Lipodystrophy syndrome in HIV-infected patients – a cohort study in Lower Silesia, Poland

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Abstract

Introduction: Human immunodeficiency virus (HIV)-associated lipodystrophy syndrome (LS) is defined as a redistribution of adipose tissue, metabolic and endocrine abnormalities, resulting from combined antiretroviral therapy (cART). Aim of this study was to evaluate LS in HIV-infected patients from Lower Silesia, Poland.

Material and methods: One hundred and ten HIV-infected patients on cART for at least 2 years were included. Two subgroups of patients were established: patients with no or slight symptoms of lipodystrophy – LS1; and patients with moderate and severe changes – LS2. The patients were also divided according to the type of LS: lipoatrophy, lipoaccumulation, both lipoatrophy and lipohypertrophy.

Results: LS2 subgroup was significantly older, had much lower body weight, lower WHR, more advanced atherosclerotic changes. Patients with advanced lipodystrophy syndrome had very high pack-year values. LS1 group had hypertension much more frequently than controls. Comparing with controls, LS2 had significantly lower low-density lipoprotein (LDL) cholesterol, higher triglyceride levels, longer time of HIV infection, longer time of cART and cumulative time on cART (including PIs and NRTIs). A higher current CD4+ T-lymphocyte count and more frequent HCV infection in patients with more severe adipose tissue changes were of little statistical significance. Fat loss of face, limbs, buttocks and together with lipoaccumulation of abdomen were most common.

Conclusions: Lipodystrophy syndrome is still observed in the vast majority of HIV-positive patients receiving antiretroviral therapy, especially those older and with longer time of cumulative NRTI and PI treatment. A great concern is needed to evaluate body composition and risk factors for metabolic changes to prevent their progression and healthy consequences.

Key words: HIV, antiretroviral therapy, lipodystrophy syndrome, metabolic abnormalities.

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**Introduction**

Human immunodeficiency virus (HIV)-associated lipodystrophy syndrome (LS) is defined as a redistribution of adipose tissue accompanied by metabolic and endocrine abnormalities, resulting from combined antiretroviral therapy (cART) [1-5].

The term was first used in 1998 by Andrew Carr et al. to describe morphological and metabolic abnormalities observed in HIV-infected patients treated with protease inhibitors (PIs) [2]. However, further studies also discovered the influence of other antiretroviral drugs, mostly nucleoside reverse transcriptase inhibitors (NRTIs), and of HIV infection itself [6-11]. Most authors emphasize the significant role of adipose tissue in pathogenesis of this condition; the role of the immune system, proinflammatory cytokines such as TNF-α and interleukin (IL)-6 and genetic predisposition are also mentioned [2, 3, 8, 12, 13].

The morphological abnormalities observed in clinical presentation of patients with LS include: lipoatrophy (loss of subcutaneous adipose tissue in the face, limbs, and buttocks), isolated or accompanied by lipoaccumulation (growth of adipose tissue in the abdomen, waist, neck and growth of visceral adipose tissue) [14-19].

Lipoatrophy should be distinguished from cachexia and malnutrition observed in advanced stages of AIDS and chronic infections accompanying HIV infection. Therapy with PI is considered by many authors as an independent risk factor for the development of insulin resistance, abnormal glucose tolerance and diabetes mellitus type 2 [20-24]. Other metabolic abnormalities include: increased triglyceride concentration, low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) cholesterol and apolipoproteins B and E levels, lower high-density lipoprotein (HDL) cholesterol level [25-27].

The aim of this study was to evaluate the lipodystrophy syndrome in HIV-infected patients living in Lower Silesia, Poland.

**Material and methods**

**Material**

One hundred and ten HIV-infected patients, treated in the Acquired Immunodeficiency Syndrome Outpatient Clinic in Wroclaw were included in the observational study. The same study population was analyzed in our previous publications [28]. The preliminary inclusion criteria were: documented HIV infection and antiretroviral therapy of no less than 2 years. The exclusion criteria were: AIDS diagnosis, acute medical condition (fever, severe infection, inflammation), serum creatinine level over 2 mg% and over fivefold increase in the alanine aminotransferase level, body mass index (BMI) > 30 kg/m², age over 65 years old, diabetes, treatment with such drugs as metformin. The following patient data were known at the beginning of the study: current virological and immune status, history of the infection and information about coinfection with hepatitis B and/or hepatitis C virus (Table 1).

