Adiponectin and Coronary Heart Disease: The Strong Heart Study

To the Editor:

The adipocyte secreted protein, adiponectin, is of particular interest in metabolic and vascular disease because of its close associations with insulin sensitivity and obesity.1 Lower levels of adiponectin are associated with later development of type 2 diabetes.2 Recent observations from the Health Professionals Follow-Up Study3 suggest that lower adiponectin concentrations might also be associated with incident myocardial infarction, findings in keeping with prior observations in patients with end-stage renal failure.4

We examined prospective relationships of adiponectin to vascular disease in a case–control series selected from the Strong Heart Study (SHS). The SHS is the largest study of cardiovascular disease in American Indians, a group at particular risk of obesity and type 2 diabetes and in whom an increasing incidence of coronary heart disease (CHD) is seen.5

Cases and controls were selected from the SHS cohort.6 The SHS recruited 4549 volunteers of American Indian heritage from 3 geographic areas (Arizona, North and South Dakota, and Oklahoma).6 Volunteers (59% female) were invited to a study examination on three occasions (SH1, 1988 to 1992; SH2, 1993 to 1995; SH3, 1997 to 1999) and remained under continued surveillance for development of vascular disease as described previously.7,8 Because of availability of plasma samples, baseline data for this study were taken from the second examination (SH2), and participants with prevalent cardiovascular disease at SH2 (definite CHD and stroke), or thyroid or glucocorticoid medication were excluded. Of eligible participants at baseline, 295 had incident CHD (69 fatal or 182 nonfatal CHD events) in subsequent follow-up. Controls were randomly selected within a frequency-matched design based on sex, diabetes status, the three geographic areas of the study (Arizona, North and South Dakota, Oklahoma), and creatinine (<1.2 mg/dL versus ≥1.2 mg/dL). A total of 251 (85%) cases had samples available and could be matched to controls. Fasting serum adiponectin concentrations were assayed by competitive radioimmunoassay (Linco Research Inc.). Both intra- and interassay coefficients of variation were <10%.

The 251 cases and matched controls were of similar age (mean±SD: controls 60.5±7.6 years, cases 61.7±8.4 years; P=0.09), BMI (controls 30.7±6.0 kg/m², cases 31.5±5.9 kg/m²; P=0.16), and waist measurement (controls 106±14 cm, cases 108±13; P=0.14). Cases had higher systolic blood pressure (controls 136±23 mm Hg, cases 131±22 mm Hg; P=0.008) and triglycerides (median [interquartile range]: controls 129 [96 to 193] mg/dL, cases 151 [109 to 221] mg/dL; P=0.004) but lower HDL cholesterol (controls 41±15 mg/dL, cases 38±11 mg/dL; P=0.04). Those with diabetes (n=185, 74% of cases and matched controls) were more likely to have albuminuria (controls 26% micro-, 15% macro-albuminuria; cases 26% micro-, 28% macro-albuminuria; P=0.002). Baseline adiponectin concentrations were similar in cases and controls (median [interquartile range]: controls 9.4 [6 to 15] μg/mL, cases 9.6 [6.8 to 13.3] μg/mL; P=0.81) even after adjustment for other baseline variables (geometric mean controls 9.8 μg/mL versus cases 9.2 μg/mL; P=0.23; age-, % fat-, waist-, albumin:creatinine ratio-, sex-, and diabetes-adjusted). Adiponectin showed no significant association with later development of coronary heart disease in all subjects (odds ratio 0.97 [0.81 to 1.16]) or after additional adjustment for other covariates or in subgroups of those with or without diabetes (Table).

