Adiponectin in glucose metabolism
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A rosiglitazone-induced increase in plasma adiponectin does not improve glucose metabolism in HIV-infected patients with overt lipoatrophy

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Submitted
Abstract

Objective:
HIV-infected patients on antiretroviral therapy frequently develop changes in body fat distribution and disturbances in glucose metabolism, associated with reduced adiponectin levels. As adiponectin, principally the HMW (high-molecular-weight) form, has insulin sensitizing properties, upregulation of adiponectin could be effective in improving glucose metabolism in HIV-lipodystrophy.

Methods:
In this randomized, double-blind, placebo-controlled trial, we included HIV-1-infected patients with severe lipoatrophy, with an undetectable viral load and who had received neither protease inhibitors nor stavudine for ≥6 months. Patients were randomized to rosiglitazone (8 mg daily (N=8)) to increase adiponectin levels or placebo (N=5) for 16 weeks. Peripheral glucose disposal, glucose production and lipolysis were measured after an overnight-fast and during a hyperinsulinemic-euglycemic clamp using stable isotopes. Body composition was assessed by CT and DEXA.

Results:
Although body fat distribution was unaffected, rosiglitazone increased total plasma adiponectin levels by 107% (p<0.02) and the ratio of HMW to total adiponectin by 73% (p<0.001). In the placebo group, neither total adiponectin levels (p=0.62), nor the ratio of HMW to total adiponectin changed (p=0.94). Despite the marked increase in plasma adiponectin, rosiglitazone had no effect on basal endogenous glucose production (p=0.90) and lipolysis (p=0.90) nor on insulin-mediated suppression of glucose production (p=0.17) and lipolysis (p=0.54) or on insulin-mediated peripheral glucose disposal (p=0.13).

Conclusions:
Although rosiglitazone induced an increase in plasma adiponectin levels, primarily of the HMW form in HIV-lipoatrophic patients, this did not result in an improvement of glucose and lipid metabolism. This questions the importance of adiponectin in regulating glucose metabolism in HIV-lipodystrophy.
Introduction

Combination antiretroviral treatment (cART) has remarkably improved the prognosis of patients with HIV-1-infection, but is associated with metabolic disturbances and changes in body fat distribution or lipodystrophy. The metabolic disturbances include dyslipidemia and alterations in glucose metabolism, ranging from insulin resistance at the level of peripheral glucose disposal, hepatic glucose production and lipolysis to overt diabetes mellitus type 2. The pathogenesis of these perturbations is likely multifactorial. Dysfunction of adipose tissue has been implicated to contribute to the disturbances in glucose metabolism.

In addition to being a fat storage depot, adipose tissue has been shown to be an endocrine organ, which synthesizes and secretes a variety of biologically active molecules that influence glucose metabolism. Among these adipocytokines is adiponectin, a relatively abundant plasma protein, which is produced and secreted predominantly by adipocytes. In healthy rodents as well as in animals with lipoatrophy or obesity, administration of adiponectin ameliorates glucose metabolism by enhancing peripheral glucose uptake and suppressing hepatic glucose output. Probably, these effects occur via AMP-activated protein kinase (AMPK)-dependent stimulation of fat oxidation. In plasma, adiponectin circulates as several different entities, including a HMW, a hexameric (medium-molecular-weight) and a trimeric (low-molecular-weight) form. The HMW oligomer has been implicated as the major active form, responsible for the insulin-sensitising effects of adiponectin.

Plasma levels of adiponectin, primarily of the HMW isoform, are reduced in insulin resistant subjects with type 2 diabetes and HIV-associated lipodystrophy. In addition, adiponectin mRNA expression in subcutaneous adipose tissue of HIV-lipodystrophic patients is lower compared to in cART-treated HIV-infected patients without lipodystrophy. Considering the insulin-mimetic properties of adiponectin, the reduction of (HMW) adiponectin could play a role in the pathogenesis and/or perseverance of insulin resistance in HIV-associated lipodystrophy. Indeed, in HIV-infected, lipodystrophic patients, plasma adiponectin levels have been negatively associated with markers of insulin resistance. Therefore it can be hypothesized that upregulation of plasma adiponectin could result in improved glucose metabolism in HIV-associated lipodystrophy. As adiponectin has not (yet) been administered to human subjects, currently plasma (HMW) adiponectin can only be increased in an indirect manner. The most potent enhancers of (HMW) adiponectin are the peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists. Although several studies...
have reported on the effects of PPAR-γ agonists in HIV-associated lipodystrophy, only one non-placebo-controlled study addressed the role of (HMW) adiponectin in glucose metabolism.

