Resting metabolic rate is an important predictor of serum adiponectin concentrations: potential implications for obesity-related disorders¹⁻³

Johannes B Ruige, Dominique P Ballaux, Tohru Funahashi, Ilse L Mertens, Yuji Matsuzawa, and Luc F Van Gaal

ABSTRACT

Background: Little is known about the regulation of adiponectin. Animal studies suggest local regulation by adipocytokines or alterations in energy expenditure, and studies in humans suggest regulation by alcohol intake and ethnicity.

Objective: To identify regulators of adiponectin in humans, we measured resting metabolic rate (RMR), serum adiponectin, glucose, insulin, triacylglycerol, alcohol intake, and anthropometric indexes in 457 white patients with overweight or obesity.

Design: A cross-sectional design was used, and multivariate regression analysis was performed with adiponectin as the dependent variable and potential predictors as independent variables.

Results: Simple linear analyses showed significant associations between adiponectin and sex, with a standardized coefficient of −0.38 (women compared with men) and an explanation of variation of the model (R²) of 14%; age (0.21; 4%); RMR (−0.52; 27%); fat-free mass (−0.40; 16%); fat mass (−0.16; 2%); visceral fat (−0.24; 6%); computed tomography at L4–L5; fasting triacylglycerol (−0.28; 8%); and insulin resistance (−0.38; 14%; homeostasis model assessment). Adiponectin and alcohol were not associated (−0.04; 0%). Multivariate analyses, which allowed adjustment for confounding, showed that RMR is the most important predictor of adiponectin (−0.31; 29%), followed successively by insulin resistance (−0.16; 31%; model containing RMR and insulin resistance), fat mass (0.20; 34%), age (0.34; 35%), visceral fat (−0.34; 40%), and fasting triacylglycerol (−0.12, 41%).

Conclusions: Low resting metabolism (RMR) is associated with high serum adiponectin. We speculate that subjects with low RMR, who are theoretically at greater risk of obesity-related disorders, are especially protected by adiponectin. Am J Clin Nutr 2005;82:21–5.

KEY WORDS Basal metabolism, adiponectin, obesity, metabolic syndrome X, insulin resistance, body constitution

INTRODUCTION

Recent progress in obesity research has shown that adipocytes are not merely fat-storing cells but that they secrete a variety of hormones, cytokines, growth factors, and other bioactive substances, conceptualized as adipocytokines. A disturbance of regulation of these adipocytokines contributes to the pathogenesis of obesity-related disorders such as insulin resistance, type 2 diabetes, dyslipidemia, endothelial dysfunction, and vascular disease (1). In particular, the adipocytokine adiponectin has been shown to play an important role; it exerts insulin-sensitizing and antiatherogenic effects (2). The adiponectin knockout (KO) mice, for example, exhibited severe diet-induced insulin resistance with reduced insulin receptor substrate–1–associated phosphatidylinositol 3 kinase activity in muscle. The KO mice also showed neointimal thickening in response to vascular injury and hypertension induced by salt diet. These phenotypes in KO mice were reversed by viral-mediated production of adiponectin (3). A causal relation between decreased plasma adiponectin and insulin resistance and atherosclerosis has been suggested in humans as well (4, 5).

Unfortunately, we do not sufficiently know how adiponectin concentration is regulated. Local effects of tumor necrosis factor-α, interleukin-6, β-adrenoceptor agonist, glucocorticoids (6), specific receptors on the adipocyte, environmental effects such as alcohol intake, and genetic effects, eg, ethnicity, have been suggested (7, 8). In addition, energy expenditure might affect adiponectin, as suggested by animal models (9). In general, energy expenditure is required to maintain basic physiologic functions (eg, heart beat, muscle contraction, respiration); to metabolize, digest, and store consumed food; and to perform physical activity (10). A relation between physical activity and adiponectin could not be established by some recent investigators (11, 12).

To explore the role of energy expenditure in the regulation of adiponectin, we measured basal metabolism or resting metabolic rate (RMR), the energy expenditure required to maintain basic physiologic functions, as well as other potential regulators or confounders and explored their relation with serum adiponectin in overweight or obese patients.

