Adiponectin and Carotid Intima-Media Thickness in the Northern Manhattan Study

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Background and Purpose—Adiponectin is an insulin-sensitizing plasma protein expressed in adipose tissue and suggested to play a role in atherosclerosis and cardiovascular disease. Data are lacking on the relationship between adiponectin and carotid intima-media thickness (IMT) in ethnically heterogeneous populations. We examined the relationship between adiponectin and IMT, a marker of atherosclerosis, in a multiethnic cohort study of stroke risk factors.

Methods—Participants were from the Northern Manhattan Study (N=1522, mean age 66±9 years, 60% female, 20% black, 18% white, 60% Hispanic). Adiponectin was measured from baseline plasma samples and IMT was assessed by high-resolution B-mode carotid ultrasound. Regression models were used to examine the association between adiponectin, assessed continuously and in quartiles, and IMT controlling for demographics and vascular risk factors.

Results—The mean adiponectin level was 10.3±5.2 μg/mL (median, 9.2 μg/mL; range, 2.3–53.3 μg/mL), and the mean IMT was 0.91±0.08 mm. Adiponectin was inversely associated with IMT, even after controlling for demographics and vascular risk factors. Individuals in the first quartile of adiponectin had mean IMT that was on average 0.02 mm greater than those in the top quartile. The relationship between adiponectin and IMT appeared to be stronger among those with diabetes.

Conclusions—Our findings suggest that low adiponectin is associated with increased IMT in a multiethnic cohort and support a protective role for adiponectin in atherosclerosis. (Stroke. 2012;43:1123-1125.)

Key Words: adiponectin = atherosclerosis = carotid artery = epidemiology = intima-media thickness

Adiponectin is an insulin-sensitizing plasma protein expressed in adipose tissue and is suggested to play a protective role in atherosclerosis and cardiovascular disease.1 Low serum adiponectin concentration has been independently related to progression of carotid intima-media thickness (IMT),2 a marker of atherosclerosis and a stroke risk factor.3 However, the adiponectin and IMT relationship has mainly been studied in white populations.2 Because stroke affects Hispanics and blacks more than whites,4 we aimed to investigate the association between adiponectin and IMT in a multiethnic urban population. Consistent with the observations in predominantly white populations, we hypothesized that adiponectin and IMT would be inversely associated in our multiethnic population.

Methods

Study Population
Subjects were participants in the Northern Manhattan Study (NOMAS) with both IMT and adiponectin levels measured. NOMAS is a prospective cohort study designed to determine stroke incidence, risk factors, and prognosis in a multiethnic urban population. The methods of subject recruitment and enrollment were previously described.5 Baseline data were collected from 1993 to 2001 by trained bilingual research assistants.6 Of 3298 NOMAS participants, 1522 had both IMT and adiponectin measured. The study was approved by the Columbia University and University of Miami Institutional Review Boards and all subjects provided written informed consent.

Adiponectin
Adiponectin in stored frozen baseline plasma was measured using a commercially available sandwich ELISA (Mercodia, Winston Salem, NC, Catalogue No. 10-1193-01). The assay uses standards in the range of 5 to 300 ng/mL; because human sera adiponectin levels are in the microgram per milliliter range, samples were diluted (approximately 1:100) before assay. The intra- and interassay coefficients of variation were <4% and <7%, respectively.

Carotid Ultrasound
Carotid IMT was assessed by high-resolution B-mode ultrasound using standardized protocols as previously described with strong validity and reliability.7 IMT in all carotid segments was measured in areas without plaque. IMT was calculated as a composite measure
controlling for demographics and vascular risk factors (Table; http://stroke.ahajournals.org).

Table. Association Between Adiponectin and IMT

<table>
<thead>
<tr>
<th>Adiponectin Quartile</th>
<th>Model 1*</th>
<th>Model 2†</th>
<th>Model 1*</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1 (2.25–6.99 μg/mL)</td>
<td>0.020 (0.002)</td>
<td>0.020 (0.005)</td>
<td>1.60 (1.11–2.32)</td>
<td>1.50 (0.98–2.30)‡</td>
</tr>
<tr>
<td>Quartile 2 (7.00–9.87 μg/mL)</td>
<td>0.009 (0.16)</td>
<td>0.008 (0.21)</td>
<td>1.25 (0.86–1.81)</td>
<td>1.16 (0.78–1.75)</td>
</tr>
<tr>
<td>Quartile 3 (9.87–13.83 μg/mL)</td>
<td>−0.0003 (0.97)</td>
<td>−0.0002 (0.97)</td>
<td>1.08 (0.74–1.57)</td>
<td>1.04 (0.70–1.55)</td>
</tr>
<tr>
<td>Quartile 4 (13.83–53.26 μg/mL)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Trend P 0.0004 0.001 0.010 0.040
1-SD increase −0.007 (0.001) −0.006 (0.01) 0.82 (0.72–0.94) 0.85 (0.73–0.99)

IMT indicates intima-media thickness; CI, confidence interval.
*Adjusted for age, sex, and race/ethnicity.
†Adjusted for age, sex, race/ethnicity, smoking, high-density lipoprotein, low-density lipoprotein, triglycerides, diabetes, hypertension, body mass index, physical activity, alcohol use, and carotid plaque.
‡P=0.06.

combining near and far walls of the common carotid artery IMT, bifurcation IMT and internal carotid artery IMT of both sides of the neck, and expressed as a mean of the maximum measurements of the 12 carotid sites.