In order to obtain more insight into the role of adiponectin in the perturbations of glucose metabolism in HIV-lipodystrophy, we conducted a randomized, double-blind placebo-controlled clinical trial of 16 weeks duration, using the PPAR-γ agonist rosiglitazone to enhance (HMW) adiponectin levels. The study was performed in HIV-1-infected patients with clinically overt lipoatrophy and an undetectable viral load. Given that, at the time the trial was designed and performed, amongst the antiretroviral drugs, mainly protease inhibitors (PI) and stavudine (d4T) had been associated with reduced adiponectin concentrations and insulin resistance, we only included HIV-infected patients who were not or no longer receiving PI and d4T for ≥6 months. The effects of rosiglitazone on insulin sensitivity at the level of peripheral glucose disposal, endogenous glucose production and lipolysis were assessed by performing hyperinsulinemic-euglycemic clamps using stable isotopes. Body fat distribution was determined by abdominal computed tomography (CT) and dual-energy X-ray absorptiometry (DEXA).

Patients and methods

Subjects

Male subjects with a documented HIV-infection and ≥18 years of age were recruited from the Academic Medical Center, Amsterdam, The Netherlands or from neighboring centers. Participants had to be on the same cART regimen for ≥4 months prior to study entry. In addition, their antiretroviral treatment could not have included any HIV PI for ≥9 months, nor d4T for ≥6 months before randomization. Furthermore, patients had to exhibit clinically overt lipoatrophy, defined as self-reported and investigator confirmed loss of subcutaneous fat (face, arms, legs and buttocks) with or without increased abdominal fat mass or the presence of a buffalo hump. HIV-1 RNA values had to be less than 50 copies/mL. Exclusion criteria were serum transaminases, bilirubin and lactate concentrations >2.5 times the upper limit of normal, haemoglobin levels <6 mmol/L or an active viral hepatitis within the previous 6 months. We also excluded patients with clinical evidence of heart failure, diabetes mellitus (fasting glucose levels >7 mmol/l), severe hyperlipidemia (triglyceride level >10 mmol/l or total cholesterol level >8 mmol/l), active infections or HIV-wasting (a recent loss of >10% of body weight) as well as patients using medication which could affect metabolism, e.g. systemic corticosteroids, anti-
diabetic agents, testosterone, growth hormone or fibrates. The study was approved by the Medical Ethical Committee of the Academic Medical Center, Amsterdam. Written informed consent was obtained from all participants prior to study entry.

Study design
The study was designed as a randomized, double-blind, placebo-controlled trial. Eligible individuals were randomly assigned to receive rosiglitazone (8 mg/day) or identical-looking placebo for 16 weeks. An independent statistician generated a treatment allocation sequence (1:2 for placebo:rosiglitazone). Allocation concealment was ensured by an independent pharmacist. After the randomized study period of 16 weeks, patients were requested to voluntarily participate in an open-label study of rosiglitazone for an additional 16 weeks.

The primary objective of the study was to assess the impact of an increase in plasma (HMW) adiponectin levels by rosiglitazone on glucose (peripheral glucose disposal, endogenous glucose production) and lipid metabolism (lipolysis, fat oxidation) over time. Secondary objectives included the effects on free fatty acids (FFA), glucoregulatory hormones, lipids, body composition and safety parameters.

Glucose metabolism was investigated by hyperinsulinemic-euglycemic clamps using stable isotopes at baseline and 16 weeks following the start of treatment. Body fat distribution was assessed at these same timepoints by abdominal CT-, whole body DEXA-scan, measurement of body mass index (BMI), waist and hip circumference as well as patient-reported- and investigators’ impressions by questionnaires rating the severity of lipodystrophy by body site and quality of life. Patients visited the hospital at week 0, 2, 4, 8 and 16 for drug safety evaluation, which included an updated history, physical examination and drawing of blood samples after an overnight fast. During the study, participants were requested to maintain their current diet and exercise pattern.

Hyperinsulinemic-euglycemic clamp protocol
The hyperinsulinemic-euglycemic clamp was performed exactly as described before. The HMW form of adiponectin was measured at T=0.