All patients were on antiretroviral treatment for 2-8 years, 4 years on average. The time of cumulative antiretroviral treatment with medications from all antiretroviral classes

<table>
<thead>
<tr>
<th>Infection data</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of transmission HET/IDU/MSM, n [%]</td>
<td>31/51/28 (28.2/46.4/25.5)</td>
</tr>
<tr>
<td>Time of HIV infection [years]*</td>
<td>8 (3.4-12.0)</td>
</tr>
<tr>
<td>AIDS, n [%]</td>
<td>32 (29.1)</td>
</tr>
<tr>
<td>HCV infection, n [%]</td>
<td>59 (53.6)</td>
</tr>
<tr>
<td>HBV infection, n [%]</td>
<td>26 (23.6)</td>
</tr>
<tr>
<td>CD4+ T-lymphocytes [cells/μl]*</td>
<td>515 (388-693)</td>
</tr>
<tr>
<td>CD4+ T-lymphocyte nadir [cells/μl]*</td>
<td>200 (66-280)</td>
</tr>
<tr>
<td>Log₁₀ HIV RNA at the moment of test [copies/ml]*</td>
<td>1.7 (1.6-1.7)</td>
</tr>
<tr>
<td>HIV RNA below the sensitivity of the method, n [%]</td>
<td>93 (84.5%)</td>
</tr>
<tr>
<td>Log₁₀ HIV RNA zenith, copies/ml, n =84*</td>
<td>4.7 (3.6-5.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>cART</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of ARV treatment [years]*</td>
<td>4 (2-8)</td>
</tr>
<tr>
<td>Cumulative time on PI [years]*</td>
<td>3.79 (0.71-7.37)</td>
</tr>
<tr>
<td>Cumulative time on NNRTI [years]*</td>
<td>0 (0-1.6)</td>
</tr>
<tr>
<td>Cumulative time on NRTI [years]*</td>
<td>8.79 (4.03-13.98)</td>
</tr>
<tr>
<td>Cumulative time on cART [years]*</td>
<td>16.6 (8.13-24.97)</td>
</tr>
</tbody>
</table>

*Median, IQR, n (%) – absolute number (percentage), other data – arithmetic mean
HET – heterosexual contacts, IDU – intravenous drug users, MSM – men who have sex with men
was from about 8 to 25 years, 16.6 years on average; the longest cumulative time of treatment concerned NRTI. We did not analyze contribution of certain antiretroviral drugs and their classes in the LS. Before the beginning of this study there were changes in the cART in many patients because of drug toxicity and viral failure.

The control group included 42 healthy individuals living in Lower Silesia, matched for age and sex with the patients, with negative medical history of chronic diseases and cardiovascular disease events (Table 2).

Characteristics of the study group (SG) and control group (CG) are presented in Table 2.

### Methods

The study protocol included collecting anamnesis and data from medical documentation, especially information about HIV infection and antiretroviral treatment (in years and cumulative treatment with NNRTI, NRTI, PI). Physical examination was performed with particular emphasis on anthropometric measurements – weight, height, waist and hip circumferences, BMI and waist-hip ratio (WHR). The evaluation of clinical features of LS was carried out using the methodology of HIV Outpatient Study (HOPS), a multi-site clinical study of over 4800 patients receiving ambulatory care in the USA in 1992-1998 [18].

