Association of Severe Insulin Resistance With Both Loss of Limb Fat and Elevated Serum Tumor Necrosis Factor Receptor Levels in HIV Lipodystrophy

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Summary: HIV-lipodystrophy (HIV-LD) is characterized by the loss of body fat from the limbs and face, an increase in truncal fat, insulin resistance, and hyperlipidemia, factors placing affected patients at increased risk for vascular disease. This study evaluated insulin sensitivity and inflammatory status associated with HIV-LD and provides suggestions about its etiology. Insulin sensitivity and immune activation markers were assessed in 12 control subjects and 2 HIV-positive groups, 14 without and 15 with LD syndrome. Peripheral insulin sensitivity (mostly skeletal muscle) was determined with the hyperinsulinemic-euglycemic clamp. Circulating insulin-like growth factor (IGF) binding protein-1 (IGFBP-1) and free fatty acid (FFA) levels, and their response to insulin infusion were indicative of insulin responsiveness of liver and adipose tissue, respectively. Serum levels of soluble type 2 tumor necrosis factor-α (TNF-α) receptor (sTNFR2) were used as an indicator of immune activation. HIV-LD study subjects had significantly reduced (twofold) peripheral insulin sensitivity, but normal levels of FFA and reduced levels of IGFBP-1, relative to the nonlipodystrophy groups, indicating that the loss of insulin sensitivity was more pronounced in skeletal muscle than in liver or fat. The significant loss of peripheral fat in the HIV-LD group (34%; \( p < .05 \)) closely correlated with the reduced peripheral insulin sensitivity (\( p = .0001 \)). Levels of sTNFR2 were elevated in all HIV-infected study subjects, but they were significantly higher in those with lipodystrophy than without, and sTNFR2 levels strongly correlated with the reduction in insulin sensitivity (\( p = .0001 \)). Loss of peripheral fat, normal levels of FFA, and reduced levels of IGFBP-1 indicate that insulin resistance in HIV-LD is distinct from type 2 diabetes and obesity. The relationship between the degree of insulin resistance and sTNFR2 levels suggests an inflammatory stimulus is contributing to the development of HIV-associated lipodystrophy. Key Words: Type 2 diabetes mellitus—Insulin resistance—Insulin-like growth factor binding protein—Free fatty acid—Tumor necrosis factor-α—Lipodystrophy—Obesity—HIV/AIDS.
This redistribution of body fat is accompanied by metabolic perturbations including insulin resistance and hyperlipidemia, both hypertriglyceridemia and hypercholesterolemia (1,4), similar to metabolic syndrome X (5). The prevalence of HIV-lipodystrophy (HIV-LD) is reported to be as high as 50% (1,6). The impact of changes in body habitus for individuals, and the widespread occurrence qualify this syndrome as a major cause for concern. Although many studies have associated this syndrome with the use of HIV protease inhibitors (1,7-9), other evidence suggests that fat redistribution is occurring in patients who have not taken protease inhibitors (2) and, indeed, that it was occurring before the introduction of protease inhibitors (10,11). Defining the etiology of the HIV-associated LD syndrome and its related metabolic abnormalities is an urgent priority.

In obesity and type 2 diabetes mellitus, two factors have been implicated in the etiology of insulin resistance. These factors are elevated free fatty acids (FFAs) and the cytokine tumor necrosis factor-α (TNF-α). In both obesity and type 2 diabetes, insulin resistance is associated with elevated levels of FFAs (5,12). Elevated FFA levels alone are sufficient to induce insulin resistance without any underlying pathology (13,14), apparently by altering insulin signaling in skeletal muscle (15). Additional markers of insulin resistance include increased abdominal fat in obesity (16) and type 2 diabetes mellitus (17-19) and elevated serum levels of insulin-like growth factor binding protein-1 (IGFBP-1) (20).

