Adiponectin Is an Important Determinant of ApoA-I Catabolism

Bruno Vergès, Jean Michel Petit, Laurence Duvillard, Guillaume Dautin, Emmanuel Florentin, Françoise Galland, Philippe Gambert

Objective—Plasma concentration of adiponectin is positively correlated with high-density lipoprotein (HDL) cholesterol level. However, the role of adiponectin on HDL metabolism remains unknown. This prompted us to perform an in vivo kinetic study of apoA-I, the main apolipoprotein of HDL, using stable isotopes, in 22 subjects with a wide range of plasma adiponectin, including 11 patients with metabolic syndrome (8 with type 2 diabetes, 3 without type 2 diabetes) and 11 normal individuals.

Methods and Results—In the 22 studied subjects, plasma adiponectin levels ranged from 2.57 to 14.44 μg/mL and apoA-I fractional catabolic rate (FCR) values ranged from 0.142 to 0.340 day⁻¹. A strong negative correlation was found between adiponectin and apoA-I FCR (r = -0.66, P < 0.001) in the whole studied population and, to a similar extent, in patients with metabolic syndrome (r = -0.73, P = 0.010) and normal subjects (r = -0.68, P = 0.020), separately. In multivariable analysis, apoA-I FCR was associated negatively with adiponectin (P = 0.005) and positively with HDL triglycerides/cholesterol ratio (P = 0.006), but not with age, sex, body mass index (BMI), waist circumference, plasma triglycerides, HDL cholesterol, fasting glycemia, and QUICKI. Both adiponectin and HDL triglycerides/cholesterol ratio explained 62% of the variance of apoA-I FCR and adiponectin on its own explained 43%.

Conclusions—Our kinetic study shows a strong negative correlation between adiponectin and apoA-I FCR, which can explain the positive link between HDL cholesterol and adiponectin. This association is independent of obesity, insulin resistance, and the content of triglycerides within HDL particles. These data suggest that adiponectin may have a direct role on HDL catabolism. (Arterioscler Thromb Vasc Biol. 2006;26:1364-1369.)

Key Words: adiponectin • apoA-I • HDL cholesterol • insulin-resistance • kinetic

Adiponectin is a peptide predominantly synthesized in the adipose tissue that plays an important role in carbohydrate and lipid metabolism and vascular biology.¹ ² It has been suggested to be a link between obesity, insulin resistance, and cardiovascular disease. Plasma adiponectin levels are reduced in individuals with abdominal obesity, metabolic syndrome, and/or type 2 diabetes.¹ ³ ⁵ Adiponectin concentration has been found negatively correlated with abdominal obesity and insulin resistance in humans⁶ ⁷ and has been shown to predict the development of type 2 diabetes.⁸ ⁹ Furthermore, several studies indicate that plasma adiponectin levels are significantly decreased in patients with coronary heart disease¹⁰ ¹¹ and high plasma adiponectin predict a lower risk of future myocardial infarction in nondiabetic¹² and diabetic individuals.¹³ However, the link between adiponectin and cardiovascular disease could be partly mediated by its effects on lipids, because several studies indicate that the inverse association between adiponectin and coronary disease is importantly attenuated or no more significant after adjustment for lipids, particularly high-density lipoprotein (HDL) cholesterol.¹² ¹³ Adiponectin is related to lipid metabolism, principally higher levels of HDL cholesterol and lower levels of triglycerides.³ The positive association between plasma adiponectin and HDL cholesterol has been found in nondiabetic⁶ ¹⁰ ¹⁵ and diabetic individuals.¹⁶ ¹⁷ Furthermore, the positive correlation between adiponectin and HDL cholesterol has been shown to be independent of body mass index (BMI), body fat distribution and insulin sensitivity.⁶ ⁷ ¹⁰ ¹⁶ ¹⁷ suggesting a potential direct link between adiponectin and HDL metabolism. The mechanism for the association between plasma adiponectin and HDL cholesterol is still unknown and has not been previously investigated. In order, to get further insight into the effect of adiponectin on HDL metabolism, we performed an in vivo kinetic study of apoA-I, the major apolipoprotein of HDL particles, using stable isotopes, in a group of individuals with a wide range of plasma adiponectin, including patients with metabolic syndrome and normal subjects.