### Table 2. Characteristics of the study group (SG) and control group (CG)

<table>
<thead>
<tr>
<th>Feature</th>
<th>SG, n = 110</th>
<th>CG, n = 42</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years] (a, sd)</td>
<td>39.8 ± 9.3 (20-62)</td>
<td>41 ± 11.5 (20-58)</td>
<td>0.48</td>
</tr>
<tr>
<td>Sex (male), n [%]</td>
<td>70 (63.6)</td>
<td>26 (61.9)</td>
<td>0.99</td>
</tr>
<tr>
<td>BMI*</td>
<td>22.86 (21-25)</td>
<td>25.6 (24-27)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Waist [cm]*</td>
<td>82.75 (76.5-91.0)</td>
<td>86.75 (75-95)</td>
<td>–</td>
</tr>
<tr>
<td>Hips [cm]*</td>
<td>94 (88-98)</td>
<td>100 (95-105)</td>
<td>–</td>
</tr>
<tr>
<td>WHR*</td>
<td>0.9 (0.84-0.96)</td>
<td>0.89 (0.78-0.94)</td>
<td>0.055</td>
</tr>
<tr>
<td>Smokers, n [%]</td>
<td>46 (84.6)</td>
<td>28 (47.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pack-years*</td>
<td>18 (8.875-27.125)</td>
<td>13.375 (4.27-5)</td>
<td>0.33</td>
</tr>
<tr>
<td>cIMT [mm]*</td>
<td>0.66 (0.58-0.78)</td>
<td>0.54 (0.46-0.62)</td>
<td>–</td>
</tr>
<tr>
<td>cIMT mean-max [mm]*</td>
<td>0.99 (0.84-1.18)</td>
<td>0.81 (0.67-0.99)</td>
<td>–</td>
</tr>
<tr>
<td>Atherosclerotic plaques, n [%]</td>
<td>35 (31.8)</td>
<td>7 (16.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypertension, n [%]</td>
<td>49 (44.5)</td>
<td>10 (23.8)</td>
<td>0.039</td>
</tr>
<tr>
<td>TC [mg/dl] (a, sd)</td>
<td>195.3 ± 45.4</td>
<td>212.67 ± 38.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-HDL [mg/dl]</td>
<td>139.2 ± 42.4</td>
<td>150.41 ± 35.7</td>
<td>0.13</td>
</tr>
<tr>
<td>LDL [mg/dl] (a, sd)</td>
<td>110.13 ± 38.1</td>
<td>126.34 ± 31.7</td>
<td>0.016</td>
</tr>
<tr>
<td>HDL [mg/dl]*</td>
<td>51 (40-64)</td>
<td>58.5 (47-71)</td>
<td>0.012</td>
</tr>
<tr>
<td>TG [mg/dl]*</td>
<td>131.5 (93-189)</td>
<td>100.5 (68-137)</td>
<td>0.0077</td>
</tr>
<tr>
<td>Fasting glucose [mg%]*</td>
<td>91 (86.0-96.5)</td>
<td>93.5 (87-101)</td>
<td>0.11</td>
</tr>
<tr>
<td>Insulin [UI/ml]*</td>
<td>7.15 (5.2-10.4)</td>
<td>7 (4.4-10.9)</td>
<td>0.64</td>
</tr>
<tr>
<td>HOMA-IR***</td>
<td>1.63 (1.1-2.23)</td>
<td>1.48 (0.98-2.67)</td>
<td>0.9</td>
</tr>
<tr>
<td>Insulin resistance, n [%]</td>
<td>21 (19.4)</td>
<td>11 (27.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>CRP [mg/l]*</td>
<td>0.62 (0.19-1.53)</td>
<td>0.72 (0.19-1.52)</td>
<td>0.89</td>
</tr>
<tr>
<td>Fibrinogen [g/l]*</td>
<td>2.7 (2.3-3.2)</td>
<td>2.9 (2.6-3.3)</td>
<td>0.037</td>
</tr>
<tr>
<td>D-dimers [ng/ml]*</td>
<td>216.6 (169-319)</td>
<td>245.7 (170-349)</td>
<td>0.78</td>
</tr>
<tr>
<td>Positive family history, n [%]</td>
<td>35 (31.8)</td>
<td>5 (11.9)</td>
<td>0.022</td>
</tr>
<tr>
<td>Metabolic syndrome, n [%]</td>
<td>22 (20)</td>
<td>5 (11.9)</td>
<td>0.35</td>
</tr>
<tr>
<td>Diabetes, n [%]</td>
<td>3 (2.7)</td>
<td>0 (0)</td>
<td>0.66</td>
</tr>
<tr>
<td>Obesity/overweight/underweight, n [%]</td>
<td>6/21/7 (5.5/19.1/6.3)</td>
<td>5/23/0 (12/54.8/0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cardiovascular disease risk factors, n [%]</td>
<td>3 (2.7)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CV – ATP III risk***</td>
<td>2 (1-6)</td>
<td>2 (1-5)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

*Median, IQR, n (%) – absolute number (percentage), other data – arithmetic mean

**Homeostatic Model Assessment of Insulin Resistance

***Cardio-vascular risk according Adult Treatment Panel III
The LS features were evaluated by two physicians – researchers, taking into consideration patients’ opinions. The physical examination included evaluation of upper and lower limbs, buttocks, hips and face regarding fat loss and of visceral regions, trunk and neck with regard to fat accumulation. The researchers graded all the changes from 0 points (absent) to 3 points (the most severe). The maximum possible score was 15 points.