Insulin resistance in obesity has been associated with a cytokine, TNF-α, which is specifically implicated in the induction of insulin resistance (21) through inhibition of the insulin signaling cascade that regulates glucose uptake (22). The role of TNF-α in the development of insulin resistance currently seen in HIV disease is not known. Cytokines, such as TNF-α, were suspected in the wasting aspects of HIV infection, but low circulating levels failed to support this (23) (see also commentary by Grunfeld [24]), whereas cytokines did contribute to hepatic lipogenesis (25). With effective antiretroviral treatment, HIV-infected patients have improved disease control, as assessed by mortality (26), low to undetectable viral load, and increased numbers of CD4+ lymphocytes (27). The components of the TNF system are reduced in patients receiving highly active antiretroviral therapy (HAART) (28) but it would be instructive to know whether they remain depressed in HIV LD.

The present study was designed to characterize insulin resistance manifest in HIV patients who have the LD syndrome, but not overt diabetes, i.e., fasting, hyperglycemia. The degree of peripheral insulin resistance in these patients was assessed by the hyperinsulinemic-euglycemic clamp (29). This method suppresses hepatic glucose output and provides an accurate measurement of the rate of insulin-stimulated glucose disposal in skeletal muscle. Insulin resistance was related to physiologic parameters known to be altered in insulin resistant states, that is, body fat distribution (30,31), circulating levels of FFAs (32–34), and IGFBP-1 (20). In addition, serum levels of soluble type 2 TNF-α receptor (sTNFR2) were assessed, inasmuch as elevated levels of sTNFR2 have not only been associated with the clinical course of HIV infection (35), but in particular were found to correlate with insulin resistance in obesity (36).

**STUDY SUBJECTS AND METHODS**

Those enrolled in the present study consisted of 12 healthy control study subjects, 14 study subjects infected with HIV without LD (noted here as HIV), and 15 HIV-positive study subjects with the LD syndrome (HIV-LD). There were two exclusion criteria, diabetes, based on a random plasma glucose level >200 mg/dl or a fasting plasma glucose >126 mg/dl (based on diagnostic criteria in the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997), and acute illness within the 3 months preceding the study. HIV-LD study subjects had self-reported loss of fat from the limbs and face with accumulation of fat in the abdomen and trunk, which was confirmed by physician assessment at the time of study. Control study subjects were matched for age and gender with the HIV and the HIV-LD groups. The HIV group consisted of 7 patients who were asymptomatic, 3 patients with AIDS, and 4 patients with AIDS and a prior history of weight loss. The HIV-LD group consisted of 7 asymptomatic patients and 8 patients with AIDS. Most HIV-infected study subjects were receiving multidrug regimens and continued these medications during the study. In the HIV group, all patients except 2 were taking nucleoside reverse transcriptase inhibitors, 2 were taking nonnucleoside reverse transcriptase inhibitors, and 11 were taking protease inhibitors. Similarly in the HIV-LD group, all except 1 patient were taking reverse transcriptase inhibitors, 3 were taking nonnucleoside reverse transcriptase inhibitors, and 13 were taking protease inhibitors. No difference was found in the degree of peripheral fat loss or insulin resistance in those patients taking protease inhibitors and those who were not, although the number of patients who were not taking protease inhibitors was small.

**Insulin Resistance**

Insulin resistance was determined as the rate of glucose infused to maintain euglycemia during an insulin infusion (hyperinsulinemic-euglycemic clamp) (29). Patients were admitted to our facility the night before the study. At 7 A.M., following baseline sampling, study subjects were infused with 1.2 mU insulin (Humulin, Eli Lilly, Indianapolis, IN, U.S.A.)/kg body weight/minute, designed to elevate plasma insulin levels to ∼40 μU/ml. Although hepatic glucose production was not measured in this study, this rate of insulin infusion has been demonstrated to suppress hepatic glucose production in other insulin-resistant states (37-40). For example, Wise et al. (37) have demonstrated that hepatic glucose production in study subjects with type 2 diabetes is suppressed by insulin levels of ∼40 μU/ml, when glucose concentra-
differences are normalized (37), suggesting that hepatic insulin resistance in type 2 diabetes is mediated by elevated glucose concentrations. Intravenous dextrose was administered to maintain plasma glucose, in all study subjects, at a level of 90 mg/dl assessed from arterialized samples, obtained by the heated hand technique (41). Insulin resistance was determined from the amount of infused glucose needed to maintain euglycemia between hours 2 and 3. Insulin sensitivity is expressed as milligrams of glucose per kilogram of lean body mass (LBM) per minute. LBM was used to normalize for differences in body composition.