Materials and Methods

Subjects
We studied 22 white individuals, including 11 patients with metabolic syndrome and 11 normal subjects. All the patients with metabolic syndrome were abnormally obese (waist circumference >102 cm) and...
were classified as having metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III criteria. All the patients with metabolic syndrome had biological indexes of insulin resistance: increased HOMA-IR (homeostasis model assessment) and decreased QUICKI (quantitative insulin-sensitivity check index). Among the 11 patients with metabolic syndrome, 8 had type 2 diabetes according to the criteria of the American Diabetes Association. Patients with type 2 diabetes were treated with diet alone (2 patients) or with glinides (6 patients). All patients with metabolic syndrome had normal renal function and were not using any medication known to affect lipid metabolism.

All normal subjects were in good health, with normal glucose tolerance and normal plasma lipid levels. They were not using any medication. All the women included in the study were not using oral contraceptives. The protocol was approved by the Dijon University Hospital ethics committee and written informed consent was obtained before the study was started.

**Experimental Protocol**

The kinetic study was performed in the fed state. Food intake, with a leucine-poor diet (1700 kcal/day–1, 55% carbohydrates, 39% fats, and 7% proteins), was fractionated in small portions, which were provided every 2 hours starting 6 hours before the tracer infusion up to the end of the study to avoid important variations in apolipoprotein levels. Very-low-density lipoprotein (VLDL) and HDL were isolated from plasma by a discontinuous sodium dodecyl sulfate-polyacrylamide gel electrophoresis system (Beckman Instruments, Palo Alto, Calif). VLDL and HDL fractions were separated by centrifugation for 10 minutes at 4°C and 3000 g. Supernatants were lyophilized in a Speed Vac (Savant Instrument, Farmingdale, NY). Lyophilized samples were dissolved in 50% acetic acid and applied to an AG-50W-X8 200 to 400 mesh cation exchange resin (Bio-Rad, Richmond, Va) and amino acids were recovered by elution with 4N NH4OH.

**Determination of Leucine Enrichment by Gas Chromatography/Combustion/Isotope Ratio Mass Spectrometry**

Amino acids were converted to N-acetyl O-propyl esters and were analyzed on a Finnigan Mat Delta Plus Advantage isotope ratio mass spectrometer (Finnigan Mat, Bremen, Germany). Leucine enrichment was initially expressed in delta % and converted in tracer/tracer ratio before modeling.

**Modeling**

Kinetic data were analyzed with the simulation analysis and modeling SAAM II program (SAAM Institute, Inc, Seattle, Wash). Apo-A-I and B-100 data were analyzed using the following mono-exponential function: A(t) = Ap(1−exp[-k(t−d)]), where A(t) is the apolipoprotein enrichment at time t, Ap the enrichment at the plateau of the VLDL apo B100 curve, d the delay between the beginning of the experiment and the appearance of tracer in the apolipoprotein, and k the fractional synthetic rate (FSR) of the apolipoprotein. It was assumed that the VLDL apoB100 tracer/tracer ratio at the plateau corresponds to the tracer/tracer ratio of the leucine precursor pool. This estimation is made on the assumption that apoB-100 and the great majority of apoA-I are synthesized by the liver, as previously demonstrated by Ikewaki et al. In the steady state, the FSR equals the fractional catabolic rate (FCR). The apoa-I production rate (PR) was calculated as the product of the apoA-I pool size and its FSR divided by body weight. Pool size was estimated by the product of apoA-I plasma concentration and plasma volume, calculated as 4.5% of body weight. In obese subjects (BMI ≥30), a correction of plasma volume was performed as previously reported by many authors. The plasma volume was modified by multiplying by a correction factor to take into account the decrease in relative plasma volume associated with an increase in body weight. The correction factor obtained from specific tables increases with body weight, ranging from 0.99 up to 0.90 for the more obese patients.

