Metabolic basis of HIV-lipodystrophy syndrome

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Sections of 1Endocrinology, 2Infectious Diseases, and 3Atherosclerosis, Department of Medicine, and 4Department of Pediatrics, Children’s Nutrition Research Center and US Department of Agriculture/Agricultural Research Service, Baylor College of Medicine, Houston 77030; and 5Ben Taub General Hospital, Houston, Texas 77030

Received 11 February 2002; accepted in final form 18 April 2002

Sekhar, Rajagopal V., Farook Jahoor, A. Clinton White, Henry J. Pownall, Fehmida Visnegarwala, Maria C. Rodriguez-Barradas, Morali Sharma, Peter J. Reeds, and Ashok Balasubramanyam. Metabolic basis of HIV-lipodystrophy syndrome. Am J Physiol Endocrinol Metab 283: E332–E337, 2002.—Human immunodeficiency virus (HIV)-lipodystrophy syndrome (HLS) is characterized by hypertriglyceridemia, low high-density lipoprotein-cholesterol, lipoatrophy, and central adiposity. We investigated fasting lipid metabolism in six men with HLS and six non-HIV-infected controls. Compared with controls, HLS patients had lower fat mass (15.9 ± 1.3 vs. 22.3 ± 1.7 kg, P < 0.05) but higher plasma glycerol rate of appearance (Ra), an index of total lipolysis (964.7 ± 103.3 vs. 611.08 ± 63.38 μmol·kg⁻¹·h⁻¹, P < 0.05), Ra, palmitate, an index of net lipolysis (731.49 ± 72.36 vs. 419.72 ± 33.78 μmol·kg⁻¹·h⁻¹, P < 0.01), Ra, free fatty acids (2,094.74 ± 182.18 vs. 1,470.87 ± 202.80 μmol·kg⁻¹·h⁻¹, P < 0.05), and rates of intra-adipocyte (799.40 ± 157.69 vs. 362.36 ± 74.87 μmol·kg⁻¹·h⁻¹, P < 0.01) and intrahepatic fatty acid reesterification (1,352.08 ± 123.90 vs. 955.56 ± 124.09 μmol·kg⁻¹·h⁻¹, P < 0.05). Resting energy expenditure was increased in HLS patients (30.51 ± 2.53 vs. 25.34 ± 1.04 kcal·kg lean body mass⁻¹·day⁻¹, P < 0.05), associated with increased non-plasma-derived fatty acid oxidation (139.04 ± 24.17 vs. 47.87 ± 18.81 μmol·kg⁻¹·h⁻¹, P < 0.02). The lipoatrophy observed in HIV lipodystrophy is associated with accelerated lipolysis. Increased hepatic reesterification promotes the hypertriglyceridemia observed in this syndrome.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)-lipodystrophy syndrome (HLS), a novel metabolic illness characterized by body fat redistribution, dyslipidemia, and insulin resistance, has become common since the widespread use of highly active antiretroviral therapy (HAART) (3, 4, 24, 26, 39). Although various HAART agents (3, 4, 24, 26, 39), HIV infection per se (12, 18), and inflammatory cytokines (7, 23) have been imputed as etiologic agents, the mechanistic basis of HLS is unknown. Current therapies do not effectively reverse the metabolic abnormalities (10, 40), particularly the lipid disorders that increase the risk of cardiovascular disease (16, 21). In addition, the syndrome interferes with effective HIV therapy, because patients are sometimes switched to less efficacious drug combinations due to the concern that various potent HAART agents may be responsible for the metabolic abnormalities. Therefore, it is important to identify the fundamental lipid kinetic defects in this unique form of lipodystrophy to direct therapy toward the specific pathogenic mechanisms.