Circulating Parameters

Serum concentrations of the sTNFR2 were assessed by enzymelinked immunosorbent assay (ELISA, TNF RI CytoSet ELISA kit, Biosource International, Camarillo, CA, U.S.A.). HIV-1 RNA quantitation was by the Amplicor HIV-1 Monitor Test (Roche Diagnostic Systems, Branchburg, NJ, U.S.A.). Insulin was analyzed by radioimmunoassay (RIA, Diagnostic Systems Laboratories, Webster, TX, U.S.A.). FFAs were analyzed by the acyl-CoA oxidase method (Wako BioProducts, Richmond, VA, U.S.A.). Plasma glucose was determined by the glucose oxidase method (Diagnostic Systems, Branchburg, NJ, U.S.A.). Serum IGFBP-1 was quantitated by ELISA (Diagnostic Systems, Branchburg, NJ, U.S.A.). Insulin was analyzed by radioimmunoassay (RIA, Diagnostic Products Corporation, Los Angeles, CA, U.S.A.). HIV-1 RNA quantitation was by the Amplicor HIV-1 Monitor Test (Roche Diagnostic Systems, Branchburg, NJ, U.S.A.). Insulin was analyzed by radioimmunoassay (RIA, Diagnostic Products Corporation, Los Angeles, CA, U.S.A.).

TABLE 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>HIV</th>
<th>HIV-lipodystrophy</th>
</tr>
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<tbody>
<tr>
<td>Gender (female/male)</td>
<td>8/4</td>
<td>4/10</td>
<td>9/6</td>
</tr>
<tr>
<td>Age (y)</td>
<td>41 ± 2.3</td>
<td>40 ± 1.3</td>
<td>43 ± 1.5</td>
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<tr>
<td>CD4 (cells/µL)</td>
<td>ND</td>
<td>472 ± 90.0</td>
<td>430 ± 60.4</td>
</tr>
<tr>
<td>Nadir CD4 (cells/µL)</td>
<td>ND</td>
<td>169 ± 57.7 (8)</td>
<td>164 ± 40.5 (11)</td>
</tr>
<tr>
<td>HIV RNA (copies/ml)×10^{-3}</td>
<td>ND</td>
<td>0.8 (&lt;0.4–190)</td>
<td>&lt;0.4 (&lt;0.4–42.7)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.2 ± 1.5</td>
<td>23.9 ± 0.8</td>
<td>27.7 ± 1.3</td>
</tr>
<tr>
<td>Lean mass index (kg/m²)</td>
<td>15.6 ± 0.5⁸</td>
<td>18.2 ± 0.7⁸</td>
<td>19.0 ± 0.5⁸</td>
</tr>
<tr>
<td>Fat mass index (kg/m²)</td>
<td>7.2 ± 1.4</td>
<td>5.3 ± 0.9</td>
<td>7.2 ± 1.0</td>
</tr>
<tr>
<td>Percentage of limb adiposity</td>
<td>52.5 ± 1.7⁸</td>
<td>48.2 ± 2.0⁸</td>
<td>34.8 ± 2.0⁸</td>
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<tr>
<td>Insulin sensitivity (mg glucose/kg LBM/min)</td>
<td>11.5 ± 1.0⁸</td>
<td>9.2 ± 1.1⁸</td>
<td>5.4 ± 0.7⁸</td>
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<tr>
<td>Fasting glucose (mg/dl)</td>
<td>91.0 ± 2.4</td>
<td>93.7 ± 1.8</td>
<td>101.6 ± 4.1</td>
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<tr>
<td>Fasting insulin (µIU/ml)</td>
<td>8.0 ± 1.2⁸</td>
<td>10.94 ± 2.2⁸</td>
<td>25.6 ± 4.1⁸</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>92.8 ± 14.9⁹</td>
<td>182 ± 30⁷</td>
<td>385 ± 81⁷</td>
</tr>
</tbody>
</table>

All values listed except viral load data, are mean ± standard error of the mean; the groups marked ⁺ differ from the groups marked ⁷ (p < .05).