**Analytical Methods**

**Laboratory Measurements**

Concentrations of apoA-I were determined by immunoturbidimetry with anti-apo-A-I antibodies from Boehringer Mannheim. All chemical lipid assays were performed on a Cobas-Fara Centrifugal Analyzer (Hoffmann-La Roche). Total cholesterol and triglyceride concentrations were measured by enzymatic method using Boehringer Mannheim and Roche reagents, respectively. Plasma glucose concentration was measured by enzymatic method (glucose oxidase) on a Vitros 950 analyzer (Ortho Clinical Diagnostics, Rochester, NY). Plasma insulin was measured by radioimmunossay (CIS Bio International, Gif sur Yvette, France).

Plasma adiponectin concentration was determined using an enzyme immunoassay kit (Quantikine R&D, Systems, Minneapolis, Minn). The kit used measures the monomeric, the dimeric, and the trimeric forms of adiponectin. The intra-assay and inter-assay coefficients of variation for this method were less than 5% and 7%, respectively.

**Insulin Resistance Evaluation**

The insulin resistance level was estimated in all individuals by using both the homeostasis model assessment (HOMA) method and the quantitative insulin-sensitivity check index (QUICKI). HOMA index (HOMA-IR) was calculated as [(fasting glycemia (mmol/L) × fasting insulin (µU/ml))/22.5]. QUICKI, which has been shown to be among the most accurate indexes for determining insulin sensitivity in humans, was calculated as 1/[(log(fasting insulin expressed in (µU/ml)+log (fasting glycemia expressed in mg/dL))].

**Statistical Analysis**

Data are reported as mean±SD. Statistical calculations were performed using the SPSS software package. For continuous variables, a Kolmogorov-Smirnov analysis was performed to test for normality. Comparisons of continuous variables between patients with metabolic syndrome and normal subjects were performed either by unpaired Student t test for normally distributed data or by nonparametric Mann-Whitney U test for non-normally distributed data (plasma triglycerides). The Pearson correlation coefficients (r) were determined by linear regression analysis. Statistical significance of the correlation coefficients was determined by the method of Fisher and Yates. Because apoA-I FCR is one of the term in the equation to calculate apoA-I PR, the correlation between plasma adiponectin and apoA-I PR has been performed using partial correlation, after
controlling for apoA-I FCR. A multivariable linear regression analysis was performed to analyze the influence of different factors on apoA-I FCR. A 2-tailed \( P=0.05 \) was accepted as statistically significant.

**Results**

**Clinical and Biological Characteristics**

Clinical and biological characteristics are shown in Table 1 for the entire studied population, including both patients with metabolic syndrome and normal subjects and for each subgroup (patients with metabolic syndrome, normal subjects). Patients with metabolic syndrome compared with normal individuals had higher values for BMI, waist circumference, fasting glycemia, fasting insulin, HOMA-IR, triglycerides, and HDL triglycerides/cholesterol ratio, and lower HDL cholesterol concentrations and QUICKI values. Plasma adiponectin level was significantly lower in patients with metabolic syndrome than in normal subjects.

![Figure 1](image.png)

**Figure 1.** Kinetic curves of HDL apoA-I obtained during a primed constant infusion of L-[1 to 13C]leucine. [13C]leucine enrichment values, expressed as percentage of VLDL apo B100 plateau, for control subjects (white circles) and patients with metabolic syndrome (black circles) are shown. The curves were obtained by monoexponential modeling. Data are shown as mean±SEM.

**Kinetic Data**

The kinetic curves of apoA-I in patients with metabolic syndrome and controls are shown in Figure 1. ApoA-I kinetic parameters are shown in Table 2. ApoA-I pool was significantly lower in patients with metabolic syndrome due to significantly increased apoA-I FCR. ApoA-I PR was not different between patients with metabolic syndrome and normal subjects.