We hypothesized that HLS patients would have an accelerated rate of whole body lipolysis to facilitate fat redistribution. If unaccompanied by an equivalent increase in fatty acid oxidation, the increased release of free fatty acids (FFA) would result in increased hepatic fatty acid reesterification to triglycerides (TG). Alternatively, decreased disposal of TG, alone or in combination with increased hepatic fatty acid reesterification, could lead to hypertriglyceridemia. To test these hypotheses, we used stable isotope tracer techniques with mass spectrometry to measure lipid kinetics and body composition in the fasted state in men with HLS compared with non-HIV-infected men.

MATERIALS AND METHODS

Subjects. The study was approved by the Baylor Institutional Review Board for human subject research. Six male patients with HLS were recruited. In the absence of a standard case definition, HLS was defined by three criteria: 1) change in body habitus, consisting of fat loss in the extremities and increased abdominal girth, as observed by the patient and confirmed by his primary physician (5); 2) Lipodystrophy Score, based on morphological abnormalities in each of five body regions, as assessed by a single investigator (A, abdominal obesity; B, “buffalo hump” (posterior cervical fat pad); C, supraclavicular fat pad; E, extremity fat loss; F, facial fat loss); a 4-point intensity scale was used (0, no change; 1, mild change; 2, moderate change; 3, severe change), and a score of ≥2 in at least two regions was required; 3) fasting plasma TG concentration ≥300 mg/dl.

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(3.39 mmol/l). All HLS subjects had the “mixed” phenotype of HIV lipodystrophy (peripheral fat atrophy and central adiposity) as described by Saint-Marc et al. (33). All HLS subjects were free of diabetes mellitus, thyroid disorders, hypercortisolism, liver or renal impairment, and hypogonadism and had had no HIV-associated opportunistic infections or illnesses for ≥5 yr. Six healthy, age- and body mass index (BMI)-matched non-HIV-infected men were recruited as controls. All subjects had sedentary lifestyles (exercising <2 times/wk), and none consumed unusual diets or dietary supplements.

HIV RNA viral load and CD4 counts were measured in all HLS patients. Five patients had been on stable, continuous HAART for ≥2 yr and had HIV-1 RNA levels <400 copies/ml at the time of the study. One patient (subject 5 Table 1), with an elevated HIV-1 RNA level, had interrupted HAART 3 mo earlier and been placed on a new regimen 2 mo before the study.

**Study design and isotope infusion protocol.** The study consisted of an intravenous infusion of stable isotopes to measure lipid kinetics in the fasted state in six HLS subjects and six controls. Lipid-lowering medications were discontinued 2 wk before each study. For 2 days preceding each study, subjects consumed a standard diet that provided 30 kcal and 1 g protein·kg body wt⁻¹·day⁻¹. All subjects were fasted for 10 h before each study.

The outcome variables were body water (from which lean body mass and fat mass were calculated); respiratory quotient and resting energy expenditure; the rate of appearance of fatty acids within the adipocyte and of reesterification; and the rate of appearance of fatty acids in the plasma. Intra-adipocyte fatty acid oxidation was measured using a glucose analyzer (YSI, Yellow Springs, OH). Plasma insulin concentrations were measured by radioimmunoassay for human insulin (Linco Research, St. Charles, MO). Plasma FFA concentrations were measured by a spectrophotometric assay utilizing reactions catalyzed by acyl-CoA synthase and acyl-CoA oxidase (Wako Chemicals, Neusse, Germany).

Plasma palmitate and glycerol concentrations were determined in vitro isotope dilution (11) with the use of [2,2-²H₂]palmitate (98% ²H) and [2,1-¹³C]glycerol (99% ¹³C, Cambridge Isotope Laboratories, Andover, MA) as internal standards. The tracer-to-tracee ratios of plasma free palmitate were determined by negative chemical ionization gas chromatography-mass spectrometry (NCL-GC-MS) using a Hewlett-Packard 5989B GC-MS system (Hewlett Packard, Fullerton, CA) (14). The pentfluoroazbenzyl derivative was prepared and analyzed by selectively monitoring ions from mass-to-charge ratios (m/z) 255 to 256. The plasma glycerol tracer/tracee ratio was measured by NCI-GC-MS on its heptafluorobutyric acid derivative, with selective monitoring of ions from m/z 680 to 685 (11). Breath ¹³CO₂ content was determined by gas isotope ratio mass spectrometry on a Europa Tracermass Stable Isotope Analyzer (Europa Scientific, Crewe, UK).