Indirect calorimetry
Oxygen consumption (VO$_2$) and CO$_2$ production (VCO$_2$) were measured continuously during the final 20 min of both the basal state and the hyperinsulinemic clamp by indirect calorimetry using a ventilated hood system (Sensormedics model 2900; Sensormedics, Anaheim, CA).
Body composition
Total and regional fat mass were quantified in all patients by DEXA (Hologic QDR-4500W, software version whole body v8.26A:5; Bedford, Massachusetts, USA) providing a quantitative assessment of peripheral (sum of arm and leg fat), trunk and total (sum of peripheral, trunk and head fat) fat mass in kg. A standardized single-slice abdominal CT-scan through the level of the 4th lumbar vertebra was performed from which the surface area of visceral (VAT) and subcutaneous adipose tissue (SAT) was determined and expressed in cm².

Analytical procedures
Plasma insulin, cortisol, catecholamines, glucagon, FFA, adiponectin and sTNFR 1 and 2 concentrations were measured as described before 30. The HMW form of adiponectin was measured in duplicate by gel electrophoresis and western blot 31. Plasma HIV-1 RNA was measured by the Roche Amplicor HIV-1 ultrasensitive assay with a lower limit of quantification of 50 copies/mL and the CD4 cell count was determined by flow cytometry. Plasma samples for enrichments of [6,6-2H2]-glucose and [2H5]-glycerol were determined as described before 32. Other laboratory measurements as lipids were obtained using standard techniques.

Calculations and statistical analysis
Ra of glucose, peripheral glucose disposal and Ra of glycerol were calculated with a modified form of Steele-equations, as described before 30. Resting energy expenditure as well as glucose and fat oxidation rates were calculated from O₂ consumption and CO₂ production as reported previously 33.

We used an intent to treat analysis. Changes within groups were analyzed by paired Student’s t-tests. In both groups, for each parameter, the difference was calculated between the value at week 16 and at baseline. Subsequently, the mean differences between the 2 treatment arms were analyzed by Wilcoxon tests. Correlations between changes in adiponectin levels and changes in glucose metabolism parameters were analyzed by the Spearman correlation coefficient. A p-value <0.05 was considered statistically significant. Data are presented as median and interquartile range (IQR). SPSS statistical software version 12.0.1 (SPSS Inc, Chicago, IL) was used for all analyses. Assuming a mean glucose disposal of 21.3 μmol/kg•min with a standard deviation of 4.9 μmol/kg•min in male patients with HIV-associated lipodystrophy and ± 50 years of age 34, a sample size of 6 patients was considered sufficient to allow detecting a change over time of ± 33% with α=0.05 and 80% power.
Results

Patient characteristics (Table 1)
Between November 2003 and March 2006, 13 male patients were included. Eight patients were randomised to rosiglitazone and 5 to placebo. Their demographic and clinical characteristics are shown in Table 1. In the placebo group the following regimens were used in the usual recommended doses: 1. lamivudine + tenofovir + nevirapine; 2. zidovudine + lamivudine + abacavir; 3. lamivudine + didanosine + nevirapine; 4+5. lamivudine + didanosine + efavirenz. In the rosiglitazone arm patients used: 1. lamivudine + abacavir + nevirapine; 2. zidovudine + lamivudine + nevirapine; 3. lamivudine + tenofovir + efavirenz; 4. zidovudine + lamivudine + didanosine + efavirenz; 5. zidovudine + lamivudine + abacavir + nevirapine; 6-8. zidovudine + lamivudine + abacavir. One patient in the placebo arm switched from abacavir (regimen of lamivudine + abacavir + tenofovir) to nevirapine after 11 weeks of study duration because of emerging concern that this regimen might be associated with an increased risk of virological failure. None of the patients started medication that could be expected to influence glucose metabolism during the study.

