Differential Effects of Rosiglitazone and Metformin on Postprandial Lipemia in Patients With HIV-Lipodystrophy


Objective—To compare the effects of rosiglitazone (8 mg/d, n = 19) and metformin (2 g/d, n = 18) on postprandial lipemia in patients with HIV-lipodystrophy.

Methods and Results—Lipodystrophy in HIV is associated with insulin resistance and disturbed postprandial triglyceride and free fatty acid (FFA) metabolism. We conducted an open randomized 6-month study with standardized 10-h oral fat-loading tests at baseline and after treatment. Rosiglitazone (−34%) and metformin (−37%) reduced homeostasis model assessment similarly (P < 0.05). Rosiglitazone did not change the area under the curve for FFA and triglyceride; however, it did reduce the area under the curve for hydroxybutyric acid (a marker of hepatic FFA oxidation) by 25% (P < 0.05). Rosiglitazone increased the area under the curve for remnantlike particle cholesterol by 40% (P < 0.01) compared with baseline. Metformin did not change any of the postprandial measurements.

Conclusion—Rosiglitazone improved insulin sensitivity and decreased postprandial hydroxybutyric acid levels in patients with HIV-lipodystrophy, suggesting improved FFA handling. Despite metabolic improvements, rosiglitazone caused a marked increase in postprandial remnantlike particle cholesterol, which may adversely affect cardiovascular risk. Metformin did not affect postprandial lipemia and could be used to treat insulin resistance in this population. (Arterioscler Thromb Vasc Biol. 2011;31:228-233.)

Key Words: HIV • atherosclerosis • insulin resistance • triglycerides • adipose tissue • postprandial

Changes in body fat distribution (lipodystrophy), including subcutaneous fat loss and intra-abdominal fat accumulation, are common in HIV-infected patients receiving highly active antiretroviral therapy (HAART). Lipodystrophy is associated with insulin resistance and dyslipidemia, which are risk factors for cardiovascular disease (CVD). Recent studies have shown that exposure to HAART is associated with an increased risk of myocardial infarction, which is partly explained by dyslipidemia.

Dyslipidemia in HIV-lipodystrophy involves increased triglyceride (TG) and decreased high-density lipoprotein cholesterol levels, similar to other insulin-resistant disease states. Furthermore, patients with HIV-lipodystrophy have increased postprandial free fatty acid (FFA) levels because of impaired adipocyte FFA trapping, leading to enhanced hepatic FFA delivery. Delayed postprandial clearance of TG-rich lipoproteins has also been demonstrated in HIV-infected patients receiving HAART. Nonfasting TG level and increased postprandial lipemia are independent risk factors for CVD. Remnantlike particles are highly atherogenic, and these particles are present in atherosclerotic lesions. Even in fasting normolipidemic subjects, increased postprandial lipemia has been linked to CVD.

Metformin and the peroxisome proliferator–activated receptor–γ (PPAR–γ) agonist rosiglitazone are used in clinical practice to improve insulin resistance and glycemic control in patients with type 2 diabetes mellitus. Both agents have also been investigated in patients with HIV-lipodystrophy. Rosiglitazone is thought to act mainly in adipose tissue by increasing FFA delivery. Rosiglitazone-induced improvement of adipocyte FFA trapping could improve lipodystrophy and some associated metabolic abnormalities, including postprandial lipemia. Metformin may also affect postprandial lipemia by modulation of insulin sensitivity.

We evaluated the effects of rosiglitazone and metformin on postprandial lipid and FFA metabolism in HIV-infected patients with lipodystrophy in an open randomized 6-month study.

Methods

Subjects
HIV-infected men were recruited from the Department of Infectious Diseases from the University Medical Center, Utrecht. Inclusion criteria were as follows: aged 18 to 70 years, HIV RNA < 10,000 copies/mL, the presence of lipodystrophy, and stable HAART for at least 18 months (with no changes in the treatment regimen for 6 months before inclusion). Exclusion criteria were as follows: the

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presence of opportunistic infectious diseases or malignancies; renal, thyroid, and/or liver disease; diabetes; and alcohol intake >3 U/d. The presence of lipodystrophy was defined as self-reported symptoms of subcutaneous fat loss with or without central fat accumulation. These findings were confirmed by an investigator (J.P.H.v.W.) before enrollment.

