Association of Hypoadiponectinemia With Coronary Artery Disease in Men

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Background—Adiponectin is an adipocyte-derived plasma protein that accumulates in the injured artery and has potential antithrombogenic properties. This study was designed to determine whether a decreased plasma adiponectin level (hypoadiponectinemia) can be independently associated with the prevalence of coronary artery disease (CAD).

Methods and Results—The consecutive 225 male patients were enrolled from inpatients who underwent coronary angiography. Voluntary blood donors (n=225) matched for age served as controls. Plasma adiponectin levels in the CAD patients were significantly lower than those in the control subjects. Multiple logistic regression analysis including plasma adiponectin level, diabetes mellitus, dyslipidemia, hypertension, smoking habits, and body mass index revealed that hypoadiponectinemia was significantly and independently correlated with CAD (P<0.0088). The entire study population was categorized in quartiles based on the distribution of plasma adiponectin levels. The interquartile cutoff points were 4.0, 5.5, and 7.0 μg/mL. The multivariate-adjusted odds ratios for CAD in the first, second, and third quartiles were 2.051 (95% confidence interval [CI], 1.288 to 4.951), 1.221 (95% CI, 0.684 to 2.186), and 0.749 (95%CI, 0.392 to 1.418), respectively.

Conclusions—Male patients with hypoadiponectinemia (<4.0 μg/mL) had a significant 2-fold increase in CAD prevalence, independent of well-known CAD risk factors. (Arterioscler Thromb Vasc Biol. 2003;23:85-89.)

Key Words: adiponectin ■ risk factor ■ coronary artery disease

Obesity, defined as excess fat accumulation, is the most common cause of cardiovascular morbidity and mortality in industrialized countries.1-3 Excess body fat, in particular, abdominal visceral fat accumulation, is frequently accompanied by diabetes mellitus, dyslipidemia, and hypertension and finally results in atherosclerotic vascular diseases.1-3 Adipose tissue secretes various bioactive molecules that may directly contribute to the development of obesity-related diseases.4-7 These results suggest that the dysregulation of adipocyte-derived endocrine factors caused by overnutrition may directly participate in the development of atherosclerosis. Adiponectin is an adipose-derived factor, which we identified in the human adipose tissue cDNA library.8 Plasma adiponectin rapidly accumulates in the subendothelial space of the injured human artery. We have reported that physiological concentrations of human recombinant adiponectin inhibited monocyte adhesion to endothelial cells and macrophage-to–foam cell transformation, as well as tumor necrosis factor-α secretion from macrophages in vitro.9-12 Recently, we found that adiponectin acts as a platelet-derived growth factor-BB–binding protein and generally inhibits growth factor–induced proliferation and migration of vascular smooth muscle cells.13

Clinically, hypoadiponectinemia has been observed in patients with obesity, diabetes mellitus, and coronary artery disease (CAD), and plasma adiponectin levels increase during weight reduction.9,14-17 These findings indicate that adiponectin acts as an endogenous antithrombogenic factor regulated by personal lifestyle. Therefore, understanding the clinical significance of plasma adiponectin may be helpful in preventing the development of atherosclerotic vascular diseases. Although we already reported that the plasma adiponectin level was low in patients with CAD, the clinical importance of hypoadiponectinemia in CAD has not been fully elucidated.9 In the present study, we measured plasma adiponectin levels in consecutive CAD patients drawn from a larger population and investigated whether hypoadiponectinemia is significantly associated with CAD prevalence after adjustment for well-known CAD risk factors.

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Methods

Study Group
Consecutive male patients were enrolled from inpatients who underwent coronary angiography at Osaka University Hospital or affiliated hospitals between November 2000 and September 2001. Cases included patients aged 40 to 69 years who had a 75% or greater organic stenosis of at least 1 major coronary artery as confirmed by coronary angiogram, who had developed a myocardial infarction, or who had previously undergone percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery. The control subjects were selected from men who visited our affiliated hospitals or clinics for a physical checkup. Controls were characterized by no history of angina and other heart disease, a normal resting ECG, and normal exercise ECG stress testing. They were matched with CAD patients for age. Patients with renal dysfunction and those taking synthetic prohonoisome proliferator-activated receptor (PPAR)-γ ligands were excluded. All patients and subjects enrolled in this study were Japanese and given written, informed consent. This study was approved by the Ethics Committee of Osaka University.