ND, not determined.

RESULTS

Healthy control study subjects, HIV study subjects, and HIV-LD study subjects, were similar in age. The BMI of the HIV-LD group tended to be more than that of the control or HIV group, although not significantly (Table 1). To determine whether BMIs, in the range of the HIV-LD group, could account for the insulin resistance observed in HIV-LD the control group was subdivided into a low BMI subgroup (20.3 ± 0.4 kg/m²; n = 6), comparable with that in the HIV study subjects without LD, and a high BMI group (28.0 ± 2.0 kg/m²; n = 6), comparable with that of the HIV-LD group. Insulin sensitivity was similar in both subgroups, 11.4 ± 1.8 mg

Body Composition

Body composition, including LBM, body fat mass (BFM), and the proportion of body fat in trunk and limbs was determined by dual-energy X-ray absorptiometry (DEXA) performed on a total body scanner (model DPS Lunar Radiation Co., Madison, WI, U.S.A.) (10). Body weight, LBM, and BFM have been expressed per h², as suggested by Quetelet for body mass index (BMI) (42).

Statistical Analysis

All data are presented as mean ± standard error of the mean (SEM). Comparison of the three study groups was made using an analysis of variance (ANOVA) and Student-Newman-Keuls test for multiple comparisons. Comparison of the control study subjects, stratified by body mass index, was made with Student’s t-test. Differences were considered statistically significant when p < .05.
glucose/kg LBM/min for the low BMI control subgroup and 11.7 ± 1.2 mg glucose/kg LBM/min for the high BMI control subgroup. Insulin sensitivity of the HIV study subjects without LD was not significantly lower than that of the controls (9.2 ± 1.1 and 11.5 ± 1.0 mg glucose/kg LBM/minute, respectively) whereas the insulin sensitivity of the HIV-LD group was significantly lower that both other groups (5.4 ± 0.7 mg glucose/kg LBM/min; p < .05; Table 1). The BFM index (kg BFM/height in m^{2}) of the HIV-LD group 7.2 ± 1.0 kg BFM/m^{2} was similar to that of the control group 7.2±1.4 kg BFM/m^{2} (Table 1) and intermediate relative to the low BMI control subgroup and the high BMI control subgroup (4.2 ± 0.7 and 10.3 ± 2.1 kg BFM/m^{2}, respectively). The LBM index (kg LBM/m^{2}) was significantly elevated in the HIV and HIV-LD groups compared with in the control group (p < .05). The LBM index of the low and high BMI control groups were similar (data not shown), indicating that the increased LBM in the HIV and HIV-LD groups was not a consequence of increased BMI.

Assignment to the HIV-LD group was by self-report and physician-confirmed loss of facial and limb fat with increased trunk fat. Patients in this group had reduced proportion of limb fat and increased proportion of trunk fat, determined by DEXA. The proportion of body fat localized to the limbs in HIV-LD patients (34.8%) was significantly diminished (p < .05), compared with the HIV group (48.2%) and the control group (52.4%; Table 1). The control group insulin sensitivity was 11.5 ± 1.0 mg glucose/kg LBM/min (Table 1, Fig. 1). A similar value was observed in HIV patients (9.2 ± 1.1 mg glucose/kg LBM/minute). In HIV-LD patients, however, the amount of glucose infused to maintain euglycemia was 5.4 ± 0.7 mg glucose/kg LBM/minute, a reduction of 53% relative to the control group (p < .05). This reduction in the amount of glucose needed to maintain euglycemia during hyperinsulinemia indicates a twofold reduction in insulin sensitivity. This decrease in insulin sensitivity was correlated with the reduction in the percentage of limb fat (r = 0.60; p = .0001; Fig. 2).