**Study Design**
This was a prospective, randomized, nonblinded study. The effects of rosiglitazone and metformin on body fat distribution, insulin sensitivity, and endothelial function have been published separately. At inclusion, a fasting blood sample was obtained and anthropometric measurements were performed. Concomitant use of medication was recorded. Eligible patients underwent an oral fat-loading test and single-slice abdominal computed tomography (CT). Subsequently, participants were randomly assigned in blocks of 4 to receive rosiglitazone (8 mg/d) or metformin (2 g/d) for 26 weeks. Patients visited the hospital after 2 and 4 months of treatment for a safety evaluation. Adherence to study medication was evaluated by an open-ended questionnaire. The study protocol was approved by the local research ethics committee of our hospital. All participants gave written informed consent.

**Cross-Sectional CT**
Single-slice cross-sectional CT at the L4–5 level was performed as previously described. A lateral scout image was obtained to identify the level of the L4 pedicle, which served as the landmark for the 1-cm single-slice image. Scan variables were as follows: 144-cm table height, 80 kV, 70 mA, 2 s, and a 48-cm field of view. On the CT image, the border of the intra-abdominal cavity was outlined and total abdominal fat and visceral abdominal fat (VAT) were quantified by selecting an attenuation range of –250 to –50 Hounsfield units. Subcutaneous abdominal fat (SAT) was calculated as the difference between total abdominal fat and VAT.

**Oral Fat-Loading Test**
After placing a cannula for venous blood sampling, subjects rested for 30 minutes before the administration of the fat load. Fresh cream was used as the fat source; this is a 40% (wt/vol) fat emulsion with a polyunsaturated/saturated fat ratio of 0.10, containing 0.001% (wt/vol) cholesterol and 3% (wt/vol) carbohydrates, representing a total energy content of 3700 kcal/L. Cream was ingested within 5 minutes at a dose of 50 g of fat and 3.75 g of glucose per square meter of body surface. Peripheral blood samples were obtained in sodium EDTA (2 mg/mL) and lithium-heparin tubes, before and at regular intervals up to 10 h postprandially. Samples were kept on ice and centrifuged immediately for 15 minutes at 800 g at 4°C; then, plasma was stored at –80°C until assayed.

**Analytical Procedures**
Glucose, cholesterol, TG, apolipoprotein (apo) B, creatinine, and aminotransferases were measured by standard clinical laboratory procedures.

**Statistical Analysis**
Data are expressed as mean±SD. For measurements during the oral fat-loading test, areas under the curves (AUCs) were calculated by the trapezoidal rule using computer software (GraphPad Prism, version 4.0). Assumptions of normality were tested by Kolmogorov-Smirnov tests and review of plots. The primary analysis was to compare treatment effects between groups. For variables with a symmetrical distribution, we used t tests on changes from baseline.
phy.1–3 We evaluated the effects of the insulin-sensitizing agents rosiglitazone and metformin on postprandial lipemia in these patients. Rosiglitazone improved insulin sensitivity and markers of adipocyte FFA trapping. Despite metabolic improvements, rosiglitazone increased postprandial RLP-C. Metformin also improved insulin sensitivity but did not change postprandial lipemia in this population.

Rosiglitazone tended to decrease fasting FFA but did not change FFA AUC. However, FFA concentrations do not provide information on the direction of FFA fluxes. Thus, HBA measurements were included in this study. HBA is a marker of hepatic FFA oxidation. HBA is formed in liver mitochondria solely from FFA, and FFA availability is the major determinant of HBA formation.26 Therefore, postprandial HBA appearance in plasma may serve as a marker of postprandial hepatic FFA delivery. Rosiglitazone markedly reduced postprandial HBA levels, suggesting decreased hepatic FFA delivery by improved adipocyte FFA trapping. This hypothesis was also supported by the increase in SAT adipose tissue, and the PPAR-γ agonist rosiglitazone regulates the transcription of genes that stimulate FFA storage in adipose tissue.18 We did not perform stable isotope studies, which could have provided more detailed information on in vivo fluxes of FFA. However, our data are in agreement with a small kinetic study27 conducted in patients with HIV-lipodystrophy, showing decreased lipolysis and hepatic reesterification in conjunction with favorable trends in body composition after treatment with rosiglitazone. Similarly, rosiglitazone lowered FFA levels after a labeled meal in diabetic patients, suggesting decreased spillover of FFA from adipose tissue depots.28 Metformin did not affect postprandial FFA and HBA levels in this population, despite beneficial effects on insulin sensitivity and reduction of VAT. Evidently, both drugs improve insulin sensitivity through different mechanisms.