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SUBJECTS AND METHODS

Patients with overweight or obesity were recruited from the outpatient clinic of the Department of Diabetology, Metabolism, and Clinical Nutrition of the University Hospital, Antwerp, Belgium. Patients with endocrine disorders (e.g., hypothalamic-pituitary disorders, hypothyroidism, Cushing’s syndrome), genetic (dysmorphic) disorders, obesity, or diabetes mellitus type 2 defined according to World Health Organization criteria (13) were excluded. The study was performed according to the standards on human experimentation in accordance with the Helsinki Declaration of 1975 as revised in 1983. Smoking and alcohol habits were estimated by careful questioning, and individuals were divided into dichotomous categories. Individuals who had quit smoking were defined as nonsmokers, and individuals who did not use alcohol on a daily basis were defined as nonalcohol drinkers.

Anthropometry and resting metabolic rate

Height was measured to the nearest 0.5 cm, body weight was measured with a digital scale to the nearest 0.1 kg, body mass index (in kg/m²) was calculated, and percentage of body fat and fat-free mass (FFM; in kg) were assessed by bioimpedance (SEAC SFB3; SEAC, Brisbane, Australia) as described by Lukaski et al (14). Visceral and subcutaneous fat were assessed by a computerized tomography scan at the L4–L5 level, determined according to the technique described by Van der Kooy and Seidell (15) and Kvist et al (16). The RMR is the amount of energy expended when an adult organism is awake but resting, fasting, and at thermal neutrality. RMR was measured and the respiratory quotient was calculated as VCO₂/VO₂, as reported previously (17). In short, RMR was measured by indirect calorimetry with a ventilated hood system (Deltatrac; Datex, Helsinki, Finland). Subjects stayed overnight at the metabolic ward of the University Hospital Antwerp, and RMR was measured in the morning on awakening after an overnight fast. Oxygen consumption and carbon dioxide production in expired air were measured each minute for 30 min after a 10-min equilibration period. Energy expenditure was calculated with the equation of de Weir (18). In addition to energy expenditure, substrate oxidation was calculated with the equations of Lusk (19).

Laboratory analyses

A fasting blood sample was drawn for measurements of glucose, insulin, triacylglycerol, and adiponectin. Plasma glucose was measured with the glucose oxidase method (on Vitros 750 XRC; Ortho Clinical Diagnostics Inc, Rochester, NY). Fasting triacylglycerol was measured on Vitros 750XRC (Ortho Clinical Diagnostics, Johnson & Johnson, Raritan, NJ). Insulin was measured by a radioimmunoassay with the use of Pharmacia Insulin RIA (Pharmacia Diagnostics, Uppsala, Sweden). This assay shows 41% cross-reactivity with proinsulin. Insulin resistance was calculated by the homeostasis model assessment (HOMA) method with the use of fasting plasma glucose and insulin concentrations. Assuming that normal-weight subjects <35 y have an insulin resistance of 1, the value for insulin resistance can be assessed by the following equation:

\[
\text{Fasting insulin (µU/mL) } \times \text{ fasting glucose (mmol/L)} / 22.5 \ (I)
\]

Results from the HOMA method correlate well with measurements obtained by means of the euglycemic clamp technique. The CV is reported to be between 7.8% and 11.7% (20, 21). Plasma adiponectin concentration was measured by enzyme-linked immunosorbent assay (Otsuka Pharmaceutical Co, Tokushima, Japan) as described previously (22).

Statistical analysis

Study population characteristics and anthropometric and laboratory measurements were presented as proportions or median values with their range and the 25th and 75th percentile. To show the associations between adiponectin and anthropometric measurements, after control for confounding influence of sex and age, partial Pearson’s correlation coefficients were presented. A \( P \) value < 0.05 was regarded as statistically significant. To explore the relation between adiponectin and potential variables,
allow control for confounding, linear regression models were explored in
strongest is FFM (0.73,
ylglycerol, and various anthropometric indicators, of which the
The RMR is also strongly correlated to insulin resistance, triacy-
for confounding influence of age and sex. Also shown in Table 3
Partial Pearson’s correlation coefficients between adiponectin and various potential predictors, adjusted for sex and age