**Correlation**

In univariate analysis, plasma adiponectin level was significantly and negatively correlated with age \( (r=-0.50, P=0.019) \), BMI \( (r=-0.45, P=0.038) \), waist circumference \( (r=-0.56, P=0.006) \), plasma triglycerides \( (r=-0.46, P=0.032) \), HDL triglycerides/cholesterol ratio \( (r=-0.49, P=0.021) \), and HOMA-IR \( (r=-0.43, P=0.046) \). Plasma adiponectin was significantly and positively correlated with HDL cholesterol \( (r=0.43, P=0.044) \) and QUICKI \( (r=0.48, P=0.024) \). The correlation coefficient between plasma adiponectin and plasma apoA-I was \( r=0.40 (P=0.063) \).

As shown in Figure 2, we found a strong negative correlation between plasma adiponectin and apoA-I FCR \( (r=-0.66, P<0.001) \). This negative correlation between plasma adiponec-

**TABLE 1.** Clinical and Biological Characteristics of the Entire Studied Population (Patients With Metabolic Syndrome and Normal Subjects) of Patients With Metabolic Syndrome and of Normal Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Entire Population (n=22)</th>
<th>Patients With Metabolic Syndrome (n=11)</th>
<th>Normal Subjects (n=11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43.6±14.4 (20–67)</td>
<td>53.6±9.7</td>
<td>33.6±11.0</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Sex ratio, M/F</td>
<td>13/9</td>
<td>8/3</td>
<td>5/6</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.0±4.2 (20.0–35.9)</td>
<td>30.4±3.1</td>
<td>23.6±1.6</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>90.4±15.5 (66–117)</td>
<td>101.7±10</td>
<td>79.1±11</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Fasting glycemia, mmol/L</td>
<td>6.99±3.44 (3.99–17.20)</td>
<td>9.10±3.91</td>
<td>4.92±0.44</td>
<td>P=0.005</td>
</tr>
<tr>
<td>Fasting insulin, µU/mL</td>
<td>8.2±7.6 (2.4–33.0)</td>
<td>12.9±8.5</td>
<td>3.6±0.84</td>
<td>P=0.005</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.63±3.24 (0.51–8.90)</td>
<td>4.49±2.19</td>
<td>0.77±0.18</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.358±0.049 (0.281–0.431)</td>
<td>0.313±0.021</td>
<td>0.403±0.018</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.70±1.17 (0.55–4.16)</td>
<td>2.56±1.08</td>
<td>0.82±0.17</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>3.40±0.87 (1.88–5.59)</td>
<td>3.72±0.92</td>
<td>3.10±0.72</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.34±0.38 (0.72–2.11)</td>
<td>1.18±0.38</td>
<td>1.50±0.28</td>
<td>P=0.04</td>
</tr>
<tr>
<td>HDL triglycerides/cholesterol</td>
<td>0.092±0.079 (0.009–0.348)</td>
<td>0.144±0.081</td>
<td>0.041±0.030</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Adiponectin, µg/mL</td>
<td>7.44±3.10 (2.57–14.44)</td>
<td>6.09±2.08</td>
<td>8.80±3.40</td>
<td>0.035</td>
</tr>
</tbody>
</table>