Across all cases and controls, adiponectin had the expected relationships with metabolic and lipid measures: positively related to measures of insulin sensitivity (QUICKI r=−0.26, P<0.0001) and HDL cholesterol (r=−0.53, P<0.0001) and inversely to fasting glucose (r=−0.15, P<0.001), % fat (r=−0.20, P<0.0001), and waist (r=−0.17, P<0.001). Adiponectin concentrations were higher in women (geometric mean 11.2 μg/mL versus 7.9 μg/mL in men, P<0.001, after adjustment for age, % fat, waist, albumin:creatinine ratio, and diabetes status) and those without prevalent type 2 diabetes (geometric mean people without diabetes 10.5 μg/mL versus with diabetes 8.6 μg/mL, P=0.02, after adjustment for age, % fat, waist, albumin:creatinine ratio, and sex). In those with diabetes, adiponectin was higher in the presence of macroalbuminuria (adiponectin geometric mean: macroalbuminuria 11.2 μg/mL; microalbuminuria 8.5 μg/mL; normoalbuminuria 8.6 μg/mL; P<0.001) even after adjustment for age, sex, % fat, and waist. This relationship remained significant after additional adjustment for plasma creatinine at baseline (P<0.001).

Relationships of adiponectin with inflammation and vascular disease are intriguing and of potential importance. Adiponectin has been shown to be lower in the presence of prevalent coronary artery disease.9–11 Higher adiponectin was associated with lower risk of incident myocardial infarction in the Health Professionals Follow-Up Study3 and protected against future cardiovascular disease in patients with end-stage renal failure.8 By contrast, adiponectin was not found to predict restenosis after coronary stenting12 and was not associated with incident CHD in our study.

The reasons for the differences between the various studies are not clear. Our study had >95% power to detect a difference of the magnitude found by Zoccali4 and Pischon3 (cases-control differences in adiponectin of 2.1 μg/mL and 2.3 μg/mL, respectively). If present, a protective effect of adiponectin may then be smaller than previously estimated. Our results may have been influenced by the effect of impaired renal function. Paradoxically (given the high vascular risk found in such patients), end-stage renal failure is associated with a doubling of adiponectin concentrations.3 Similarly, adiponectin is inversely correlated with creatinine clearance13 and is raised in the presence of nephrotic syndrome.14 In our study, adiponectin was found to be higher in the presence of macroalbuminuria, in keeping with previous results.14,15

Table 1. Relationship of Adiponectin to Incident Coronary Heart Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>No.</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin, age- and sex-adjusted</td>
<td>All</td>
<td>251 cases, 251 controls</td>
<td>0.97</td>
<td>0.81–1.16</td>
</tr>
<tr>
<td>Adiponectin, multivariate-adjusted</td>
<td>All</td>
<td>251 cases, 251 controls</td>
<td>0.91</td>
<td>0.74–1.12</td>
</tr>
<tr>
<td>Adiponectin, multivariate-adjusted</td>
<td>No DM</td>
<td>66 cases, 66 controls</td>
<td>0.82</td>
<td>0.54–1.25</td>
</tr>
<tr>
<td>Adiponectin, multivariate-adjusted</td>
<td>DM</td>
<td>185 cases, 185 controls</td>
<td>0.92</td>
<td>0.72–1.17</td>
</tr>
</tbody>
</table>

Effect of adiponectin in multivariate models for prediction of incident cardiovascular disease. Odds ratio scaled to a 1 SD difference in variable (* = log transformed variable).

Odds ratio adjusted for waist, age, % fat, SBP, smoking, and albumin:creatinine ratio. For subgroup analyses, DM indicates diabetes; NDM, no diabetes.
Differences in the results between studies may reflect underlying differences in the study populations. Neither positive study included as many participants with diabetes (15% in Zoccali, 9% of controls in Pischon) or obesity. Notably, almost three-quarters of all of our cases were diabetic (74%), and 54% were obese (BMI ≈ 30 kg/m²). In keeping with this, adiponectin concentrations in the present study are much lower (median ≈ 9.5 µg/dL) than those of Pischon et al (median ≈ 15 µg/dL). It may be then that the relationship of adiponectin to later vascular disease may be less apparent in the presence of type 2 diabetes or obesity. Nevertheless, our results suggest that adiponectin will not be a consistent marker for predicting CHD and that its role is more important in insulin resistance and diabetes.

Acknowledgments

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