In the non-LD HIV group, 6 of 14 patients had viral loads below the detection limit of the assay (400 HIV RNA copies/ml) and in the HIV-LD group, 8 of 15 were below the limit of detection. For the HIV-infected patients with measurable viral loads, insulin sensitivity did not correlate with viral load (r = 0.229; p = .45; data not shown). In addition, within the HIV-LD group, individuals with viral loads >400 HIV RNA copies/ml (n = 7) and <400 HIV RNA copies/ml (n = 8) had similar insulin sensitivities (5.89 ± 1.26 and 4.95 ± 1.05 mg glucose/kg LBM/minute, respectively).

At the time of screening, random plasma glucose levels were similar in all groups (data not shown). Following an overnight fast, basal glucose levels were higher in the HIV-LD group, but not significantly (Table 1). The fasting insulin and triglyceride levels were significantly higher in the HIV-LD group than in both the control and HIV groups (p < .05; Table 1). The HIV-LD cholesterol levels (225 ± 15) were significantly greater that those of the HIV group (182 ± 8; p < .05), but not those of the control group (194 ± 6).

Patients in both the HIV and HIV-LD groups were doing well clinically, with decreasing levels of HIV...
RNA copies and increased numbers of CD4+ lymphocytes, relative to recorded nadir levels (Table 1). However, all these patients had significantly elevated circulating levels of sTNFR2, relative to those in the control study subjects ($p < .05$; Fig. 3). More significantly, the HIV-LD group had greater levels of the sTNFR2 than the HIV group ($p < .05$; Fig. 3). Surprisingly, there was no significant difference in the soluble type 2 TNF-α receptor levels in patients with viral loads >400 copies/ml and <400 copies/ml; both groups had soluble type 2 TNF-α receptor levels of 5.5 ± 0.6 ng/ml. Levels of the sTNFR2 in the two HIV-infected groups did not correlate with viral load in those study subjects with measurable viral loads ($r = 0.28; p = .35$). These elevated levels of the sTNFR2 were associated with diminished insulin sensitivity ($r = 0.59; p = .0001$; Fig. 4).

The fasting levels of IGFBP-1 (Fig. 5) and FFAs (Fig. 5) were not increased in the HIV-LD group. The IGFBP-1 levels of the HIV-LD group were significantly lower ($p < .05$) than those of the control (55%) and the HIV (50%) groups (Fig. 5), but similar to those of the high BMI control subgroup (data not shown). IGFBP-1 levels in all groups were responsive to insulin during the hyperinsulinemic-euglycemic clamp (Fig. 5). FFAs levels, however, were less depressed by insulin in the HIV-LD group than in the control and HIV groups (Fig. 5). The ability of insulin to suppress serum FFAs, expressed as the percentage reduction in serum FFA levels under
hyperinsulinemic conditions, relative to fasting conditions, was significantly diminished in the HIV-LD group (56.5 ± 7.9) compared with the control group (88.3 ± 4.6) or the HIV group (80.8 ± 3.1; \( p < .05 \)). The diminished sensitivity of FFA levels to insulin was significantly correlated with the glucose disposal rates from the clamp studies (\( r = 0.5552; p = .0002 \); Fig. 6).