The quantitative parameter for lipodystrophy was used for analyzing dependencies between lipodystrophy and atherosclerosis. All changes were classified in a four-degree scale reflecting the severity of lipodystrophy syndrome: no LS symptoms, subtle changes – noticeable only if specifically looked for, with no change in clothing fit (up to 3 points), moderate changes – easily noted by the patient or physician, often requiring a change in clothing size (3-7 points), severe changes obvious to the casual observer, requiring a change in clothing size (over 7 points) (Figure 1).

Following the HOPS method, two main subgroups of patients were established:
1) patients with no or slight symptoms of lipodystrophy (57 individuals) – LS1,
2) patients with moderate and severe changes (53 individuals) – LS2.

The purpose of this division was to compare their virological, immunological and clinical state and to evaluate the data concerning cART in both subgroups. The patients were also divided according to the type of lipodystrophic changes, into the following subgroups: lipoatrophy (n = 34), lipoaccumulation (n = 14), mixed forms – features of both lipoatrophic and lipohypertrophic changes (n = 46). In the control group, no features of lipoatrophic or mixed lipodystrophic changes were observed; 15 controls had symptoms of visceral obesity.

In all patients, a duplex ultrasound of carotid was performed in order to evaluate subclinical atherosclerosis by means of computer-measured cIMT. Carotid ultrasound was performed using a high-resolution ultrasound GE LOGIQ 7 GE with broadband linear probe 6-12 MHz. The main parameters for each patient were cIMT (the average IMT value obtained for all the series) and IMT mean-max (defined as the average of 12 maximal IMT measurements from each projection) [29].

Statistical analysis

Quantitative variables were presented as an arithmetic mean, geometric mean or median, depending on normality of distribution. To achieve normality, the logarithmic transform was applied to the variable elements. For each estimator, 95% confidence intervals were calculated. Qualitative variables are presented as the number of patients in each group. Differences in quantitative features between groups were analyzed by Student’s t-test, the Mann-Whitney test or Kruskal-Wallis wit post-hoc analysis. Differences in the qualitative features were analyzed using the χ² test or Fisher’s exact test (for small groups). The effect of clinical

Figure 1. Classification of patients according to the severity of lipodystrophy syndrome

features on lipodystrophy was assessed using logistic regression. The analysis was made using R and MedCalc statistical packages. All results with a significance level $p < 0.05$ were found significant.

The study was conducted with the approval of the Bioethics Committee. All participants provided their written informed consent to participate in the study, according to the Helsinki Declaration.

Results

At the beginning of the study, the patients were classified according to the severity of lipodystrophy syndrome, from no LS symptoms to severe changes in adipose tissue distribution. The subgroups with subtle and moderate changes were the most numerous (Figure 1).

Table 3 presents and compares the characteristics of both subgroups. The patients from LS2 subgroup were significantly older, had much lower body weight and smaller hip circumference and, as a result, lower WHR. Patients from advanced lipodystrophy syndrome had very high pack-year values. After further post-hoc analysis of subgroups and the control group, it was discovered that LS1 had hypertension much more frequently than controls (0.033). In comparison with the control group, LS2 had significantly lower LDL cholesterol and higher triglyceride values ($p = 0.015$, $p = 0.028$ respectively). No other statistically significant differences in basic laboratory parameters or concerning cardiovascular disease risk factors were observed (Table 3).

Patients in LS2 subgroup had noticeably longer documented time of HIV infection (Table 4). General time of cART and cumulative time on antiretroviral drugs, including cumulative time on PIs and cumulative time on
Within the whole group, all types of dystrophic changes were observed: lipoatrophy (30.9%), lipoaccumulation (12.7%) and, most frequently, mixed forms (41.7%). Figure 3 shows numbers of patients in specific subgroups, according to various dystrophic changes. Table 5 presents statistically significant differences observed in patients with different types of lipodystrophy. There were significant differences between the subgroups, concerning anthropometric measurements: BMI and waist circumference were noticeably higher in lipaccumulation and mixed subgroups than in the lipoatrophy group; hip circumference was significantly lower in the atrophy group.

