Decreased plasma adiponectin concentration in major depression

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Received 26 June 2006; received in revised form 12 August 2006; accepted 20 August 2006

Abstract

Adiponectin is the most abundant adipose-derived plasma protein. Recently adiponectin levels have been linked to most variables of metabolic syndrome and conventional risk factors for cardiovascular disease. However, its relation with major depression is yet unclear. We evaluated plasma adiponectin levels in 32 first-episode drug-naïve major depression (DSM-IV-TR) patients without conventional risk factors for cardiovascular disease and 32 matched healthy subjects. Major depression patients displayed lower adiponectin plasma levels compared to controls (P < 0.01). Adiponectin significantly correlated with depression severity, as assessed by HAM-D (rho = 0.83, P < 0.001). This study shows decreased plasma adiponectin concentrations in major depression patients and relates adiponectinemia reduction to major depression severity.

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Keywords: Adiponectin; Depression; Risk factors

Major depression (MD) and cardiovascular disease frequently co-occur [12,11,10]. The pathophysiological pathways explaining this relationship are largely unexplored, including poor compliance, autonomic dysregulation with lower heart rate variability, hypothalamic-pituitary-adrenal axis overactivity, low grade inflammation, greater platelet activation, enhanced blood coagulation, endothelial dysfunction and insulin resistance [5,2,13]. Adipose tissue per se is a large endocrine organ [6]. Adiponectin is the most abundant adipose-specific protein [6,9]. Its expression is inversely associated with conventional risk factors for cardiovascular disease, such as visceral obesity, insulin resistance and type 2 diabetes, hypertension and dyslipidemia, while it is positively related to HDL [6,9]. Furthermore, adiponectin has anti-inflammatory, anti-atherogenic and anti-diabetic properties [6,9]. Therefore, we examined plasma adiponectin levels in drug-naïve first-episode MD patients without conventional risk factors for cardiovascular disease to answer the following questions: (1) Are adiponectin levels different between MD patients and healthy subjects? (2) Is there any relation between plasma adiponectin concentrations and MD?

Between March 2004 and April 2006, we screened 831 subjects with mood disorders referred to the Department of Psychiatry and 32 patients [16 females and 16 males (mean age 34.85 ± 5.88 years)] with first-episode MD (39% in a day hospital programme and 61% outpatients) met inclusion criteria to enter the study. At the same time 32 gender- and age-matched healthy subjects [17 females and 15 males (mean age 35.11 ± 5.22 years)], recruited among hospital staff, with no past or current diagnosis of psychiatric disorder, were enrolled into the study as controls. Controls underwent the same diagnostic procedures as MD patients to rule out any exclusion criteria mentioned below. All subjects were interviewed using the Structured Clinical Interview for Diagnostic and Statistical Manual IV (DSM-IV TR) Axis I Disorders (SCID-I), Italian Clinician Version [7,1]. Each subject meeting all DSM-IV TR criteria for a current diagnosis of Major Depression Disorder have been enrolled. Depression symptoms severity was measured by the HAM-D (Hamilton Depression Rating Scale; 21-item version) [3] at admission. Average alcohol and nutrient intakes were computed from semiquantitative food-frequency internal ques-

Abbreviations: MD, major depression; HAM-D, Hamilton Depression Rating Scale; BMI, body mass index; HOMA-IR, homeostatic model assessment – insulin resistance