Liver fat is an important determinant of insulin resistance.29 Rosiglitazone reduces liver fat in diabetic patients in conjunction with improved hepatic insulin sensitivity.29 A limitation of our study is that we did not measure liver fat and, thus, cannot evaluate the potential role of liver fat

### Table 2. Effects of Rosiglitazone and Metformin on Body Fat Distribution and Metabolic Profile

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline*</th>
<th></th>
<th>Change After 26 wk*</th>
<th></th>
<th>P Value (Difference Between Rosiglitazone and Metformin)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rosiglitazone Group</td>
<td>Metformin Group</td>
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<td></td>
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<tr>
<td></td>
<td>(n=19)</td>
<td>(n=18)</td>
<td>(n=19)</td>
<td>(n=18)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.1±2.6</td>
<td>24.6±3.1</td>
<td>0.4±0.6†</td>
<td>−0.4±0.5†</td>
<td>0.02</td>
</tr>
<tr>
<td>Subcutaneous abdominal fat, cm²</td>
<td>98±47</td>
<td>103±38</td>
<td>16±31†</td>
<td>−11±17†</td>
<td>0.007</td>
</tr>
<tr>
<td>Visceral abdominal fat, cm²</td>
<td>158±65</td>
<td>189±63</td>
<td>−1±36</td>
<td>−25±35†</td>
<td>0.01</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
<td>41±17</td>
<td>42±22</td>
<td>−6±26†</td>
<td>−8±16†</td>
<td>0.83</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>37±13</td>
<td>43±21</td>
<td>−7±13†</td>
<td>−9±20†</td>
<td>0.76</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.6±0.7</td>
<td>5.7±0.7</td>
<td>0.4±1.0</td>
<td>−0.4±0.8†</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.2±0.5</td>
<td>3.4±0.6</td>
<td>0.2±0.6</td>
<td>−0.4±0.6†</td>
<td>0.02</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.23±0.20</td>
<td>1.03±0.21</td>
<td>−0.15±0.20†</td>
<td>0.01±0.18</td>
<td>0.05</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>1.09±0.24</td>
<td>1.17±0.27</td>
<td>0.09±0.16</td>
<td>−0.10±0.13†</td>
<td>0.02</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.2±0.4</td>
<td>5.3±0.4</td>
<td>−0.3±0.3†</td>
<td>−0.2±0.4</td>
<td>0.73</td>
</tr>
<tr>
<td>Insulin, mU/L</td>
<td>7.3±3.8</td>
<td>8.1±4.1</td>
<td>−3.8±2.4†</td>
<td>−4.1±2.9†</td>
<td>0.65</td>
</tr>
<tr>
<td>Homeostasis model assessment</td>
<td>1.63±0.85</td>
<td>2.16±1.03</td>
<td>−0.6±0.5†</td>
<td>−0.8±0.6†</td>
<td>0.76</td>
</tr>
</tbody>
</table>

*Data are given as mean±SD.
†Significant change from baseline (P<0.05).