Laboratory Methods
Venous blood was drawn from all patients and control subjects after an overnight fast. Plasma samples were kept at −80°C for subsequent assay. The plasma concentration of adiponectin was evaluated by a sandwich ELISA system (adiponectin ELISA kit, Otsuka Pharmaceutical Co Ltd) as previously reported. Serum total cholesterol and triglyceride concentrations were determined by an enzymatic method. HDL cholesterol was also measured by an enzymatic method after heparin and calcium precipitation. Plasma glucose was measured by a glucose oxidase method. Body mass index (BMI) was calculated as weight divided by the square of height. Risk factors were defined as follows. Diabetes mellitus was defined according to World Health Organization criteria. Dyslipidemia was defined as a total cholesterol concentration >5.69 mmol/L, a triglyceride concentration >1.69 mmol/L, an HDL cholesterol concentration <1.03 mmol/L, and/or having received treatment for dyslipidemia. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or having received treatment for hypertension. Smoking was defined as current smoker.

Statistical Methods
For continuous variables, results are presented as mean±SD or median (minimum, maximum), and the differences between the 2 groups were evaluated with an unpaired t test or the Mann-Whitney U test. Categorical variables are presented by frequency counts, and intergroup comparisons were analyzed by a χ² test. Data that did not demonstrate a gaussian distribution were logistically transformed. The CAD patients and control subjects were categorized in quartiles based on the plasma adiponectin level. The interquartile cutoff points of plasma adiponectin level were 4.0, 5.5, and 7.0 μg/mL: category 1, <4.0 μg/mL; 4.0 μg/mL ≤ category 2 < 5.5 μg/mL; 5.5 μg/mL ≤ category 3 < 7.0 μg/mL; and category 4, ≥7.0 μg/mL. Associations between CAD and all other parameters were first analyzed by simple logistic regression analysis and then by multivariate analysis. Variables included in the analysis were plasma adiponectin level (quantitative), diabetes mellitus (yes or no), dyslipidemia (yes or no), hypertension (yes or no), smoking habit (yes or no), and BMI (quantitative). The multivariate-adjusted odds ratios (ORs) are presented with 95% confidence intervals (CIs). All calculations were performed by using a standard statistical package (JMP for Macintosh, version 4.0).

Results

Patient Characteristics
The clinical characteristics of male CAD patients and control subjects are shown in Table 1. Plasma adiponectin levels in the CAD patients were significantly lower than those in control subjects (P<0.0001). The median (minimum, maximum) level was 4.7 (0.7, 15.9) in the CAD patients and 5.9 (1.6, 15.2) in control subjects. The number of subjects according to logarithmically transformed adiponectin levels in CAD and control are shown in Figure 1. In the first quartile (plasma adiponectin level <4.0 μg/mL), the number of CAD patients were significantly lower than those in control subjects (P<0.0001). The median (minimum, maximum) level was 4.7 (0.7, 15.9) in the CAD patients and 5.9 (1.6, 15.2) in control subjects. The number of subjects according to logarithmically transformed adiponectin levels in CAD and control are shown in Figure 1. In the first quartile (plasma adiponectin level <4.0 μg/mL), the number of CAD