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0304-3940/$ – see front matter © 2006 Published by Elsevier Ireland Ltd.
doi:10.1016/j.neulet.2006.08.043
The average dietary glycemic load for each participant was calculated by summing the products of the carbohydrate content per serving for each food, times the average number of servings of that food per day, times its glycemic index derived from published data. None of the patients had received psychotropic medication before they participated in the study. Medical or neurological diseases were ruled out by clinical examination and medical history, clinical chemistry, electrocardiogram and electroencephalogram. Exclusion criteria were: comorbid medical illnesses; comorbid psychotic, eating, substance or anxiety disorders; conventional cardiovascular risk factors, including hypertension, hyperlipidemia, obesity (BMI >30 kg/m²), diabetes, family history and smoking. Finally, patients whose insulin resistance score (HOMA-IR) was higher than the mean −1 S.D. compared to controls were also excluded in order to prevent insulin resistance effect on adiponectin levels. The study was conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all participants and volunteers after our University Ethical Committee study protocols approval. Overnight fasting antecubital vein blood samples were collected from each consenting subject, using 1/10 volume EDTA-aprotinin tubes and immediately placed on ice. All tubes were centrifuged at 2000 rpm for 20 min at 4°C, then supernatant was collected and stored at −80°C until analysis. To minimize random measurement error, all subjects returned for a follow-up session 1 week later, and variables (other than depression status) were reassessed in an identical fashion. Adiponectin plasma levels were measured by commercially available enzyme immunoassays (Quantikine, R&D Systems) according to manufacturer instructions. Lowest detection limit was with this assay 0.78 μg/mL. Intra- and interassay CVs were 3 and 5%, respectively. Measurements were done blinded. All samples were performed in duplicate and average values were used for statistical analysis. To evaluate marker temporal stability in the absence of treatment, Spearman rank-order correlations were computed between values from the 2 baseline blood draws. Markers were stable over time with rho values ranging from 0.70 to 0.88 for all markers. Plasma insulin was measured by ELISA (Merco-dia, Uppsala, Sweden). Lowest detection limit was 2.5 μU/mL. Intra- and interassay CVs were 6 and 10%, respectively. Total cholesterol, HDLs, triglycerides, and glucose concentrations were determined by enzymatic methods. HOMA-IR (homeostatic model assessment – insulin resistance) was calculated as the product of plasma insulin value (in μU/mL) and the fasting glucose values (in mg/dL), divided by 22.5. HOMA-IR, a representative value for insulin resistance, ordinarily ranges between 0 and 15 (insulin resistance, HOMA>3). Groups bivariate comparisons were performed using chi-square test, and appropriate Student’s t test. A two-way ANOVA was applied to investigate the effect of gender and diagnostic status (between-subjects factors: male vs. female; MD patients vs. controls) on adiponectin levels. Spearman rank correlation test was carried out to calculate bivariate correlations between adiponectin and HAM-D in MD and control groups. Statistical significance was defined at P<0.05. All data are presented as mean ± S.D. All statistics were performed using SPSS 11.0.1 software package.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MD patients (n = 32)</th>
<th>Controls (n = 32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>34.85 ± 5.88</td>
<td>35.11 ± 5.22</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.70 ± 1.99</td>
<td>28.29 ± 2.06</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>174.11 ± 18.67</td>
<td>169.51 ± 19.28</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>46.86 ± 3.64</td>
<td>47.83 ± 4.58</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>116.86 ± 24.10</td>
<td>114.66 ± 23.54</td>
<td>NS</td>
</tr>
<tr>
<td>HAM-D</td>
<td>22.63 ± 5.14</td>
<td>7.3 ± 1.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mg/L)</td>
<td>93.06 ± 8.31</td>
<td>92.42 ± 7.38</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>6.21 ± 1.46</td>
<td>5.99 ± 1.45</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.35 ± 0.41</td>
<td>1.29 ± 0.37</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting adiponectin (μg/mL)</td>
<td>9.1 ± 4.3</td>
<td>13.8 ± 5.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

No significant differences in age, BMI, total cholesterol, HDL, triglycerides, insulin levels and HOMA indexes were detected between MD patients and controls (Table 1). No significant differences in alcohol and nutrient intake and glycemic load were observed between MD patients and controls (data not shown). As expected, MD patients had significantly higher HAM-D score than controls (t = 37.355, P < 0.001). ANOVA showed a strong diagnostic group effect: MD patients had significantly lower adiponectin levels than controls (9.1 ± 4.3 vs. 13.8 ± 5.4 μg/mL, P < 0.001). Moreover, there was a significant gender effect on adiponectin levels: women had higher levels than men in both control group (14.9 ± 6.1 vs. 11.7 ± 5.1 μg/mL, P < 0.01) and MD patients (9.7 ± 4.1 vs. 7.3 ± 3.2 μg/mL, P < 0.01). No interaction gender X diagnostic group effect was achieved (P = NS). A significant negative correlation was found between plasma adiponectin levels and HAM-D in MD group (r = −0.757, P < 0.001). In addition there was no correlation between adiponectin levels and HOMA indexes, insulin levels and the lipid parameters in both groups.