Statistical Analysis
Linear regression models were constructed to examine the association between adiponectin and IMT, and logistic regression models were constructed with the top quartile of IMT as the outcome. Adiponectin was examined continuously (per SD increase) and in quartiles. A sequence of regression models was used: (1) adjusted for demographics only (age, sex, and race/ethnicity); and (2) adjusted for demographics, body mass index, diabetes, never/former/current smoking, moderate alcohol consumption, moderate to heavy physical activity, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, hypertension, and carotid plaque. We examined potential interactions between adiponectin and demographics, body mass index, and diabetes in relation to IMT.

Results
The mean age at baseline was 66±9 years, 60% were female, 20% black, 18% white, 60% Hispanic, mean body mass index was 28±5 kg/m², and mean IMT was 0.91±0.08 mm. The mean adiponectin level was 10.3±5.2 μg/mL and was greater in whites (12.8±6.9) than in blacks (9.9±4.9) or Hispanics (9.7±4.5; multivariate-adjusted P<0.0001).

Adiponectin was inversely associated with IMT, even after controlling for demographics and vascular risk factors (Table: β per 1-SD increase in adiponectin = −0.006; P=0.01). Individuals in the first quartile of adiponectin had mean IMT that was on average 0.02 mm greater than those in the top quartile (P<0.01). The association between adiponectin and IMT also persisted in secondary analyses that controlled for creatinine, high-sensitivity C-reactive protein (N=666), and Homeostasis Model Assessment insulin resistance (not shown). There was no significant interaction between adiponectin and age, sex, race/ethnicity, or body mass index in relation to IMT. However, there was a marginally significant (P=0.06) negative interaction between diabetes and adiponectin (continuous) in relation to IMT. The inverse association between adiponectin and IMT was stronger among those with diabetes than those without (online-only Supplemental Table 1; http://stroke.ahajournals.org).

The findings were consistent in a sensitivity analysis restricted to 944 participants whose IMT was measured over 2 years after baseline (linear regression with continuous IMT: 1-SD increase in adiponectin β = −0.006; P=0.03).

Discussion
The results demonstrate that low adiponectin levels are associated with increased IMT in our multiethnic cohort. Our results are consistent with previous reports of an inverse association between adiponectin and atherosclerosis in primarily white populations.2,8 Consistent with our finding that the relationship between adiponectin and IMT was stronger among those with diabetes, a previous study among patients with coronary artery disease showed that adiponectin levels predicted major cardiovascular events only in patients with diabetes.9

Adiponectin inhibits proatherogenic processes. The exact mechanism is yet to be elucidated but may include enhancing endothelial nitric oxide synthase activity, inhibiting inflammatory changes that lead to increased expression of endothelial adhesion molecules, suppression of macrophage activation required for development of foam cells, and overexpression of adiponectin, which in animal models of precocious atherosclerosis has been shown to inhibit plaque size.10

Previous studies measuring adiponectin levels were performed mainly in white populations. There are race/ethnic differences in several vascular risk factors,11 and our results indicate that adiponectin levels also vary by race/ethnicity. However, the relationship between adiponectin and IMT did not significantly differ across race/ethnic groups after accounting for vascular risk factors, although the power to detect effect modification was low. Multicollinearity between adiponectin and vascular risk factors may have masked race–ethnic differences and warrant further investigation. We did not measure leptin, another adipose-derived hormone that regulates energy intake and expenditure. The ratio of leptin and adiponectin may be etiologically relevant,12 although recent data suggest that adiponectin alone is a stronger predictor of atherosclerosis.2 Although we did not measure...
the high-molecular-weight form of adiponectin, total adiponectin levels have been highly correlated with the high-molecular weight form.13

Our study supports adiponectin as a novel and potentially modifiable risk factor for atherosclerosis with potentially substantial clinical benefits for the reduction of stroke risk.

Sources of Funding
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Disclosures
None.

References
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An erratum has been published regarding this article. Please see the attached page for:
http://stroke.ahajournals.org/content/suppl/2012/01/05/STROKEAHA.111.641761.DC1

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The article, “Adiponectin and Carotid Intima-Media Thickness in the Northern Manhattan Study” by Gardener et al (Stroke. 2012;43:1123–1125) included an error in the Methods section. The correct text is below as well as in the current online version.

Adiponectin in stored frozen baseline plasma was measured using a commercially available sandwich ELISA (Mercodia, Winston Salem NC; Catalogue No. 10-1193-01). The assay uses standards in the range of 5 to 300 ng/mL; because human sera adiponectin levels are in the microgram per milliliter range, samples were diluted (approximately 1:100) before assay. The intra- and interassay coefficients of variation were <4% and <7%, respectively.
Supplemental Table 1. Association between adiponectin and total carotid IMT stratified by diabetes

<table>
<thead>
<tr>
<th>Adiponectin, per 1 SD increase</th>
<th>mm change in IMT (p-value)</th>
<th>Model 1*</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among those with diabetes (N=298)</td>
<td>-0.013 (0.01)</td>
<td>-0.014 (0.01)</td>
<td></td>
</tr>
<tr>
<td>Among those without diabetes (N=1224)</td>
<td>-0.006 (0.02)</td>
<td>-0.005 (0.07)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race/ethnicity

†Adjusted for age, sex, race/ethnicity, smoking, high-density lipoprotein, low-density lipoprotein, triglycerides, diabetes, hypertension, body mass index, physical activity, alcohol use, carotid plaque