### Table 3. Clinical and laboratory characteristics of patients from subgroups LS1 and LS2

<table>
<thead>
<tr>
<th>Feature</th>
<th>LS1, n = 57</th>
<th>LS2, n = 53</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years] (a, sd)</td>
<td>39 (31.75-43)</td>
<td>42 (35-48)</td>
<td>0.048</td>
</tr>
<tr>
<td>Sex (male), n [%]</td>
<td>33 (57.9)</td>
<td>37 (69.8)</td>
<td>0.38</td>
</tr>
<tr>
<td>BMI*</td>
<td>23.9 (21.6-25.7)</td>
<td>22 (20.6-24.0)</td>
<td>0.015</td>
</tr>
<tr>
<td>Waist [cm]*</td>
<td>81 (75.6-90.0)</td>
<td>84 (79.0-91.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>Hips [cm]*</td>
<td>95 (90-100)</td>
<td>90.5 (87-95)</td>
<td>0.014</td>
</tr>
<tr>
<td>WHR*</td>
<td>0.88 (0.80-0.94)</td>
<td>0.93 (0.88-1.00)</td>
<td>0.0024</td>
</tr>
<tr>
<td>cIMT [mm]*</td>
<td>0.64 (0.56-0.76)</td>
<td>0.71 (0.61-0.82)</td>
<td>0.026</td>
</tr>
<tr>
<td>cIMT mean-max [mm]*</td>
<td>0.93 (0.83-1.12)</td>
<td>1.06 (0.90-1.21)</td>
<td>0.076</td>
</tr>
<tr>
<td>Atherosclerotic plaques, n [%]</td>
<td>15 (26.3)</td>
<td>20 (37.7)</td>
<td>0.28</td>
</tr>
<tr>
<td>Smokers, n [%]</td>
<td>45 (79.0)</td>
<td>48 (90.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>Pack-years*</td>
<td>12 (5.75-21.50)</td>
<td>23.375 (13.3-29.5)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Hypertension, n [%]</td>
<td>28 (50.9)</td>
<td>20 (37.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>TC [mg/dl] (a, sd)</td>
<td>204 (164-226)</td>
<td>187 (156-223)</td>
<td>0.82</td>
</tr>
<tr>
<td>Non HDL-C [mg/dl]</td>
<td>143 (105-168.75)</td>
<td>128 (100.75-166)</td>
<td>0.71</td>
</tr>
<tr>
<td>LDL-C [mg/dl] (a, sd)</td>
<td>114 (82.75-145.75)</td>
<td>101.8 (80.00-124.5)</td>
<td>0.36</td>
</tr>
<tr>
<td>HDL-C [mg/dl]*</td>
<td>53 (40-62)</td>
<td>49 (40.5-68.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>TG [mg/dl]*</td>
<td>131 (95.25-183.25)</td>
<td>132 (91.50-196.75)</td>
<td>0.75</td>
</tr>
<tr>
<td>Fasting glucose [mg%]*</td>
<td>91 (86.00-97.53)</td>
<td>91 (85.75-96.00)</td>
<td>0.71</td>
</tr>
<tr>
<td>Insulin [IU/ml]*</td>
<td>6.7 (5.45-8.93)</td>
<td>7.8 (4.80-11.43)</td>
<td>0.15</td>
</tr>
<tr>
<td>HOMA-IR***</td>
<td>1.46 (1.14-1.91)</td>
<td>1.91 (1.08-2.59)</td>
<td>0.13</td>
</tr>
<tr>
<td>Insulin resistance, n [%]</td>
<td>7 (12.7)</td>
<td>14 (26.4)</td>
<td>0.18</td>
</tr>
<tr>
<td>CRP [mg/l]*</td>
<td>0.47 (0.18-1.40)</td>
<td>0.89 (0.2-2)</td>
<td>0.13</td>
</tr>
<tr>
<td>Fibrinogen [g/l]*</td>
<td>2.61 (2.3-3.1)</td>
<td>2.71 (2.28-3.40)</td>
<td>0.47</td>
</tr>
<tr>
<td>D-dimers [ng/ml]*</td>
<td>201.8 (169.0-316.0)</td>
<td>253.2 (171.9-331.0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Positive family history, n [%]</td>
<td>18 (31.6)</td>
<td>17 (32.1)</td>
<td>0.89</td>
</tr>
<tr>
<td>Metabolic syndrome, n [%]</td>
<td>12 (21.1)</td>
<td>10 (18.9)</td>
<td>0.96</td>
</tr>
<tr>
<td>Diabetes, n [%]</td>
<td>1 (1.8)</td>
<td>2 (3.8)</td>
<td>0.94</td>
</tr>
<tr>
<td>Obesity/overweight/underweight, n [%]</td>
<td>5/11/5 (8.8/19.3/8.8)</td>
<td>1/10/4 (1.9/18.9/7.5)</td>
<td>0.43</td>
</tr>
<tr>
<td>Cardiovascular disease risk factors, n [%]</td>
<td>0 (0)</td>
<td>3 (5.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>CV – ATP III risk*</td>
<td>2 (1-6)</td>
<td>2 (1-8)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*Median, IQR, n (%) – absolute number (percentage), other data – arithmetic mean
**Homeostatic Model Assessment of Insulin Resistance
***Cardio-vascular risk according Adult Treatment Panel III

