis of LSHIV is ultimately based on investigator impression, and hence we studied risk factors associated with dyslipidemia, considering nutritional history in our population.

Among the risk factors described in the literature, dyslipidemia was associated with older age, higher Tanner scores, and use of ARV (such as stavudine, lopinavir/ritonavir, and NNRTIs), white ethnicity, or higher viral load. In our study, the risk factors independently associated with dyslipidemia were low intake of vegetables/fruits and current use of lopinavir/ritonavir.

Arpadi et al. observed significant associations between worse virological and immunological status at the baseline visit and the presence of changes consistent with LSHIV in a group of children. A study of the European Pediatric Group of Lipodystrophy demonstrated a significant relationship between children diagnosed as clinical category C (CDC) with lower CD4+ T lymphocytes and onset of changes consistent with LSHIV. A Thai pediatric study also described an association between the baseline C clinical category and LSHIV, but had not encountered any association with

**Fig. 1 – Distribution of children according to clinical and laboratory characteristics of LSHIV.**
Table 1 – Demographic, clinical, and laboratory characteristics of the patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with LSHIV&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Patients without LSHIV</th>
<th>OR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender – female</td>
<td>27/46 (59%)</td>
<td>25/44 (57%)</td>
<td>1.08</td>
<td>0.86</td>
</tr>
<tr>
<td>HIV-vertically infected</td>
<td>44/46 (96%)</td>
<td>40/44 (91%)</td>
<td>1.10</td>
<td>0.05</td>
</tr>
<tr>
<td>Race – Caucasian</td>
<td>16/46 (35%)</td>
<td>11/44 (25%)</td>
<td>0.62</td>
<td>0.31</td>
</tr>
<tr>
<td>Admitted to the hospital in the last year</td>
<td>10/46 (22%)</td>
<td>4/44 (9%)</td>
<td>2.77</td>
<td>0.10</td>
</tr>
<tr>
<td>Regular physical activity</td>
<td>11/46 (24%)</td>
<td>10/44 (23%)</td>
<td>1.06</td>
<td>0.89</td>
</tr>
<tr>
<td>History of food deprivation</td>
<td>13/46 (28%)</td>
<td>9/44 (20%)</td>
<td>1.53</td>
<td>0.39</td>
</tr>
<tr>
<td>Income – per person (minimum Brazilian salary wages) (mean)</td>
<td>0.56</td>
<td>0.83</td>
<td>0.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Birth weight (mean – g)</td>
<td>2586</td>
<td>2329</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Age (at the interview), months (mean – months)</td>
<td>121.8</td>
<td>133.1</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Clinical classification C (CDC)</td>
<td>23/46 (50%)</td>
<td>15/44 (34%)</td>
<td>1.93</td>
<td>0.07</td>
</tr>
<tr>
<td>On any protease inhibitor</td>
<td>27/46 (59%)</td>
<td>20/44 (45%)</td>
<td>1.71</td>
<td>0.21</td>
</tr>
<tr>
<td>Time on the current ARV regimen (mean – months)</td>
<td>25.5</td>
<td>28.7</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>100% adherence, 3 days prior to the interview</td>
<td>17/46 (37%)</td>
<td>11/44 (25%)</td>
<td>1.76</td>
<td>0.22</td>
</tr>
<tr>
<td>Inadequate intake of sugars and fat</td>
<td>23/46 (50%)</td>
<td>10/44 (23%)</td>
<td>3.40</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inadequate intake of milk and dairy products</td>
<td>16/46 (35%)</td>
<td>10/44 (23%)</td>
<td>1.81</td>
<td>0.21</td>
</tr>
<tr>
<td>Inadequate intake of protein</td>
<td>12/46 (26%)</td>
<td>8/44 (18%)</td>
<td>1.59</td>
<td>0.37</td>
</tr>
<tr>
<td>Inadequate intake of vegetables/fruits</td>
<td>40/46 (87%)</td>
<td>29/44 (67%)</td>
<td>3.40</td>
<td>0.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Inadequate intake of cereals</td>
<td>9/46 (20%)</td>
<td>4/44 (9%)</td>
<td>2.43</td>
<td>0.18</td>
</tr>
<tr>
<td>Nadir % CD4+ T cells (mean)</td>
<td>15.17</td>
<td>19.70</td>
<td>0.06&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Actual % CD4+ T cells (mean)</td>
<td>25.67</td>
<td>25.93</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Baseline viral load – log (mean)</td>
<td>5.84</td>
<td>5.79</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Current viral load – log (mean)</td>
<td>4.47</td>
<td>3.74</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Current AST&lt;sup&gt;c&lt;/sup&gt; – units/mL (mean)</td>
<td>33</td>
<td>28</td>
<td>0.07&lt;sup*&gt;&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Current ALT&lt;sup&gt;d&lt;/sup&gt; – units/mL (mean)</td>
<td>20</td>
<td>18</td>
<td>0.54</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Variables included in multivariate analysis.  
<sup>b</sup> LSHIV: lipodystrophy syndrome associated with HIV.  
<sup>c</sup> Lopinavir/ritonavir.  
<sup>d</sup> Odds ratio.  
<sup>*</sup> Aspartate aminotransferase.  
<sup>f</sup> Alanine aminotransferase.