Table 1. Baseline patient characteristics, virological and immunological parameters

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>Number</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Age (y)</td>
<td>45 (40-50)</td>
<td>43 (42-58)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 (22-27)</td>
<td>23 (22-26)</td>
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<tr>
<td>Duration of ART (y)</td>
<td>8.8 (6.9-11.6)</td>
<td>7.5 (5.1-9.6)</td>
</tr>
<tr>
<td>Duration of current regimen (mo)</td>
<td>22 (7-47)</td>
<td>20 (13-39)</td>
</tr>
<tr>
<td>Duration after stop PI (mo)</td>
<td>52 (42-64)</td>
<td>48 (30-84)</td>
</tr>
<tr>
<td>Duration after stop d4T (mo)</td>
<td>36 (7-48)</td>
<td>39 (18-47)</td>
</tr>
<tr>
<td>Lipo-atrophy (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Fat accumulation (%)</td>
<td>88</td>
<td>60</td>
</tr>
<tr>
<td>HIV-1 RNA&lt;50 c/ml (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CD4-cell count (x10⁶ cells/l)</td>
<td>565 (488-663)</td>
<td>540 (425-825)</td>
</tr>
</tbody>
</table>

Data represent median (IQR)

Body composition (Table 2)
There were no significant changes in any of the body composition parameters over the course of 16 weeks. Neither the patients, nor the investigators reported subjective improvement of lipodystrophy (data not shown).
Plasma adiponectin levels (Table 2, Figure 1)

Rosiglitazone increased total basal plasma adiponectin levels by 107% (p<0.02). The ratio of HMW to total adiponectin increased by 73% (p<0.001). In the placebo group, neither total adiponectin levels (p=0.62), nor the ratio of HMW to total adiponectin changed (p=0.94). As a result, both the changes in total plasma adiponectin levels and in the ratio of HMW to total adiponectin were significantly different when comparing the study arms (both p<0.01).
Glucose and lipid metabolism (Table 3)

In the rosiglitazone group, there were no significant changes in basal plasma glucose (p=0.22) or insulin levels (p=0.23) after 16 weeks. Rosiglitazone had no effect on insulin-mediated peripheral glucose disposal (p=0.13), endogenous glucose production or glucose oxidation, neither basally (glucose production: p=0.90; glucose oxidation: p=0.77) nor during hyperinsulinemia (glucose production: p=0.17; glucose oxidation: p=0.66). Additionally, there were no differences over time in the rosiglitazone arm considering lipolysis or fat oxidation neither after a 12h-fast (lipolysis: p=0.90; fat
oxidation: p=0.64) nor during the clamp (lipolysis: p=0.54; fat oxidation: p=0.37). Rates of resting energy expenditure did not change either (basal: p=0.83; clamp: p=0.39). Rosiglitazone treatment did not change basal FFA levels (p=0.11), but decreased FFA levels during hyperinsulinemia (p<0.05).

In the placebo arm, there was a small but significant decline over time in glucose production rates both basally and during the hyperinsulinemic clamp (both p<0.05). Regarding all other parameters of glucose metabolism, there were no significant changes over the course of 16 weeks in the placebo arm. When comparing the 2 study arms, there were no significant differences in the changes in parameters of glucose metabolism during the study period.
Gluco-regulatory hormones, lipids and immunological parameters (Table 2)
There were no significant differences in basal plasma concentrations of cortisol, epinephrine, norepinephrine, sTNFR 1 and 2 over time in either treatment group. Rosiglitazone significantly increased basal plasma glucagon levels (p<0.05), whereas glucagon was not affected by placebo. There was no difference in the change in basal glucagon between the 2 arms. Plasma total- and LDL-cholesterol levels significantly increased during treatment with rosiglitazone (both p<0.05), resulting in significantly increased total- and LDL-cholesterol in patients randomized to rosiglitazone versus placebo (both p<0.05). Levels of HDL-cholesterol and triglycerides did not change significantly in either arm. CD4 cell count and HIV-1 RNA remained unchanged over the study course in both arms.

Correlates of (HMW) adiponectin (Figure 2)
In the rosiglitazone arm there were no significant correlations between the changes over time in both total plasma adiponectin levels (data not shown) as well as the ratio of HMW to total adiponectin and the changes over time in basal plasma glucose levels (r=0.522, p=0.19), basal plasma insulin levels (r=0.133, p=0.75), insulin-mediated peripheral glucose disposal (r=0.289, p=0.49), glucose production or lipolysis, neither basally (r=0.193, p=0.65 and r=0.265, p=0.53, respectively) nor during hyperinsulinemia (r=0.145, p=0.73 and r=0.205, p=0.63, respectively).