**Calculations.** The following calculations were used. For Rₐ palmitate and Rₐ glycerol,

\[ R_a (\mu mol·kg⁻¹·h⁻¹) = \frac{(Tr/Tr_{inf})}{(Tr/Tr_{palmitate})} \times i \]

where \( Tr/Tr_{inf} \) is the tracer/tracee ratio (mole %) in the infusate, \( Tr/Tr_p \) is the ratio in plasma at tracer/tracee steady state, and i is the tracer infusion rate.

Palmitate oxidation rate (\( \mu mol·kg⁻¹·h⁻¹ \)) = \([V_{CO₂} × IECO₂]/(Tr/Tr_{palmitate})\)

where \( V_{CO₂} \) is the excretion rate of CO₂ in breath, the constant 0.56 adjusts for the fraction of labeled breath CO₂ recovered after an infusion of \([¹³C]acetate \) in the fasted state (37), IECO₂ is the isotopic enrichment of CO₂ (atom %), and \( Tr/Tr_{palmitate} \) is the steady-state tracer/tracee ratio of plasma palmitate (mole %).

Rₐ FFA (\( \mu mol·kg⁻¹·h⁻¹ \)) = Rₐ palmitate/plasma (palmitate/FFA) ratio.

Plasma-derived FFA oxidation rate (\( \mu mol·kg⁻¹·h⁻¹ \)) = palmitate oxidation/plasma (palmitate/FFA) ratio.

Intra-adipocyte FFA reesterification rate (\( \mu mol·kg⁻¹·h⁻¹ \)) = (\( R_a \) glycerol × 3) – Rₐ FFA.

Intrahepatic FFA reesterification rate (\( \mu mol·kg⁻¹·h⁻¹ \)) = Rₐ FFA – FFA oxidation.

Whole body fatty acid oxidation was calculated from \( V_{CO₂} \) according to the equation of Frayn (8).

Nonplasma fatty acid oxidation was calculated as the difference between whole body fatty acid oxidation and plasma-derived FFA oxidation (2)

\[ \text{whole body water (TBW; ml)} = \frac{(E_{H₂O} × \text{dose})}{(E_{P_{H₂O}} × 1.04)} \]

where \( E_{H₂O} \) is the enrichment of the deuterated water administered, \( E_{P_{H₂O}} \) is the enrichment of plasma H₂O at steady state, and the factor 1.04 corrects for the deuterium distribution space

\[ \text{lean body mass (kg)} = \frac{\text{TBW}}{K} \]

where \( K = 0.72 \), the hydration constant for fat-free tissues in adults (41).

fat mass (kg) = body weight – lean body mass

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**Table 1. HLS subjects: HIV and lipodystrophy parameters**