CD4+ T lymphocytes<sup>21</sup> In our study, we did not observe a relationship between dyslipidemia and immunosuppression, probably because this association is related with clinical manifestations of the LSHIV more than laboratory abnormalities. Flint et al. suggested that both treatment with antiretroviral drugs and some chronic inflammatory response to HIV stimulated the homeostatic response to stress at the cellular level, leading to adverse effects on the adipocytes metabolism. This process leads to a cycle of pathological lipotoxicity, lipoatrophy and, consequently, the phenotype of fat distribution with high waist–hip ratio, and of course the more severe HIV disease the child had, the worse the homeostatic response to stress at the cellular level they would present.<sup>22</sup> Another important issue possibly associated with the inflammatory response was the positive association between aspartate aminotransferase (AST) and the presence of LSHIV. AST is a component of the AST platelet ratio index (APRI). This index (AST/platelets) is associated with liver fibrosis among HIV infected patients with and without other viral hepatitis<sup>23</sup> patients, and a possible etiology for this fibrosis is the inflammatory disorder associated

Table 2 – Multivariate analysis – factors associated with LSHIV.<sup>a</sup>

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR&lt;sup&gt;c&lt;/sup&gt;</th>
<th>95%CI&lt;sup&gt;d&lt;/sup&gt;</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Income – per person (minimum Brazilian wage salary wages) (mean)</td>
<td>0.96</td>
<td>0.77–1.21</td>
<td>0.74</td>
</tr>
<tr>
<td>Nadir % CD4+ per cell</td>
<td>0.96</td>
<td>0.92–1.00</td>
<td>0.08</td>
</tr>
<tr>
<td>Inadequate intake of vegetables/fruits</td>
<td>1.81</td>
<td>1.05–3.20</td>
<td>0.04</td>
</tr>
<tr>
<td>Inadequate intake of sugars and fat</td>
<td>3.05</td>
<td>1.00–10.00</td>
<td>0.05</td>
</tr>
<tr>
<td>On LPV/r&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.51</td>
<td>0.94–6.75</td>
<td>0.06</td>
</tr>
<tr>
<td>Admitted to the hospital in the last year</td>
<td>1.87</td>
<td>0.45–7.74</td>
<td>0.39</td>
</tr>
<tr>
<td>Current AST&lt;sup&gt;c&lt;/sup&gt; – per Unit/mL</td>
<td>1.05</td>
<td>1.00–1.11</td>
<td>0.05</td>
</tr>
</tbody>
</table>

<sup>a</sup> LSHIV: lipodystrophy syndrome associated with HIV.  
<sup>b</sup> Lopinavir/ritonavir.  
<sup>c</sup> Odds ratio.  
<sup>d</sup> 95% confidence interval.  
<sup>*</sup> Aspartate aminotransferase.
with HIV. The increased AST observed in the univariate analysis would also be a surrogate marker of fatty hepatic steatosis, more frequently described in obese children. However, if this was the case, the alanine aminotransferase should have also been elevated, which was not the case.26 Another hypothesis for this finding is that AST is increased due to the use of ARV; Ottop et al. studied 230 HIV infected adults in Cameroon, and patients who were on ARV had higher AST levels when compared with those without ARV.25

Although interventions to avoid and improve dyslipidemia were frequently based on improving the quality of diet,26 few studies evaluated the diet among LSHIV patients, and none in children, including children from developing countries. The analysis of dietary survey was carried out according to specific food groups and was considered inadequate when above or below the recommended daily amount for the age-specific children. Individually, we observed that lower vegetables and sugar intake were significantly associated with LSHIV. These data support the hypothesis that, despite the absence of food deprivation, the quality of nutrition was far below the recommended levels. Such children with poor nutrition have greater chance of developing dyslipidaemia. A review by Almeida et al., of 20 dietary intervention studies in adults, concluded that changes in lifestyle, diet, and physical activity were always recommended as the first approach in the treatment of dyslipidaemia, related or not to HIV, and our results corroborate this findings.27 In conclusion, any intervention to tackle dyslipidaemia in children must aim at not only improving nutrition quality of the children, but also, whenever possible avoiding the use of ARV that would raise cholesterol or triglyceride levels, such as lopinavir/ritonavir.28

The design of this study was cross-sectional and aimed only to describe the presence of LSHIV and factors associated with dyslipidemia among children followed at the IPPMG’s outpatient clinic. Some of the variables, such as the use of stavudine and lack of physical activity, although biologically plausible were not associated with dyslipidemia in our study, possibly due to the small sample size available.

We believe that longitudinal studies to investigate the role of diet on LSHIV prevention in this population must be pursued.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval

This study was approved by IPPMG – Ethical Committee.

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