NRTIs, were significantly longer in LS2. Some interesting findings of little statistical significance indicate a higher current CD4+ T-lymphocyte count and more frequent HCV infection in patients with more severe adipose tissue changes.

Various combinations of fat distribution abnormalities were observed in LS patients. The most common one was cumulative fat loss in areas of the face, limbs, waist and hips (lipoatrophy); another frequent pattern was lipoatrophy combined with lipaccumulation in the visceral area (mixed lipodystrophy). The percentages of particular combinations are presented in Figure 2.
Lipodystrophy syndrome in HIV-infected patients

It was found that the highest prevalence of lipodystrophy was in the accumulation subgroup, compared with accumulation and mixed subgroups; it was the highest in the accumulation subgroup in comparison to mixed and no-LS groups. WHR was noticeably higher in the mixed subgroup than in no-LS and atrophy groups. Patients with mixed changes were significantly older and had more advanced atherosclerotic changes (cIMT mean-max), compared with no-LS group. cIMT values and pack-years were of little statistical significance. Metabolic syndrome was observed among the patients with adipose tissue accumulation and with mixed forms. The subgroups of patients with various dystrophic changes did not differ in: occurrence of atherosclerotic plaques, results of labo-

Table 4. Infection characteristics in subgroups LS1 and LS2

<table>
<thead>
<tr>
<th>Infection data</th>
<th>LS1</th>
<th>LS2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of transmission HET/IDU/MSM**, n [%]</td>
<td>16/24/17 (28.1/42.1/29.8)</td>
<td>15/27/11 (28.3/50.9/20.8)</td>
<td>0.51</td>
</tr>
<tr>
<td>Time of HIV infection [years]*</td>
<td>4.5 (2.5-9.0)</td>
<td>11 (5.75-17.00)</td>
<td>0.0003</td>
</tr>
<tr>
<td>AIDS, n [%]</td>
<td>15 (26.3)</td>
<td>17 (32.1)</td>
<td>0.65</td>
</tr>
<tr>
<td>HCV infection, n [%]</td>
<td>25 (43.9)</td>
<td>34 (64.2)</td>
<td>0.071</td>
</tr>
<tr>
<td>HBV infection, n [%]</td>
<td>11 (19.3)</td>
<td>15 (28.3)</td>
<td>0.37</td>
</tr>
<tr>
<td>CD4+ T-lymphocytes [cells/µl]*</td>
<td>488 (386.5-632.25)</td>
<td>609 (400.75-760.25)</td>
<td>0.053</td>
</tr>
<tr>
<td>CD4+ T-lymphocyte nadir [cells/µl]*</td>
<td>200 (49.00-267.75)</td>
<td>198 (77.25-293.00)</td>
<td>0.68</td>
</tr>
<tr>
<td>Log10 HIV RNA at the moment of test [copies/ml]*</td>
<td>1.69 (1.6-1.7)</td>
<td>1.6 (1.6-1.7)</td>
<td>0.28</td>
</tr>
<tr>
<td>HIV RNA below the sensitivity of the method, n [%]</td>
<td>45 (78.9)</td>
<td>48 (90.6)</td>
<td>0.21</td>
</tr>
<tr>
<td>Log10 HIV RNA zenith, copies/ml* (n = 84)</td>
<td>4.27 (3.31-5.13)</td>
<td>4.93 (4.06-5.38)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*Median, IQR, n (%) – absolute number (percentage), other data – arithmetic mean
HET – heterosexual contacts, IDU – intravenous drug users, MSM – men who have sex with men

Figure 2. Combinations of dystrophic changes in lipodystrophy syndrome patients

Figure 3. Numbers of patients with various dystrophic changes
ratory tests (lipid profile, glucose, insulin, CRP, fibrinogen, D-dimers), and in such risk factors as: cardiovascular disease risk factors, hypertension, diabetes or positive family history.