TABLE 1. Clinical Characteristics of Control Subjects and CAD Patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Control Subjects (n=225)</th>
<th>CAD Patients (n=225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.8±4.1</td>
<td>59.7±7.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.2±2.7</td>
<td>24.5±3.2*</td>
</tr>
<tr>
<td>Adiponectin, μg/mL</td>
<td>5.9 (1.6, 15.2)</td>
<td>4.7 (0.7, 15.9)‡</td>
</tr>
<tr>
<td>Category 1; &lt;4.0, n</td>
<td>25</td>
<td>81</td>
</tr>
<tr>
<td>Category 2; ≥4.0, &lt;5.5, n</td>
<td>68</td>
<td>61</td>
</tr>
<tr>
<td>Category 3; ≥5.5, &lt;7.0, n</td>
<td>62</td>
<td>35</td>
</tr>
<tr>
<td>Category 4; ≥7.0, n</td>
<td>70</td>
<td>48</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>22 (10)</td>
<td>73 (32)§</td>
</tr>
<tr>
<td>FPG, mmol/L</td>
<td>5.33 (2.05, 11.82)</td>
<td>5.83 (3.61, 22.48)‡</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>109 (48)</td>
<td>171 (76)§</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.16 (0.29, 4.23)</td>
<td>1.56 (0.42, 4.40)‡</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.37±0.41</td>
<td>1.13±0.35*</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.07±0.75</td>
<td>3.26±0.88</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>50 (22)</td>
<td>129 (57)§</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>124.9±17.9</td>
<td>130.0±18.1†</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>73.5±12.2</td>
<td>74.7±11.7</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>43 (19)</td>
<td>65 (29)</td>
</tr>
</tbody>
</table>

Data are mean±SD, median (minimum, maximum), or frequency counts, as appropriate. FPG indicates fasting plasma glucose; BP, blood pressure. *P<0.0001; †P<0.01 vs control subjects (unpaired t test); ‡P<0.0001 vs control subjects (Mann-Whitney U test). §P<0.0001 vs control subjects (χ² test).

Figure 1. The number of subjects according to log adiponectin levels in patients with CAD (solid bars) and control subjects (open bars). Logarithmic transformation of the plasma adiponectin concentrations was performed as needed to improve normality.
patients was 3 times that of control subjects, but in the fourth quartile (plasma adiponectin level ≥ 7.0 μg/mL), the number of CAD patients was less than that of control subjects. The CAD patients had significantly higher levels of BMI, fasting plasma glucose, triglycerides, LDL cholesterol, and systolic blood pressure and lower levels of HDL cholesterol. There were no significant differences in age, total cholesterol, diastolic blood pressure, and the number of smokers between the 2 groups.

Adiponectin and CAD

The results of logistic regression analysis are shown in Table 2. To evaluate each factor in Table 1, simple logistic regression analysis was performed. There were significant differences between the 2 groups in terms of BMI, plasma adiponectin level, triglyceride, HDL cholesterol, LDL cholesterol, fasting plasma glucose, systolic blood pressure, diabetes mellitus, dyslipidemia, hypertension, and smoking habit. However, triglycerides, HDL cholesterol, LDL cholesterol, and dyslipidemia were dependent on each other. Systolic blood pressure and hypertension as well as fasting plasma glucose and diabetes mellitus were also dependent on each other. Among these parameters, dyslipidemia, hypertension, and diabetes mellitus were selected as the representative factors from their higher correlation with CAD. For multiple logistic regression analysis, all parameters were clustered into 5 groups (dyslipidemia, diabetes mellitus, hypertension, smoking habit, and BMI). Multiple logistic regression analysis with plasma adiponectin level, dyslipidemia, diabetes mellitus, hypertension, smoking habit, and BMI revealed that hypoadiponectinemia was independently correlated with CAD (P<0.0088) as well as known CAD risk factors.