<table>
<thead>
<tr>
<th>Patient</th>
<th>CD4 Count, cells/mm³</th>
<th>Viral Load, RNA copies/cm³</th>
<th>Lipodystrophy Scale</th>
<th>HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>257</td>
<td>&lt;400</td>
<td>A2B1C1E2F1</td>
<td>ISLD</td>
</tr>
<tr>
<td>2</td>
<td>262</td>
<td>400</td>
<td>A2B0C1E2F1</td>
<td>ISD</td>
</tr>
<tr>
<td>3</td>
<td>710</td>
<td>&lt;400</td>
<td>A3B1C1E2F3</td>
<td>ISL</td>
</tr>
<tr>
<td>4</td>
<td>720</td>
<td>&lt;400</td>
<td>A3B2C2E2F2</td>
<td>ISL</td>
</tr>
<tr>
<td>5</td>
<td>255</td>
<td>214,818</td>
<td>A3B3C2E2F3</td>
<td>IE</td>
</tr>
<tr>
<td>6</td>
<td>320</td>
<td>&lt;400</td>
<td>A3B2C3E2F2</td>
<td>ISL</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus; HLS, HIV-lipodystrophy syndrome; HAART, highly active antiretroviral therapy; I, indinavir; S, stavudine; L, lamivudine; D, didanosine; Z, zidovudine; E, efavirenz. Lipodystrophy scale: letters refer to body region (A, abdominal obesity; B, buffalo hump; C, supraclavicular fat pad; E, extremity fat loss; F, facial fat loss). In each region, nos. refer to severity of change: 0, no change; 1, mild change; 2, moderate change; 3, severe change. Subject 5 had previously been on indinavir, stavudine, and zidovudine for 2 yr. He had discontinued this regimen 3 mo before his first study and had been placed on indinavir and efavirenz 2 mo before the study. Normal CD4 count ≥ 500/mm³.
Table 2. Subjects: physical, biochemical, and hormonal characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HLS Subjects (n = 6)</th>
<th>Controls (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51.17 ± 3.06</td>
<td>49.00 ± 4.31</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84.74 ± 5.29</td>
<td>88.43 ± 7.60</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>15.89 ± 1.29</td>
<td>22.29 ± 1.69</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>63.94 ± 4.43</td>
<td>66.14 ± 4.65</td>
</tr>
<tr>
<td>BMI</td>
<td>26.83 ± 1.35</td>
<td>27.01 ± 1.12</td>
</tr>
<tr>
<td>Fasting glucose, mg/dl</td>
<td>107.9 ± 4.8±</td>
<td>90.7 ± 1.9</td>
</tr>
<tr>
<td>Fasting insulin, IU/ml</td>
<td>28.0 ± 1.8±</td>
<td>11.3 ± 3.1</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.1 ± 0.1</td>
<td>5.2 ± 0.1</td>
</tr>
<tr>
<td>ALT, U/l</td>
<td>31.9 ± 4.4</td>
<td>34.9 ± 7.3</td>
</tr>
<tr>
<td>AST, U/l</td>
<td>34.7 ± 3.2</td>
<td>31.4 ± 2.0</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/l</td>
<td>65.3 ± 6.3</td>
<td>57.9 ± 2.8</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>262.4 ± 13.5‡</td>
<td>159.4 ± 16.4</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>499.7 ± 96.3†</td>
<td>78.1 ± 7.7</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dl</td>
<td>154.8 ± 16.7</td>
<td>122.7 ± 6.1</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dl</td>
<td>31.6 ± 2.6‡</td>
<td>43.7 ± 4.2</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>15.3 ± 1.7</td>
<td>13.4 ± 1.2</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.03</td>
</tr>
<tr>
<td>TSH, mU/l</td>
<td>2.8 ± 0.4</td>
<td>2.8 ± 0.3</td>
</tr>
<tr>
<td>Free thyroxine, ng/dl</td>
<td>1.3 ± 0.05</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>Testosterone, ng/dl</td>
<td>642.4 ± 15.6</td>
<td>555.3 ± 27.4</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>15.3 ± 0.2</td>
<td>15.2 ± 0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. Conversion factors for SI units: glucose (0.05551), cholesterol (0.02586), triglycerides (0.01129), blood urea nitrogen (BUN) (0.3570), creatinine (331). BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL and HDL, low- and high-density lipoprotein, respectively; TSH, thyroid-stimulating hormone. *P < 0.05, †P < 0.01, ‡P < 0.001.

Statistical analysis. Group data were compared using a paired t-test. Differences were considered significant at P < 0.05. The correlation coefficient r was determined using the formula of Pearson and Lee (see Ref. 38). Data are expressed as means ± SE.