The time of HIV infection, cumulative time of NRTIs and cumulative time on cART were significantly longer in the mixed subgroup than in no-LS group (Table 5). No significant differences were discovered in the mode of HIV transmission and immunological or virological state. The time of antiretroviral treatment and total time of PIs and NNRTIs treatment were similar.

In further analysis of logistic regression cumulative cART and smoking had an influence on the severity of lipodystrophy syndrome (Table 6). In subsequent models, after disregarding cumulative cART and including cumulative NRTIs and PIs treatment, and then NNRTIs treatment, it was discovered that cumulative NRTIs treatment and smoking had an independent influence on severity of lipodystrophy syndrome \( (p = 0.004 \text{ and } p = 0.0152, \text{ respectively}) \) (Table 6). Adding the current number of CD4+ T-lymphocytes to the model did not change the result and had no impact on the severity of LS.

**Discussion**

Prevalence of LS in HIV-infected patients varies from 8% to 84% in different studies; it is usually correlated to the characteristics of the research project, inclusion criteria and observation time [1, 10, 18, 19, 22, 30-32].

In this study, 94 out of 110 patients were diagnosed with LS, which represents 85% of the study group. This is not an isolated case of such a high percentage of LS diagnosis. Similar results were observed by Rozenbaum et al. (84%) and by Carr et al. (83%) [14, 19]. However, some studies indicate a much lower prevalence of LS, e.g. Martinez et al. diagnosed it in 17% of patients, Mercie et al. – in 26% of patients [25, 27].

All types of dystrophic changes were observed in our study, with the majority of mixed forms (41.7%), lipodystrophy (30.9%) and, least frequently, lipoaccumulation (12.7%). These results are consistent with the findings of the HIV Outpatient Study, where LS was diagnosed in 49% of patients, mixed forms were most frequent (22.7%) and prevalence of lipodystrophy (13.3%) and lipoaccumulation (13.2%) were similar [18]. Different findings were presented by Thiebaut et al. in a French cohort, where mixed forms were least
Lipodystrophy syndrome in HIV-infected patients

Table 6. Influence of various factors on severity of lipodystrophy

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MODEL 1</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>MODEL 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.0479</td>
<td>0.9912-1.1078</td>
<td>0.099</td>
<td>Age</td>
<td>1.0518</td>
<td>0.9936-1.1134</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex</td>
<td>1.4816</td>
<td>0.5399-4.0658</td>
<td>0.45</td>
<td>Sex</td>
<td>1.6447</td>
<td>0.5851-4.6234</td>
<td>0.35</td>
</tr>
<tr>
<td>Pack-years</td>
<td>1.0245</td>
<td>0.9908-1.0594</td>
<td>0.16</td>
<td>Pack-years</td>
<td>1.0247</td>
<td>0.9910-1.0595</td>
<td>0.15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.0866</td>
<td>0.7542-5.7732</td>
<td>0.16</td>
<td>Hypertension</td>
<td>1.9614</td>
<td>0.7019-5.4810</td>
<td>0.2</td>
</tr>
<tr>
<td>HOMA-IR*</td>
<td>1.4392</td>
<td>0.9025-2.2952</td>
<td>0.13</td>
<td>HOMA-IR*</td>
<td>1.3715</td>
<td>0.8629-2.1799</td>
<td>0.18</td>
</tr>
<tr>
<td>HCV</td>
<td>0.4784</td>
<td>0.1806-1.2678</td>
<td>0.14</td>
<td>HCV</td>
<td>0.4993</td>
<td>0.1868-1.3344</td>
<td>0.17</td>
</tr>
<tr>
<td>Cumulative cART</td>
<td>1.0571</td>
<td>1.0128-1.1033</td>
<td>0.011</td>
<td>Cumulative NRTI</td>
<td>1.0856</td>
<td>1.0027-1.1754</td>
<td>0.0428</td>
</tr>
<tr>
<td>Cumulative PI</td>
<td>1.094</td>
<td>0.9653-1.2398</td>
<td>0.16</td>
<td>Cumulative NRTI</td>
<td>1.1148</td>
<td>1.0353-1.2003</td>
<td>0.004</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stepwise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pack-years</td>
<td>1.0373</td>
<td>1.0066-1.0689</td>
<td>0.0168</td>
<td>Pack-years</td>
<td>1.0377</td>
<td>1.0072-1.0693</td>
<td>0.0152</td>
</tr>
<tr>
<td>Cumulative cART</td>
<td>1.0628</td>
<td>1.0198-1.1076</td>
<td>0.0039</td>
<td>Cumulative NRTI</td>
<td>1.1148</td>
<td>1.0353-1.2003</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Logistic regression