Figure 2 Left: correlation between the absolute changes (Δ) over time in the basal plasma HMW to total adiponectin ratio (%) and the absolute changes over time in insulin-mediated peripheral glucose disposal (Rd) in the rosiglitazone arm (N=8). Right: correlation between the absolute changes (Δ) over time in the basal plasma HMW to total adiponectin ratio (%) and the absolute changes over time in endogenous glucose production during the clamp in the rosiglitazone arm (N=8). Correlation with Spearman correlation coefficient.
Study extension

After the randomized study period of 16 weeks, patients were offered to participate in an open-label study of rosiglitazone for another 16 weeks. Three patients who had been receiving placebo during the randomized phase, accepted to be treated with rosiglitazone during 16 weeks. Inclusion of the data from these 3 patients (N=11) resulted in an increase in trunk fat (change 0.3 (0.0-0.9) kg: p<0.05) as well as in total body fat (change 0.4 (0.0-1.8) kg: p<0.05). The results concerning adiponectin levels and glucose metabolism did not change: rosiglitazone significantly increased total basal plasma adiponectin levels as well as the ratio of HMW to total adiponectin. Despite this increase in (HMW) adiponectin, there were no significant improvements in any of the parameters of glucose metabolism (data not shown).

Six patients who had already been receiving rosiglitazone during the placebo-controlled phase of the study, consented to participate in the study extension and thus eventually
had received rosiglitazone for a total of 32 weeks. Inclusion of their data in the analysis showed an increase in trunk fat (change 1.2 (0.8-1.9) kg: p<0.02), limb fat (change 0.5 (0.2-1.1) kg: p<0.05) and total body fat (change 1.8 (1.3-2.6) kg: p<0.02). Despite a further increase in plasma (HMW) adiponectin levels (data not shown) after 32 weeks of rosiglitazone, likewise no improvements in glucose metabolism were observed.

### Discussion

HIV-infected patients treated with cART frequently develop changes in body fat distribution and disturbances in glucose metabolism, including insulin resistance at the level of peripheral glucose disposal, hepatic glucose production and lipolysis. Plasma levels of adiponectin, primarily the HMW form, are reduced in insulin resistant patients with type 2 diabetes as well as HIV-associated lipodystrophy and have been...
associated with markers of insulin resistance. The present study, to the best of our knowledge, is the first prospective, placebo-controlled clinical trial that describes the effects of a rosiglitazone-induced increase in plasma (HMW) adiponectin levels on the perturbations of glucose and lipid metabolism in HIV-associated lipodystrophy by conducting hyperinsulinemic-euglycemic clamps using stable isotopes. Our study shows that although rosiglitazone markedly increased both total adiponectin levels as well as the ratio of HMW to total adiponectin in HIV-infected lipoatrophic patients, this did not result in an improvement of glucose and lipid metabolism.

In animal experiments, administration or overexpression of adiponectin ameliorates glucose metabolism by enhancing peripheral glucose uptake and suppressing hepatic glucose production. As adiponectin has not (yet) been administered to human subjects, information on the effects of this hormone on human glucose metabolism is limited. Several studies have investigated the influence of adiponectin in humans by increasing the levels of this adipocytokine indirectly via administration of PPAR-γ agonists. In patients with type 2 diabetes, PPAR-γ agonists enhanced insulin sensitivity both at the level of the liver as well as peripherally. The improvements in insulin sensitivity were associated with an increase in total adiponectin levels. More recently, it was shown that in patients with type 2 diabetes this association could be further strengthened by taking the HMW to total adiponectin ratio into account. These data suggest that adiponectin, in particular the HMW form, has a major role in improving disturbances in glucose metabolism.