TABLE 3
Partial Pearson’s correlation coefficients between adiponectin and various potential predictors, adjusted for sex and age

<table>
<thead>
<tr>
<th>Adiponectin</th>
<th>RMR</th>
<th>Total fat mass</th>
<th>FFM</th>
<th>BMI</th>
<th>Visceral fat</th>
<th>Subcutaneous fat</th>
<th>Insulin resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMR</td>
<td>−0.36 (^{2})</td>
<td>−0.15 (^{2})</td>
<td>0.65 (^{2})</td>
<td>0.47 (^{2})</td>
<td>0.57 (^{2})</td>
<td>0.41 (^{2})</td>
<td>0.32 (^{2})</td>
</tr>
<tr>
<td>Total fat mass</td>
<td>−0.23 (^{2})</td>
<td>0.73 (^{2})</td>
<td>0.88 (^{2})</td>
<td>0.49 (^{2})</td>
<td>0.92 (^{2})</td>
<td>0.59 (^{2})</td>
<td>0.27 (^{2})</td>
</tr>
<tr>
<td>FFM</td>
<td>−0.23 (^{2})</td>
<td>0.67 (^{2})</td>
<td>0.88 (^{2})</td>
<td>0.49 (^{2})</td>
<td>0.92 (^{2})</td>
<td>0.41 (^{2})</td>
<td>0.59 (^{2})</td>
</tr>
<tr>
<td>BMI</td>
<td>−0.32 (^{2})</td>
<td>0.50 (^{2})</td>
<td>0.88 (^{2})</td>
<td>0.49 (^{2})</td>
<td>0.92 (^{2})</td>
<td>0.41 (^{2})</td>
<td>0.59 (^{2})</td>
</tr>
<tr>
<td>Visceral fat</td>
<td>−0.32 (^{2})</td>
<td>0.50 (^{2})</td>
<td>0.49 (^{2})</td>
<td>0.41 (^{2})</td>
<td>0.30 (^{2})</td>
<td>0.23 (^{2})</td>
<td>0.23 (^{2})</td>
</tr>
<tr>
<td>Subcutaneous fat</td>
<td>−0.28 (^{2})</td>
<td>0.37 (^{2})</td>
<td>0.28 (^{2})</td>
<td>0.26 (^{2})</td>
<td>0.26 (^{2})</td>
<td>0.26 (^{2})</td>
<td>0.26 (^{2})</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>−0.26 (^{2})</td>
<td>0.28 (^{2})</td>
<td>0.08</td>
<td>0.09</td>
<td>0.12 (^{2})</td>
<td>0.16 (^{2})</td>
<td>0.01</td>
</tr>
<tr>
<td>Fasting triacylglycerol</td>
<td>−0.26 (^{2})</td>
<td>0.28 (^{2})</td>
<td>0.08</td>
<td>0.09</td>
<td>0.12 (^{2})</td>
<td>0.16 (^{2})</td>
<td>0.01</td>
</tr>
</tbody>
</table>

\(^{1}\) RMR, resting metabolic rate; FFM, fat-free mass.
\(^{2}\) P < 0.001.
\(^{3}\) P < 0.05.

linear regression analysis was applied. Linear regression analysis provides insight into linear associations and allows adjustment for the influence of potential confounders. If appropriate, variables were normalized by transformation into their natural logarithm to improve the plots of residual analyses. Results were expressed as standardized coefficients and \(R^2\), or proportion of variation “explained” by the predictor of interest. Analyses were performed with the SPSS-PC software, version 11.0.1 (SPSS Inc, Chicago, IL).

RESULTS

Four hundred fifty-seven patients were recruited with a median body mass index of 38 (range: 22-60), and 75% were women. The population characteristics and anthropometric and laboratory measurements are shown in Table 1.

Men as well as women with a low RMR expressed per kilogram FFM have higher adiponectin concentrations (Table 2). This association between adiponectin and RMR is further explored in Table 3, which confirms a negative correlation between adiponectin and RMR (−0.36, \(P < 0.001\)), after control for confounding influence of age and sex. Also shown in Table 3 are significant inverse correlations of adiponectin to insulin resistance, triacylglycerol, and various anthropometric measurements, of which the strongest is visceral fat (−0.38, \(P < 0.001\)). The RMR is also strongly correlated to insulin resistance, triacylglycerol, and various anthropometric indicators, of which the strongest is FFM (0.73, \(P < 0.001\)), as has clearly been established previously (10, 23).