DISCUSSION

In the present study, patients with clinically defined HIV LD had a 34% reduction in percentage of limb fat, relative to findings in the control group (Table 1). These patients exhibited severe insulin resistance (Fig. 1) of a magnitude similar to that seen with type 2 diabetes mellitus (43,44). The loss of limb fat was highly correlated (\( p = .0001 \)) with insulin resistance, as shown in Figure 2, demonstrating, for the first time, that insulin resistance accompanies the pathologic loss of peripheral fat. The well recognized association between trunk adiposity and insulin resistance appears not to be a significant factor in HIV-LD. When patients with HIV-LD were stratified into groups with the greatest versus the least amount of trunk adipose tissue (19.0 kg versus 6.8 kg trunk fat), the two groups had similar insulin sensitivities (data not shown). An alarming feature of HIV-LD is that in the context of a routine clinic examination, the HIV-LD group may be unremarkable, with normal screening glucose levels (data not shown), and elevated triglyceride levels, a feature that has become an expected finding of HIV infection (45). The HIV-LD patients also had significantly elevated levels of the sTNFR2 (Fig. 3). This finding is of interest, given that these patients are doing well clinically, with well-controlled HIV replication and improved numbers of CD4⁺ lymphocytes. Furthermore, insulin resistance in the HIV-infected population was highly correlated (\( p = .0001 \)) with the serum levels of the sTNFR2 (Fig. 4), suggesting that inflammation may contribute to the pathophysiology of LD and insulin resistance. At present, the cellular source of the sTNFR2 is
unknown, and investigations are currently under way to identify this source.

Type 2 diabetes mellitus is characterized by peripheral insulin resistance and fasting hyperglycemia. The latter is indicative of hepatic insulin resistance, resulting from the inability of endogenous insulin to suppress hepatic glucose production. None of these study subjects were hyperglycemic at screening. This afforded the opportunity to examine insulin resistance associated with HIV-LD, in the absence of overt diabetes. Following an overnight fast, glucose levels of the HIV-LD study subjects were elevated, but within the normal range (Table 1), and insulin levels were significantly elevated (threefold relative to those of controls). Thus, although the HIV-LD study subjects appear normal at screening, they exhibit marked peripheral insulin resistance during the stress of the hyperinsulinemic-euglycemic clamp (Fig. 1). The HIV-LD study subjects have fasting levels of IGFBP-1 below normal, unlike in type 2 diabetes mellitus wherein IGFBP-1 levels are elevated (20). This unique ability of the liver to suppress fasting glucose and IGFBP-1 production may be linked mechanistically. The genetic regulatory elements by which insulin controls the gene expression of the rate-limiting enzyme of gluconeogenesis, phosphoenolpyruvate carboxykinase, are identical to those controlling IGFBP-1 expression (46), indicating that this aspect of hepatic insulin action has not become insulin resistant, in contrast to skeletal muscle and adipose tissue. One of the exclusion criteria for participating in this study was a fasting plasma glucose level >126 mg/dl, to exclude individuals with frank diabetes. A recent report (8) documented a group of HIV-infected individuals with frank diabetes, based on hyperglycemia and hyperinsulinemia under fasting conditions. In contrast, the present study and that of Walli et al. (47) clearly demonstrate that there are also HIV-infected individuals who are severely insulin resistant, but whose fasting glucose levels remain within the normal range. At present, it is unknown whether these individuals will progress to frank diabetes, but the association of insulin resistance with hypertriglyceridemia places them at risk for the development of vascular disease.

The HIV-LD subjects in our study have normal fasting serum FFA levels in the presence of slightly elevated levels of insulin. However, insulin resistance in adipose tissue is revealed by the clamp studies. The reduced capacity for suppression of FFA levels by insulin in HIV-LD study subjects is demonstrated by the correlation of insulin sensitivity with hyperinsulinemic suppression of serum FFA levels shown in Figure 6. The subtle resistance of adipose tissue to insulin in HIV-LD may result from increased truncal fat, given that abdominal fat is more resistant than peripheral fat to the antilipolytic effects of insulin (48).

The clinical characteristics of HIV-LD bear a resemblance to the rare forms of acquired and congenital lipodystrophies (49–52), as well as an animal model of lipodystrophic diabetes (53). The congenital and acquired generalized lipodystrophies are characterized by loss of both trunk and limb fat, increased LBM (51), severe insulin resistance (52), normal levels of FFAs (51,52), and suppressed levels of IGFBP-1 (50). All these characteristics, except loss of trunk fat, are also shared with HIV-LD, suggesting that loss of peripheral fat alone may be sufficient to induce a state of peripheral insulin resistance. The increases in the LBM index of the HIV-LD group may also be causally linked to the LD syndrome.