Plasma adiponectin levels have been demonstrated to be closely related to metabolic syndrome and conventional risk factors for cardiovascular disease [6,9]. Nevertheless, adiponectin regulation in MD is yet unknown.

To explore the relation between MD and adiponectin levels we studied a simple model of young adult drug-naïve MD patients without conventional cardiovascular risk factors, without metabolic abnormalities to rule out any psychotropic drugs or other pathologies effect on our analysis [4]. The present study is the first showing decreased adiponectin plasma levels in these patients, and relating hypoadiponectinemia to MD severity.

Recently, Weber-Hamman et al. [14] reported no changes in MD patients adiponectin concentrations during 6 weeks of antidepressive amitriptiline or paroxetine treatment, but the study did not include healthy controls. In another study, Narita et al. [8] examined adiponectin plasma levels in patients with remitted MD receiving antidepressent therapy for more than 12 months and demonstrated that adiponectin concentrations were significantly higher than in controls. Also this report should be interpreted with caution, because it is not placebo controlled.
and it lacks of an experimental group consisting of MD patients evaluated before antidepressant treatment. In this case the results may be related to antidepressant therapy rather than depressive symptoms.

Although these findings are promising, their interpretation is complicated by potential confounders such as the presence of conventional cardiovascular risk factors, co-morbidities and different psychotropic drugs that may affect the analysis [4]. This is the reason why we conducted a cross-sectional comparison showing absolute adiponectin concentrations during the development between young adult drug-naïve MD patients without conventional risk factors for cardiovascular disease and controls.

In humans circulating adiponectin concentrations are higher in females than in males [6,9], and we confirmed this data in MD patients.

Insulin resistance might contribute to decreased adiponectin levels [6,9]. However, in our study, non-insulin resistant MD patients showed low adiponectin levels; we did not establish any association between HOMA indexes, insulin and adiponectin levels. A possible cause of this lack of association is that patients had narrow BMI ranges and were not insulin resistant.

Moreover, our patients were only moderately overweight; thus, further studies are necessary in MD to clarify if fat distribution may influence adiponectin secretion.

Experimental studies have indicated that adiponectin attenuates excessive inflammatory responses in the vascular wall [6,9]. At the early stages of atherosclerosis, endothelial cells activation by various inflammatory stimuli, including TNF-alpha, results in monocytes adhesion molecules synthesis, a crucial step for the development of vascular diseases [6,9]. Adiponectin inhibits both TNF-alpha production and action, in a dose dependent manner [6,9]. Moreover, adiponectin inhibits specific oxidized LDLs binding and uptake by macrophages thus blocking their transformation into foam cells [6,9]. The overall data indicate that adiponectin is an anti-inflammatory and anti-atherogenic protein [6,9] and further studies are needed to investigate the association between adiponectin, inflammation and atherogenesis in MD.

Study limitation should be noted. The study population was rather small, thus large-scale studies would be helpful. The mechanisms leading to decreased adiponectin levels in MD is yet unclear. Here we did not provide a detailed phenotypic characterization in terms of inflammatory markers and we did not measure patients body composition. Dietary intake was based on self-report.

In conclusion, taking into account the aforementioned limitations, our findings indicate that plasma adiponectin levels are low in MD patients who are not insulin resistant, with a correlation with MD severity.

Therefore, lifestyle and pharmaceutical approaches increasing adiponectin levels might be valuable to reduce atherosclerotic risk, particularly in MD patients, who are at high risk.

References