RESULTS

All HLS subjects were on a HAART regimen that included the protease inhibitor indinavir, and five subjects were also taking the nucleoside analog stavudine (Table 1). The RNA viral load was suppressed to <400 copies/ml in all subjects except one. The CD4 count was below the normal range (≥500/mm³) in four patients. Lipodystrophy Score assessment revealed that all patients had peripheral and facial fat loss together with abdominal obesity, and five had an abnormality in every region.

Compared with controls, the HLS group had a significantly lower (P < 0.02) fat mass but no difference in body weight, BMI, TBW, or lean body mass (Table 2). HLS patients had significantly higher fasting concentrations of plasma glucose (P < 0.01), insulin (P < 0.001), total cholesterol (P < 0.001), and TG (P < 0.01) and significantly lower (P < 0.05) fasting concentrations of plasma high-density lipoprotein (HDL)-cholesterol (Table 2). The plasma concentrations of low-density lipoprotein-cholesterol, Hb A1c, thyroid-stimulating hormone, free thyroxine, 8 AM cortisol, testosterone, and hemoglobin and indexes of renal and liver functions were within the normal range in both groups.

Compared with controls, the HLS group had significantly higher (P < 0.05) resting energy expenditure (Table 3). Whole body carbohydrate oxidation was similar in the groups, but whole body fatty acid oxidation was significantly higher (P < 0.02) in the HLS patients. Plasma-derived FFA oxidation was similar in the groups; hence, the increase in whole body fatty acid oxidation in the HLS group was due to a significantly higher (P < 0.02) rate of oxidation of fatty acids derived from sources other than the plasma FFA pool (Table 3).

Rₐ glycerol, an index of the rate of total lipolysis, was significantly faster (P < 0.05) in the HLS subjects, as was Rₐ palmitate (P < 0.01), an index of the rate of net lipolysis (Table 4). Rₐ FFA, calculated from Rₐ palmitate, was also faster in the HLS group (P < 0.05). The faster rates of entry of glycerol, palmitate, and FFA into the circulation were associated with significantly higher (P < 0.01) plasma concentrations of glycerol (+80%), palmitate (+100%), and total FFA (+42%) in the HLS group. The increase in the rate of net lipolysis in the HLS subjects occurred despite a concomitant, and significant (P < 0.05) increase in the rate of fatty acid reesterification within the adipocyte. Because plasma-derived FFA oxidation was similar in both groups, a significantly greater (P < 0.05) amount of the FFA released into the plasma compartment as a result of the increased net lipolysis was available for hepatic reesterification in the HLS patients (Table 4).

There was a positive correlation between the rate of hepatic reesterification and fasting plasma TG concentration in control subjects (r = 0.88) but not in HLS patients (r = −0.17).

DISCUSSION

The clinical, anthropomorphic, and biochemical features of our HLS subjects are consistent with a well described phenotype that includes peripheral and facial lipodystrophy, central adiposity, elevated plasma TG, total cholesterol, glucose, and insulin concentrations, and a low plasma HDL-cholesterol concentration.

Table 3. Substrate fuel partitioning for energy expenditure in the fasted state

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HLS Subjects (n = 6)</th>
<th>Controls (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting energy expenditure, kcal·kg LBM⁻¹·day⁻¹</td>
<td>30.51 ± 2.53*</td>
<td>25.34 ± 1.04</td>
</tr>
<tr>
<td>Carbohydrate oxidation, μmol·kg LBM⁻¹·h⁻¹</td>
<td>360.51 ± 88.94</td>
<td>399.72 ± 75.07</td>
</tr>
<tr>
<td>Fatty acid oxidation, μmol·kg LBM⁻¹·h⁻¹</td>
<td>320.44 ± 27.46</td>
<td>218.16 ± 21.47</td>
</tr>
<tr>
<td>Plasma-derived FFA oxidation, μmol·kg LBM⁻¹·h⁻¹</td>
<td>181.45 ± 20.43</td>
<td>171.73 ± 26.17</td>
</tr>
<tr>
<td>Non-plasma-derived fatty acid oxidation, μmol·kg LBM⁻¹·h⁻¹</td>
<td>139.04 ± 24.17</td>
<td>47.87 ± 18.81</td>
</tr>
</tbody>
</table>