Cutoff Point of Hypoadiponectinemia

The multivariate-adjusted ORs for CAD in each of the quartiles based on the plasma adiponectin level are shown in Figure 2. For clinical translation, cut off points were selected, although a dose-response relation was statistically observed between the probability of CAD (p(CAD)) and plasma adiponectin level: 

\[
\log p(CAD)/(1-p(CAD)) = -2.1963 + 3.0410 \times \log(\text{plasma adiponectin level})
\]

Wald’s \( \chi^2 \) test, \( P<0.001 \), \( R^2=0.0557 \) (n=450). The cutoff points were 4.0, 5.5, and 7.0 μg/mL plasma adiponectin. This model was adjusted for other known risk factors. ORs for CAD in the first, second, and third quartiles were 2.051 (95%CI, 1.288 to 4.951), 1.221 (95%CI, 0.684 to 2.186), and 0.749 (95%CI, 0.392 to 1.418) compared with the fourth quartile.

**Figure 2.** ORs for CAD in the first, second, and third quartiles compared with the fourth quartile. This model was adjusted for other known risk factors. Vertical bars indicate 95% CI.
Discussion

In the present study, hypoadiponectinemia was found to be highly associated with CAD prevalence after adjustment for well-known CAD risk factors such as diabetes mellitus, dyslipidemia, hypertension, smoking habit, and BMI in male subjects. For translation into the clinical setting, it is very important to determine the abnormal range of plasma adiponectin concentrations. The multivariate-adjusted OR for CAD revealed that male patients with hypoadiponectinemia (<4.0 μg/mL) had a 2-fold increase in CAD prevalence, independent of well-known CAD risk factors. We previously reported that the plasma adiponectin level in female CAD patients was also significantly lower than that in age- and BMI-adjusted healthy female control subjects. However, the plasma adiponectin levels in female subjects were significantly higher than those in male subjects. Our recent findings suggest that androgen-induced hypoadiponectinemia is related to the high risk of atherosclerosis in men. Because male sex is an important risk factor for CAD, we focused on middle-aged men in the current study. Further study will be necessary to elucidate the cutoff point of hypoadiponectinemia in women with regard to CAD prevalence.

Adiponectin and Insulin Resistance in CAD

In addition to CAD, we previously reported that the plasma adiponectin level was decreased in obesity and type 2 diabetes. However, multiple logistic regression analysis revealed that hypoadiponectinemia is significantly associated with CAD prevalence, even after adjustment for BMI and diabetes mellitus. Recently, we and others have reported that adiponectin itself may affect glucose metabolism in mice. Therefore, hypoadiponectinemia may be relevant to the states of insulin resistance in men. In this study, however, hypoadiponectinemia in the CAD patients was observed even when the presence or absence of diabetes mellitus was adjusted for. Interestingly, the plasma adiponectin concentrations in diabetic patients with macroangiopathy were significantly lower than those of diabetic patients without macroangiopathy. Therefore, hypoadiponectinemia may have an adverse effect on the development of diabetic macroangiopathy.

Adiponectin as a Protective Factor in CAD

Adiponectin is an adipocyte-specific plasma protein, which is abundantly present in the human blood stream. We have previously reported that adiponectin acts as a modulator of the inflammatory response in the vascular wall. Plasma adiponectin rapidly accumulates in the subendothelial space of the injured human artery, and recombinant adiponectin was found to have inhibited monocyte adhesion to endothelial cells and the macrophage-to–foam cell transformation, as well as vascular smooth muscle cell proliferation, in vitro. Because these steps are believed to be crucial in the development of atherosclerosis, adiponectin can be considered an endogenous biologically relevant modulator of vascular remodeling, and hypoadiponectinemia may cause an excessive inflammatory response in the coronary artery. Recently, we investigated whether plasma adiponectin levels were an inverse predictor of cardiovascular outcomes among patients with end-stage renal disease. Therefore, hypoadiponectinemia can be considered a candidate risk factor for CAD, although a large-scale prospective study in the general population is necessary.

Conclusions

In summary, hypoadiponectinemia (<4.0 μg/mL) was found to be independently associated with the presence of CAD after adjustment for other well-known CAD risk factors in men. Our findings suggest that the adipocyte-specific plasma protein adiponectin is one of the clinically important molecules associated with atherosclerosis and that measurement of plasma adiponectin level will be helpful to evaluate CAD risk.

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