To further explore the regulation of serum adiponectin and to allow control for confounding, linear regression models were built with adiponectin as the dependent variable and potential predictors and confounders as independent variables, as shown in Table 4. In the simple linear analyses, various variables were associated with adiponectin: sex, age, RMR, FFM, fat mass, visceral fat, fasting triacylglycerol, and insulin resistance. Adiponectin was not associated with alcohol in the present study, which might be the result of a limitation in precision of assessment of alcohol intake.

On the basis of the results of Table 4, one multivariate regression model was built using the stepwise regression procedure. The strongest correlate appeared to be the RMR, which explained 29% of the variation of adiponectin (Table 5). The second strongest correlate appeared to be insulin resistance, which explained, together with the RMR, 31% of the variation of adiponectin, followed successively by fat mass (34%), age (35%), visceral fat (40%), and fasting triacylglycerol (41%). These results clearly show that adiponectin and RMR are strongly and inversely associated. Additional adjustment for potential confounders, such as age, visceral fat, or HDL cholesterol (data not shown), did not affect the relation between adiponectin and RMR significantly. Using the same variables in a backward procedure resulted in similar findings (data not shown). The results of these multivariate analyses also show the importance of fasting triacylglycerol concentrations in regulation of adiponectin. The model that included RMR, insulin resistance, fat mass, age, visceral fat, and fasting triacylglycerol explained 41% of the variation of adiponectin (Table 5). When HDL cholesterol was included in the model, fasting triacylglycerol would be excluded by the stepwise

### Table 2

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Serum adiponectin concentrations according to tertiles of the resting metabolic rate (RMR) per fat-free mass (FFM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile of RMR/FFM</td>
<td>Serum adiponectin (µg/mL)</td>
</tr>
<tr>
<td>(kcal · kg (^{-1}) · 24 h (^{-1}))</td>
<td>1st (&lt; 34)</td>
</tr>
<tr>
<td>Women (n = 175)</td>
<td>10.7</td>
</tr>
<tr>
<td>Men (n = 52)</td>
<td>7.7</td>
</tr>
</tbody>
</table>

\(^{1}\) The interaction of sex and tertile was not significant, \(P = 0.73\). The main effects of sex (\(P = 0.008\)) and of tertile of RMR/FFM (\(P = 0.001\)) were significant.

### Table 4

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Results from simple linear regression analyses with serum adiponectin as the dependent variable and various potential predictors as independent variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential predictors in the model</td>
<td>β</td>
</tr>
<tr>
<td>Sex (female vs male)</td>
<td>−0.38</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.21</td>
</tr>
<tr>
<td>Resting metabolic rate (kcal/24 h)</td>
<td>−0.52</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>−0.40</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>−0.16</td>
</tr>
<tr>
<td>Visceral fat (cm(^2))</td>
<td>−0.24</td>
</tr>
<tr>
<td>Fasting triacylglycerol (mg/dL)</td>
<td>−0.28</td>
</tr>
<tr>
<td>Insulin resistance (HOMA) (^{1})</td>
<td>−0.38</td>
</tr>
<tr>
<td>Alcohol (no vs yes)</td>
<td>−0.14</td>
</tr>
</tbody>
</table>

\(^{1}\) HOMA, homeostasis model assessment.
procedure. Because triacylglycerol and HDL cholesterol are inversely and undeniably associated and because increased triacylglycerol concentrations more clearly explain their contribution to the development of the metabolic syndrome (24), fasting triacylglycerol instead of HDL cholesterol was included in the final model.

**DISCUSSION**

We report here on a significant link between serum adiponectin concentrations and RMR. The present study shows high serum adiponectin concentrations in subjects with low RMR. We speculate that protection by adiponectin against obesity-related disorders is especially important for subjects with low RMR. Theoretically, subjects with low RMR are at increased risk of developing these disorders; a larger portion of their daily food intake is stored as fat, in the situation of similar calorie intake. However, the literature reports discrepant findings between RMR and the risk of developing obesity (10, 23, 25). We speculate that this discrepancy in the literature can be explained by a difference in magnitude of protection mechanisms; high risk can be tempered by a better protection by adiponectin.