Values are means ± SE. LBM, lean body mass; FFA, free fatty acids. *P < 0.05, †P < 0.02.
These rates of both total and net lipolysis were increased and conversion to glycerol lipids. TG comprise an increased amount of plasma FFA was available for hepatic extraction and conversion to glycerolipids. TG comprise the largest fraction of hepatic glycerolipids and are assembled into VLDL and secreted into the plasma compartment. Hepatic VLDL-TG production is known to increase linearly with plasma FFA concentration. Our data indicate that this mechanism could contribute significantly to hypertriglyceridemia in HLS. Elevated plasma FFAs would also exacerbate hypertriglyceridemia by inhibiting lipoprotein lipase activity. Elevation plasma FFAs resulting from the hyperlipolytic state could also stimulate the activity of cholesterol ester transfer protein (CETP) and thus provide a mechanism for the low HDL-cholesterol levels in HLS patients. An expanded pool of TG-rich lipoproteins in HLS patients is available to accept a greater amount of cholesterol esters from HDL, thereby depleting HDL of its cholesterol content and lowering the measured plasma HDL-cholesterol level. Previous studies have shown that CETP-mediated transfer of HDL-cholesteryl esters to TG-rich lipoproteins increases with plasma TG levels with respect to the anthropomorphic changes, lipodystrophy and diminution of whole body fat mass would be facilitated by the high rate of net lipolysis, impaired TG storage, and increased energy expenditure that are largely met by increased oxidation of non-plasma-derived fatty acids. However, these mechanisms do not directly explain the occurrence of central visceral fat accumulation in patients with HLS. Increased central adiposity would require an additional defect, namely, either decreased lipolysis or increased fatty acid deposition outstripping the rate of lipolysis in visceral fat depots.

The present study was not designed to define the cause of HIV lipodystrophy but primarily to define the abnormal lipid kinetics that underlie it. However, previous studies of lipid metabolism in HIV-infected patients suggest etiologies that may underlie these defects. Hypertriglyceridemia and low plasma HDL-cholesterol levels were observed in HIV-infected patients before the advent of HAART. Hence, factors intrinsic to HIV-1 infection per se could contribute to the dysregulation of lipolysis, hepatic TG synthesis, and TG disposal, as they do to other defects associated with dyslipidemia in HIV-infected patients, such as accelerated de novo hepatic lipogenesis and decreased hepatic synthesis of HDL-apolipoprotein AI. In the context of HLS, which occurs mainly in patients treated with HAART, protease inhibitors may play an etiologic role. Purnell et al. showed in healthy, non-HIV-infected subjects that ritonavir increases plasma TG, mainly in the VLDL fraction, while decreasing hepatic lipase activity by 20% and leaving lipoprotein lipase activity unchanged. They suggested that protease inhibitors cause hypertriglyceridemia by increasing hepatic VLDL synthesis, a mechanism that is consistent with our kinetic data.
There is a strong positive correlation between the hepatic reesterification rate and the fasting plasma TG concentration in the control group but not in the HLS group. The absence of a correlation suggests a profound degree of dysregulation of the kinetics of reesterification in patients with HIV lipodystrophy, whereas the greater discrepancy between the two groups in the fasting TG levels compared with the rates of hepatic reesterification implies the existence of another source of plasma TG in the HLS patients. We speculate that this additional pool is derived from dietary TG that is cleared poorly and therefore persists in the plasma despite the fact the HLS subjects have been fasting for 12 h. This is consistent with our preliminary results from an ongoing study of dietary TG clearance in HLS patients.