### Table 3. Effects of Rosiglitazone and Metformin on Postprandial Lipid and Fatty Acid Metabolism

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline*</th>
<th></th>
<th>Change After 26 wk*</th>
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<td></td>
</tr>
<tr>
<td></td>
<td>(n=19)</td>
<td>(n=18)</td>
<td>(n=19)</td>
<td>(n=18)</td>
<td></td>
</tr>
<tr>
<td>Fasting FFA, mmol/L</td>
<td>0.49±0.28</td>
<td>0.48±0.30</td>
<td>−0.08±0.14</td>
<td>0.08±0.17</td>
<td>0.03</td>
</tr>
<tr>
<td>FFA AUC, mmol×h/L</td>
<td>7.5±2.2</td>
<td>7.5±2.5</td>
<td>−0.6±0.9</td>
<td>0.3±0.8</td>
<td>0.16</td>
</tr>
<tr>
<td>Fasting TG, mmol/L</td>
<td>2.30±1.29</td>
<td>3.04±1.97</td>
<td>0.5±1.8†</td>
<td>−0.6±1.4†</td>
<td>0.02</td>
</tr>
<tr>
<td>TG AUC, mmol×h/L</td>
<td>39.6±20.4</td>
<td>48.3±23.4</td>
<td>4.2±18.0</td>
<td>−1.7±16.2</td>
<td>0.34</td>
</tr>
<tr>
<td>Fasting HBA, μmol/L</td>
<td>79±42</td>
<td>72±50</td>
<td>4±24</td>
<td>12±49</td>
<td>0.83</td>
</tr>
<tr>
<td>HBA AUC, μmol×h/L</td>
<td>1946±882</td>
<td>1501±749</td>
<td>−555±286†</td>
<td>90±191</td>
<td>0.02</td>
</tr>
<tr>
<td>RLP-C, mmol/L</td>
<td>18.6±5.3</td>
<td>25.2±7.1</td>
<td>14.2±12.6†</td>
<td>−0.1±11.8</td>
<td>0.01</td>
</tr>
<tr>
<td>RLP-C AUC, mmol×h/L</td>
<td>251±112</td>
<td>310±155</td>
<td>95±64†</td>
<td>−3±50</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Data are given as mean±SD.
†Significant change from baseline (P<0.05).
accumulation in postprandial lipemia. Aminotransferases, which may indicate the presence of steatosis when elevated, decreased in both treatment groups.

Insulin plays an important role in the regulation of lipoprotein production and clearance. Despite improvement of insulin sensitivity, neither agent improved TG AUC. In previous studies, metformin improved postprandial lipemia in patients with type 2 diabetes or glucose intolerance, possibly because of the reduction of hyperglycemia. In our study, rosiglitazone reduced the postprandial TG increase, despite increased fasting TG concentrations, resulting in unchanged total TG AUC. Such an isolated postprandial TG reduction has already been described with rosiglitazone in patients with type 2 diabetes. The postprandial TG reduction may be secondary to an increased rate of removal by lipoprotein lipase, which was not measured in our study. In addition, rosiglitazone may decrease hepatic production of TG-rich lipoproteins by reducing postprandial hepatic FFA delivery and improving insulin sensitivity.

High levels of remnant lipoproteins are closely linked to CVD. RLP-C levels reflect lipoprotein remnant levels, and increased RLP-C levels have been associated with surrogate markers for CVD. Furthermore, RLP-C levels were increased in patients with established CVD; and elevated RLP-C levels were predictive of future coronary events in patients with CVD, independently of other risk factors. In our study, rosiglitazone markedly increased postprandial RLP-C levels and, thus, caused a shift toward a more atherogenic lipoprotein phenotype. Whether rosiglitazone affects cardiovascular risk in HIV-infected patients is not known. Recent meta-analyses raised concerns regarding an increased risk of myocardial infarction associated with rosiglitazone treatment of type 2 diabetes. Prospective data of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) trial were inconclusive about any possible effect on myocardial infarction, but rosiglitazone did not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs. These findings have resulted in ongoing review of cardiovascular safety of rosiglitazone by the Food and Drug Administration. Our data confirm and extend observations made in other studies regarding worsening of the lipid profile after treatment with rosiglitazone in HIV-infected patients. Although we acknowledge that our
sample size was relatively small, and prospective data in HIV-infected patients are not available, we would not recommend the use of rosiglitazone in HIV-infected patients with marked dyslipidemia and high cardiovascular risk.