A disadvantage of the present cross-sectional study is that it does not allow definite conclusions with respect to cause and effect. RMR might affect adiponectin or vice versa. Previous animal studies showed an increase in adiponectin after exposure to cold and suggest a link, not only between adiponectin and thermogenesis but also between adiponectin and genetic-, instead of nutrition-induced obesity (9). Other rodent studies suggest regulation of energy expenditure by adiponectin (26, 27). The latter might be the case as well, but analyses in the present study were performed to test the hypothesis that adiponectin is regulated by energy expenditure. It is, however, also possible that a third underlying unknown factor, eg, genetics, affects both energy expenditure and adiponectin.

In the present study, neither physical activity nor thermogenesis was measured. A link between adiponectin and physical activity is unlikely (11, 12). Except for the previously mentioned report on adiponectin and thermogenesis (9), which represents a maximum 10% of the RMR, to the best of our knowledge, our present study is the first to correlate RMR and adiponectin concentrations.

The present study confirms the earlier described link between adiponectin and triacylglycerol concentrations (28, 29). Increased concentrations of free fatty acid (FFA) and triacylglycerol may ultimately cause an abnormal triacylglycerol storage, which results, in turn, in an increased FFA flux from adipose tissue to nonadipose tissue, which participates in and amplifies many of the fundamental derangements of the metabolic syndrome (24). A recent report mentioned a decrease of adiponectin concentrations after lowering of FFA (30) and suggested an influence of adiponectin on FFA and triacylglycerol (31); thus, a feedback mechanism may exist.

The present study also shows that the inverse association between adiponectin and visceral fat increases after adjustment for fat mass (Table 5), which implies that adiponectin, exclusively secreted by the fat cell, is especially compromised in subjects with visceral obesity (32). This finding, together with the well-known inverse relation between adiponectin and insulin resistance, fit in the same framework and confirm earlier findings on the important interplay between adiponectin and the pathogenesis of the metabolic syndrome (33).

In conclusion, an inverse association between basal metabolism and serum adiponectin concentrations was shown. This inverse association might point to protection by adiponectin against obesity-related disorders particularly when low RMR is present, which itself is theoretically associated with development of obesity (and related disorders).

We thank Sachio Tanaka for technical assistance and the nurses of the outpatient clinic of the Department of Diabetology, Metabolism, and Clinical Nutrition at the University Hospital of Antwerp for their assistance. LFG was the main investigator, who coordinated and monitored the study. JBR performed the statistical analyses. All authors participated in evaluating the results and in the writing and editing of the manuscript. None of the authors had any financial conflicts related to the work.

**REFERENCES**


**TABLE 5**

Results from stepwise multivariate linear regression analyses with serum adiponectin as dependent variable and potential predictors as independent variables

<table>
<thead>
<tr>
<th>Predictor variables in one model</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>R² of model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting metabolic rate (kcal/24 h)</td>
<td>−0.31</td>
<td>0.000</td>
<td>0.001</td>
<td>0.29</td>
</tr>
<tr>
<td>Insulin resistance (HOMA)²</td>
<td>−0.16</td>
<td>0.013</td>
<td>0.009</td>
<td>0.31</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>0.20</td>
<td>0.002</td>
<td>0.002</td>
<td>0.34</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.34</td>
<td>0.003</td>
<td>0.001</td>
<td>0.35</td>
</tr>
<tr>
<td>Visceral fat (cm²)</td>
<td>−0.34</td>
<td>0.001</td>
<td>0.001</td>
<td>0.40</td>
</tr>
<tr>
<td>Fasting triacylglycerol (mg/dL)</td>
<td>−0.12</td>
<td>0.000</td>
<td>0.034</td>
<td>0.41</td>
</tr>
</tbody>
</table>

¹ Potential predictors are sex, age, resting metabolic rate, fat-free mass, fat mass, visceral fat, fasting triacylglycerol, and insulin resistance.
² HOMA, homeostasis model assessment.