Our HLS patients were taking HAART regimens that included indinavir in all and stavudine in all but one. These drugs, alone or together, have been implicated in the pathophysiology of HIV lipodystrophy. Nucleoside analogs such as stavudine impair mitochondrial DNA replication in liver, muscle, and white adipose tissue, and this could result in lipodystrophy by depleting cellular energy stores (9, 33). In HIV-infected men, stavudine is associated directly with increased rate of total lipolysis and inversely with subcutaneous fat area (15). Protease inhibitors inhibit differentiation of transformed preadipocytes in vitro (6, 44). HAART-associated HIV lipodystrophy has also been associated with insulin resistance, and this was manifested in our HLS subjects who had elevated fasting insulin levels, central obesity, hypertriglyceridemia and low HDL-cholesterol levels. In addition to the HAART agents themselves, several factors could have contributed to the insulin resistance, including genetic background, degree of physical activity, smoking, and stress. We tried to control for these factors to the extent possible. Our subjects, both HLS patients and controls, were similar in relation to family history of diabetes (none having first degree relatives with diabetes) and physical activity (all sedentary). However, it is likely that the key contributor to insulin resistance in these patients was the elevated plasma entry rate of FFAs resulting from the elevated rates of intra-adipocyte lipolysis without a concomitant increase in plasma fatty acid oxidation. The resultant deposition of fatty acids and TG in myocytes and hepatocytes would result in significant reductions in glucose uptake and oxidation (25) and in other manifestations of insulin resistance (e.g., hypertriglyceridemia from increased hepatic reesterification and VLDL-TG synthesis in the liver).

Many features of HLS resemble those of hypercortisolism. Healthy persons undergoing hypercortisolism “clamps” exhibit increased whole body lipolysis but decreased intra-abdominal lipolysis (35). In vitro studies of adipocytes taken from patients with Cushing’s syndrome show that abdominal adipocytes have diminished hormone-sensitive lipase activity and increased lipoprotein lipase activity, whereas peripheral subcutaneous adipocytes have greater sensitivity to catecholamine-mediated lipolysis (32). These biochemical characteristics are consistent with the whole body lipid kinetics of our HLS patients and could underlie the phenotype of peripheral lipodystrophy and visceral adiposity. Although hypercortisolism is not a feature of HLS (27, 43), it is possible that the glucocorticoid receptor is activated by alternative mechanisms in HLS patients (20).

Because of the association of HLS with various HAART agents, patients are frequently switched to alternative therapeutic combinations of reduced antiretroviral efficacy. This may increase their risk of acquiring HIV-associated infections. In view of this risk, as well as the abnormal cardiovascular and metabolic profile, there has been an understandable urgency to treat HLS despite a lack of clear understanding of the underlying metabolic defects. To date, conventional antilipid agents (e.g., statins, fibric acid derivatives) (11) have proven relatively ineffective in reversing the abnormalities. Our results suggest that rational therapy of HLS might be directed at inhibiting lipolysis (17) and enhancing triglyceride disposal (29, 42).

We thank Margaret Frazer and Melanie Del Rosario for expert technical assistance in mass spectrometry. Dr. Mario Maldonado and Barbara Sepcie for help in recruiting HLS subjects, Holly Paskell, Lynne Scott, and the nursing, pharmacy, and dietary staffs of the Baylor General Clinical Research Center for excellent care of subjects and meticulous attention to protocol, and John Gaubatz for help in measuring lipoprotein subfraction concentrations.

Much of this work was performed in the Baylor Children’s Nutrition Research Center, which is supported by the US Department of Agriculture/Agricultural Research Service (USDA/ARS) under Cooperative Agreement No. 5862–5–01006. The contents of this manuscript do not necessarily reflect the views or policies of the USDA. Mention of trade names, commercial products, or organizations does not imply endorsement by the US Government.

This work was also supported by a Developmental Award of the Baylor Center for AIDS Research Core Support Grant AI-36211 (National Institute of Allergy and Infectious Diseases), a Chao Scholar award, an award from the Siegler Foundation, and the Baylor GCRC (National Institutes of Health Grant RR-0188).

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