Fat distribution, physiologic parameters, and serum markers associated with different insulin-resistant states are summarized in Table 2. These data demonstrate that the insulin resistance in HIV-LD is distinct from that associated with most forms of type 2 diabetes, based on
hepatic insulin sensitivity, reflected by both fasting glyce-
emia (Table 1) and IGFBP-1 levels (Fig. 5), and insulin
sensitivity of adipose tissue reflected by fasting FFA
levels (Fig. 5). The distinction between HIV-LD and
obesity, although not so dramatic as with type 2 diabetes,
is still clearly demonstrated by the differences in fasting
FFA levels (Table 2). Table 2 also demonstrates that the
insulin resistant state associated with HIV-LD has most
in common with the exceedingly rare congenital and ac-
quired lipodystrophies (52). The similarities include the
loss of peripheral fat, increased LBM, severe insulin
resistance, normal fasting FFA levels, and reduced
IGFBP-1 levels. Although both increased trunk fat and
elevated FFAs are commonly associated with insulin re-
sistance, the presence of insulin resistance in acquired
and congenital LD with loss of trunk fat and normal
FFAs, suggests that loss of peripheral fat alone may also
be sufficient to cause insulin resistance.

The elevation of sTNFR2 levels in the HIV-LD group
is surprising and suggests that the stimulus for the shed-
ing of the type 2 TNF-α receptor is associated with the
development of insulin resistance in this group (Fig. 4).
Elevated sTNFR2 levels are also seen in association with
insulin resistance in myotonic dystrophy (54) and obesity
(36). The patients with HIV-LD have elevated TNF re-
ceptor levels despite the fact that they are doing well
clinically and have been free of acute illness for >3
months. The lack of correlation between viral load and
sTNFR2 levels may indicate that the shedding of the
TNF receptors may be unrelated to the activity of the
HIV infection. The correlation of insulin resistance with
elevated sTNFR2 suggests that an inflammatory stimulus
may contribute to the induction of HIV-LD and insulin
resistance.

The syndrome (or syndromes) of HIV-associated ac-
quired LD is an alarming development in the treatment
of HIV infection. The potential for the accelerated de-
velopment of type 2 diabetes mellitus and coronary ar-
tery disease, in this at risk population, places a high
priority on establishing the etiology and developing ra-
tional therapies for this metabolic condition. The data of
the present study provide strong evidence that individu-
als infected with HIV who have experienced body fat
redistribution from the limbs and face to the trunk have
a syndrome that is closely related to the acquired and
congenital, generalized LD. The association of this syn-
drome with elevated levels of the soluble type 2 TNF-α
receptor indicates that an inflammatory process is
associated with the loss of peripheral insulin sensitivity.
In conclusion, this study emphasizes that HIV patients
with fat redistribution and elevated triglyceride levels are
likely to be severely insulin resistant in the periphery,
even with normal screening plasma glucose levels, and
should be observed closely to prevent their progression
to premature type 2 diabetes mellitus and coronary artery
disease.

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highly active antiretroviral therapy (HAART). *J Acquir Immune
fat in HIV-infected women undergoing combined antiretroviral

**TABLE 2.** Body composition, insulin resistance, and serum markers of insulin resistant states

<table>
<thead>
<tr>
<th></th>
<th>Peripheral fat loss</th>
<th>Trunk adiposity</th>
<th>Increased lean body mass</th>
<th>Insulin resistance</th>
<th>Fasting free fatty acids</th>
<th>Fasting IGFBP-1</th>
<th>Soluble type 2 TNF receptor</th>
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<tr>
<td>Type 2 diabetes</td>
<td>↑↓</td>
<td>↑↑</td>
<td>↔</td>
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<td>↑↑↑</td>
<td>↑↑↑↑</td>
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<td>Obesity</td>
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<td>Congenital or acquired lipodystrophy</td>
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TNF, tumor necrosis factor.