**TABLE 2.** ApoA-I Kinetic Parameters in Patients With Metabolic Syndrome and in Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients With Metabolic Syndrome</th>
<th>Normal Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma apoA-I, mg/dL</td>
<td>122±0.23</td>
<td>145±0.17</td>
<td>P=0.017</td>
</tr>
<tr>
<td>ApoA-I pool, mg/kg⁻¹</td>
<td>52.52±9.86</td>
<td>65.24±7.71</td>
<td>P=0.003</td>
</tr>
<tr>
<td>ApoA-I FCR, day⁻¹</td>
<td>0.243±0.065</td>
<td>0.186±0.025</td>
<td>P=0.015</td>
</tr>
<tr>
<td>ApoA-I PR, mg/kg⁻¹</td>
<td>12.51±3.49</td>
<td>12.12±1.97</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD. FCR indicates fractional catabolic rate; PR, production rate; NS, not significant.
and apoA-I FCR was also found in each group of subjects to a similar extent, the patients with metabolic syndrome ($r = -0.73$, $P = 0.010$) and the normal subjects ($r = -0.68$, $P = 0.020$). The negative correlation between plasma adiponectin and apoA-I FCR was similar for both men ($r = -0.68$, $P < 0.05$) and women ($r = -0.68$, $P < 0.05$). Plasma adiponectin was not correlated with apoA-I PR (after controlling for apoA-I FCR).

In univariate analysis, apoA-I FCR was significantly and positively correlated with BMI ($r = 0.52$, $P = 0.012$), plasma triglycerides ($r = 0.62$, $P = 0.002$), HDL triglycerides/cholesterol ratio ($r = 0.65$, $P = 0.001$), fasting glycemia ($r = 0.45$, $P = 0.036$), and HOMA-IR ($r = 0.56$, $P = 0.007$). ApoA-I FCR was negatively correlated with QUICKI ($r = -0.57$, $P = 0.005$), HDL cholesterol ($r = -0.55$, $P = 0.008$), and plasma adiponectin ($r = -0.66$, $P < 0.001$). ApoA-I FCR was not correlated with age.

**Multivariable Analysis**

A multivariable linear regression analysis was performed to analyze the association between apoA-I FCR and several variables. The variables introduced into the model were those that were significantly associated with apoA-I FCR in the univariate analysis (BMI, waist circumference, plasma triglycerides, HDL cholesterol, HDL triglycerides/cholesterol ratio, fasting glycemia, QUICKI, plasma adiponectin), age, and sex, because of potential apoA-I FCR differences between men and women. The multivariable analysis showed that apoA-I FCR was negatively associated with plasma adiponectin ($P = 0.005$) and positively associated with HDL triglycerides/cholesterol ratio ($P = 0.006$) (Table 3). These 2 variables explained 62% of apoA-I FCR variance ($r^2 = 0.62$).

**Table 3. Relationship Between apoA-I FCR and Several Variables Assessed by Multivariable Linear Regression in the Entire Studied Population ($r^2 = 0.62$)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>SD</th>
<th>T</th>
<th>P</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma adiponectin, $\mu$g/mL</td>
<td>-0.0088</td>
<td>0.0027</td>
<td>-3.204</td>
<td>0.005</td>
<td>0.43</td>
</tr>
<tr>
<td>HDL triglycerides/cholesterol ratio (log)</td>
<td>0.3322</td>
<td>0.1070</td>
<td>3.102</td>
<td>0.006</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Nonsignificant variables: age, BMI, waist circumference, plasma triglycerides (log), HDL-cholesterol, sex, fasting glycemia, QUICKI.

The association between plasma adiponectin and apoA-I FCR was shown to be important, with plasma adiponectin explaining 43% of apoA-I FCR variance.

**Discussion**

Several studies have clearly shown a significant correlation between plasma adiponectin and HDL cholesterol level in nondiabetic and diabetic individuals. This association between adiponectin and HDL cholesterol has been shown to be independent of BMI, body fat distribution, and insulin sensitivity in cross-sectional studies. Moreover, in a recent intervention study, it has been shown that the augmentation of plasma adiponectin after weight loss in obese patients was positively correlated with the increase in plasma HDL cholesterol independently of changes in adiposity and insulin sensitivity. All these data strongly suggest a possible direct link between adiponectin and HDL cholesterol.