*Homeostatic Model Assessment of Insulin Resistance

frequent (10%), lipoatrophy was most common (16%) and isolated lipoaccumulation was observed in 12% out of 38% of patients diagnosed with LS [26].

Trevisol et al. observed high frequencies of lipoaccumulation (46%) and lipoatrophy (53.2%) in a group where 53.2% of HIV-infected patients were diagnosed with LS [33].

In the presented cohort, significant differences in anthropometric measurements were observed, depending on the type and severity of LS. Patients with more advanced LS had lower BMI and higher WHR. The higher WHR was a consequence of a significantly lower hip circumference, resulting from adipose tissue loss in this region.

A higher BMI and waist circumference was observed in patients with lipoaccumulation and with mixed forms. Patients with lipoatrophy had a noticeably lower hip circumference. Patients with mixed forms had significantly higher WHR in comparison to no-LS and atrophy subgroups. The relation between dystrophic changes and anthropometric measurements was studied by Thiebaut et al. Among patients receiving cART, the prevalence of lipoatrophy grew with age and was higher in males and in patients with BMI ≤ 25. Lipoaccumulation was correlated to higher BMI and WHR; no significant relationship between lipoaccumulation and age has been discovered. The percentage of mixed forms was correlated to older age and higher WHR [26]. However, Alencastro et al. observed a different correlation between dystrophic changes and age or BMI. In their research, patients on antiretroviral therapy were older and had significantly higher BMI. Lipodystrophy and lipohypertrophy were correlated to age and BMI, whereas lipoatrophy was only correlated to BMI, BMI. Lipodystrophy and lipohypertrophy were correlated to age or BMI, whereas lipoatrophy was only correlated to BMI, BMI.

In one of the first LS studies in 1999, Carr et al. observed a different correlation between dystrophic changes and age or BMI. The influence of various factors on severity of lipodystrophy and occurrence of mixed forms. The influence of time of cART on LS and its relationship with various types of lipodystrophy have been observed in numerous clinical studies [1, 7, 11, 18, 26, 27].

In many clinical studies, the influence of various classes of antiretroviral drugs and of specific antiretroviral drugs on LS in HIV-infected patients was observed. Since the introduction of antiretroviral treatment, PIs has been the first class whose side effects have been described as lipodystrophy syndrome. The influence of this class of medications, specific drugs and time of PI treatment on LS development and severity have been widely described [1, 2, 6, 11, 14, 27].

One of the main inclusion criteria for the present study was antiretroviral treatment. Its significant influence was observed especially in the subgroup of patients with severe LS. The influence of both total cumulative time of cART on LS types and severity has been discovered. Cumulative protease inhibitors treatment was related to LS severity, but not to LS types. NRTIs medications were correlated to LS development. Cumulative time of NRTIs treatment had influence on severity of lipodystrophy and occurrence of mixed forms. The influence of time of cART on LS and its relationship with various types of lipodystrophy have been observed in numerous clinical studies [1, 7, 11, 18, 26, 27].

However, Thiebaut et al. did not observe a significant relationship between LS and particular antiretroviral medications, except for the influence of time on cART on LS types and severity of symptoms [26].

In one of the first LS studies in 1999, Carr et al., after an over twenty-month long observation, discovered fat distribution disorders in PI-treated patients in comparison to HIV-infected, untreated patients [14]. PIs were closely associated with visceral adipose tissue growth and adverse changes in patients’ metabolic profile. Since LS was also observed in patients never treated with PIs, further studies proved the negative influence of other classes of antiretro-
Lipodystrophy syndrome is still observed in the vast majority of HIV-positive patients receiving antiretroviral therapy, especially those older and with longer time of cumulative NRTI and PI treatment. Smoking is an independent risk factor of the severity of adipose tissue redistribution. A great concern is needed to evaluate body composition and risk factors for metabolic changes to prevent their progression and healthy consequences.

Acknowledgment

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Conflict of interest

The author’s declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References