The underlying mechanism for the RLP-C increase after rosiglitazone treatment warrants further investigation. Several different mechanisms may contribute. First, the observed effects may be drug related. In obese insulin-resistant subjects, rosiglitazone increased postprandial apo B48. Because apo B48 levels reflect the number of intestinally derived lipoproteins, this may suggest impaired receptor-mediated uptake of chylomicron (remnant) particles by the liver. Regrettably, apo B48 was not measured in our study. In nondiabetic men, rosiglitazone also tended to reduce clearance of TG-rich particles. In contrast, rosiglitazone did not change postprandial RLP-C levels in diabetic patients.

Second, HIV has been reported to decrease high-density lipoprotein and LDL cholesterol levels and impair lipoprotein lipase–mediated TG clearance. Hypertriglyceridemia in treatment-naive HIV-infected patients is related to poor virological control. However, this is unlikely in our patients because they were receiving stable HAART with good virological control. Third, the results may have been influenced by HAART. Protease inhibitors especially may impair postprandial clearance of TG-rich lipoproteins and their remnants by downregulation of the LDL receptor. Fourth, the patients in our study had a normal body mass index, in contrast to patients in previous studies with rosiglitazone. In that regard, metabolic syndrome in patients with HIV may differ from that in the general population. Our patient selection was based on the presence of lipodystrophy, including peripheral fat loss. The presence of lipodystrophy could also have influenced the treatment effects of rosiglitazone on postprandial lipemia. Finally, the lipid-lowering responses of fibrates and statins are enhanced in patients with more pronounced dyslipidemia at baseline. In our study, baseline TG AUC was slightly higher in the metformin group compared with the rosiglitazone group; however, this difference did not reach statistical significance. We cannot fully exclude that in our study the treatment effects on postprandial lipemia were influenced by differences in baseline lipids.

It is not clear how the other registered thiazolidinedione, pioglitazone, would have affected posprandial lipemia in HIV-infected patients. In contrast to rosiglitazone, pioglitazone reduces the composite of all-cause mortality, nonfatal myocardial infarction, and stroke in patients with type 2 diabetes. Rosiglitazone and pioglitazone differ in their effects on lipid profile, despite similar effects on insulin sensitivity and glycemic control. Compared with rosiglitazone, pioglitazone has greater benefits on high-density lipoprotein cholesterol, LDL particle concentration, and LDL particle size; these benefits are related to improved TG metabolism. Pioglitazone, but not rosiglitazone, decreases apo CIII, which is an inhibitor of lipoprotein lipase. Observations in vitro suggest that pioglitazone has a greater potential than rosiglitazone to react with PPAR-α, the main target for fibrates. Although these data point to a potentially greater benefit of pioglitazone compared with rosiglitazone, to our knowledge, there are no randomized clinical studies directly comparing these agents in HIV-infected patients. The number of clinical trials conducted with pioglitazone is small, and more data are needed to determine whether it is a safe and effective treatment option in this population. Available data in HIV-infected patients suggest that the benefits of pioglitazone on fasting lipids are small, whereas data on postprandial lipemia are virtually absent. We had chosen not to use pioglitazone because it is partly metabolized by cytochrome P450 3A4 (CYP3A4), increasing the risk of clinically relevant drug interactions with protease inhibitors, which were used by most patients in our study.

Fibrates are generally effective in HIV dyslipidemia management. Moreover, there is no significant drug–drug interaction among protease inhibitors and fibrates. So far, the results of clinical trials on cardiovascular end points with fibrates have been disappointing, but the absolute benefits of fenofibrate are likely to be greater when metabolic syndrome features are present. The highest risk and greatest benefits of fenofibrate are seen among those with marked hypertriglyceridemia. Consequently, patients with HIV dyslipidemia may also benefit from treatment with fibrates.

In conclusion, the results of our study suggest improved postprandial FFA handling after treatment with rosiglitazone that contributes to improved insulin sensitivity in patients with HIV-lipodystrophy. Nevertheless, rosiglitazone markedly increased postprandial RLP-C, which may adversely affect cardiovascular risk in these patients. Metformin did not affect postprandial lipemia but could be used to treat insulin resistance in this population.

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Disclosures
None.

References
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