To get further insight into the role of adiponectin on HDL metabolism, we report the first study of the relationship between plasma adiponectin and apoA-I kinetics in humans. To have a good estimate of the relationship between adiponectin and apoA-I metabolism, we have performed a study in individuals with a wide range of plasma adiponectin and a wide range of apoA-I FCR including patients with metabolic syndrome and normal subjects. Age was different between the 2 groups. However, this age difference is not likely to affect our results because it has been shown that apoA-I kinetic is independent of age. Moreover in our study, data from the univariate and multivariate analyses clearly show that apoA-I FCR is not influenced by age. Our study shows that adiponectin is significantly and negatively associated with apoA-I FCR and that this association is independent of other factors usually associated with apoA-I FCR (sex, abdominal obesity, plasma triglycerides, HDL triglycerides, insulin sensitivity). Because 8 of our patients had type 2 diabetes, we screened for a possible association between plasma adiponectin and fasting glycemia. But fasting glycemia was not shown to be associated with plasma adiponectin level neither in the univariate analysis nor in the multivariate analysis. In our study, plasma adiponectin can explain 43% of the variance of apoA-I FCR, indicating a tight link between both variables. Furthermore, the strong negative correlation between plasma adiponectin and apoA-I FCR is found not only in the whole studied population (including patients with metabolic syndrome and normal subjects) but also in each group (the patients with metabolic syndrome and the normal subjects). This confirms the results of the multivariable analysis showing that the association between adiponectin and apoA-I FCR is independent of insulin sensitivity.

The positive correlation between HDL cholesterol and plasma adiponectin, previously reported, is confirmed in the present study. HDL cholesterol is also significantly negatively correlated with apoA-I FCR and it is now admitted that increased apoA-I catabolism, indicating accelerated HDL catabolism, is the kinetic factor responsible for decreased HDL cholesterol level in insulin-resistant subjects. In our study, HDL cholesterol, which is negatively correlated with apoA-I FCR in the univariate analysis, is no more associated with apoA-I FCR in the multivariable analysis when plasma...
adiponectin is present into the model. This indicates that the association between adiponectin and HDL cholesterol is explained by the relationship between adiponectin and apoA-I FCR.

The multivariable analysis indicates that apoA-I FCR is independently associated with plasma adiponectin (negatively) and HDL triglycerides/cholesterol ratio (positively) and that the 2 variables explain 62% of its variance. HDL particles of patients with metabolic syndrome are enriched in triglycerides.35 As previously reported,10,36 we found that triglyceride enrichment of HDLs is a factor for increased apoA-I catabolism. It has been shown that HDLs with a higher triglyceride content are better substrates for hepatic lipase leading to their faster catabolism.36 An association between adiponectin and triglycerides has been reported in several studies3,14,16,17,32,33 and is confirmed in the present one. Because plasma triglycerides (or HDL triglyceride content) is usually correlated with both apoA-I catabolism and plasma adiponectin, we could have suspected that the association between adiponectin and apoA-I FCR might be explained by the known link between plasma adiponectin and triglycerides. Our data exclude this hypothesis and clearly show that plasma adiponectin is an important determinant of apoA-I catabolism independently of triglycerides, explaining by its own 43% of apoA-I FCR variance.

Interestingly, we show that clinical (waist circumference) and biological (HOMA-IR, QUICKI) indexes for insulin resistance are significantly associated with apoA-I FCR in the univariate analysis, but no more in the multivariable analysis when plasma adiponectin is present in the statistical model. These results suggest that adiponectin could be an important link between insulin resistance and increased apoA-I catabolism.

Our data suggest that adiponectin may have a direct role on HDL catabolism. However, the mechanisms linking plasma adiponectin and HDL metabolism remain unknown and further studies are needed to explore them.

In conclusion, our in vivo kinetic study shows a significant negative correlation between plasma adiponectin and apoA-I FCR in individuals with a wide range of plasma adiponectin, including patients with metabolic syndrome and normal subjects. The significant association between plasma adiponectin and apoA-I FCR is independent of other factors, such as HDL triglyceride content or clinical and biological indexes of insulin sensitivity. Plasma adiponectin, on its own, explains 43% of the variance of apoA-I FCR. These data suggest that adiponectin may have a direct role on HDL catabolism.

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References
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