Several studies investigated the effects of PPAR-γ agonists in HIV-associated lipodystrophy. Most but not all of these studies demonstrated an improvement in the derangements of glucose metabolism. However, the majority of these reports focused on the effects of PPAR-γ agonists on body composition and therefore did not examine glucose homeostasis in detail. Only 2 studies investigated glucose metabolism more thoroughly by performing hyperinsulinemic-euglycemic clamps. These clamp studies reported an improvement in whole body insulin sensitivity 3 months after starting rosiglitazone in HIV-infected patients with insulin resistance and lipoatrophy. In addition, hepatic insulin sensitivity as measured by the Homeostatic Model Assessment (HOMA)-index improved as well. Concomitantly with these ameliorations in insulin sensitivity, there was a significant increase in total plasma adiponectin levels, in the plasma levels of the adiponectin HMW form as well as in the ratio of HMW to total adiponectin. The change in HMW adiponectin significantly correlated with the increase in hepatic insulin sensitivity. These data implicate that (HMW) adiponectin may be important in the regulation of insulin sensitivity in HIV-lipodystrophic patients.
In the present study 16 weeks of treatment with rosiglitazone resulted in a marked increase in plasma adiponectin levels, primarily of the HMW form as indicated by the increased HMW to total adiponectin ratio. These elevations are in accordance with the results of other studies performed in HIV-associated lipodystrophy \(^{19, 25}\) and type 2 diabetes \(^{16, 36, 37}\). Despite the increase in (HMW) adiponectin levels however, we did not find an improvement in any of the parameters of glucose metabolism. This is in contrast with the earlier described studies in HIV-lipodystrophic patients \(^{19, 25}\). These different results may be related (partly) to differences in study design. Compared to the other trials, we used lower insulin infusion rates (40 mU/m\(^2\) in \(^{19, 25}\) vs. 20 mU/m\(^2\) in our study) to investigate hepatic and peripheral insulin sensitivity. Additionally, instead of the HOMA-index, we measured (hepatic) insulin sensitivity by utilizing stable isotopes, which is considered to be the golden standard. Besides these differences in experimental design, there was also a difference in study population. In the present study, in contrast to the other trials \(^{19, 25}\) we exclusively examined HIV-patients, who were not or no longer receiving PI for \(\geq 9\) and d4T for \(\geq 6\) months before randomization. It can be postulated that rosiglitazone merely antagonizes any negative effects of ongoing PI and/ or d4T exposure on glucose metabolism and therefore had no effect in our patients. Finally, the different results could be explained by differences in the effects of rosiglitazone on body composition. In contrast to our and several other studies \(^{17, 20, 21, 24}\), there was an increase in subcutaneous and a decrease in visceral fat mass in the participants of the 2 studies, which showed a positive effect on insulin sensitivity \(^{19, 25}\). It can be hypothesized that this change in body fat distribution may have been responsible for the observed improvements in glucose metabolism via redistribution of insulin-desensitizing FFA metabolites \(^{39}\) from the liver and muscle to subcutaneous adipose tissue.

A potential confounding factor in our study might be the increase in basal plasma glucagon levels in the rosiglitazone group. As glucagon is known to enhance hepatic glucose production, the increased basal glucagon levels in the rosiglitazone arm could have counteracted potential positive effects of adiponectin on basal glucose production. However, as we only found a minimal increase in glucagon levels of 7 ng/l, we find it an unlikely confounding factor \(^{40}\). Additionally, we do not believe glucagon has affected our data during hyperinsulinemia, as we did not find a significant increase in glucagon levels during the clamp after 16 weeks of treatment with rosiglitazone (data not shown).

Adiponectin, primarily the HMW form, has been suggested to play an important role in the regulation of glucose metabolism in insulin resistant, HIV-associated lipodystrophic patients \(^{5, 10, 15, 16, 19, 25}\). The results of the present study however questions the importance of (HMW) adiponectin in this setting. We show that rosiglitazone increased...
plasma concentrations of total adiponectin to levels above those found in ART-naive, non-lipodystrophic, HIV-infected patients. Moreover, we found that the rise in adiponectin was primarily due to an increase in the HMW form, which has been suggested to be responsible for the insulin-sensitising effects. However, despite the normalization of (HMW) adiponectin, rosiglitazone did not improve any of the parameters of glucose and lipid metabolism in our HIV-lipoatrophic patients. Inclusion of the data obtained during rosiglitazone exposure beyond the placebo-controlled phase (n=11 exposed for 16 weeks and n=6 exposed for 32 weeks) likewise did not show an effect on glucose and lipid metabolism either. These data suggest that in HIV-lipodystrophic patients, low (HMW) adiponectin levels per se do not play a (major) role in the pathogenesis and/or perseverance of the disturbances in glucose and lipid metabolism but rather reflect dysfunction of adipose tissue. This implies that therapies, which are solely aimed at enhancing reduced adiponectin levels are not expected to be beneficial at counteracting the insulin resistance in HIV-associated lipodystrophy.

In conclusion, rosiglitazone markedly increased both total adiponectin levels as well as the ratio of HMW to total adiponectin in HIV-lipoatrophic patients. However, despite this increase in plasma adiponectin, there was no improvement in glucose and lipid metabolism. This questions the role of adiponectin in the regulation of glucose homeostasis in HIV-lipodystrophy.

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Reference List


