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

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## Abstract

**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 multi-ethnic 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, range=2.3-53.3), 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.

**Conclusion—**Our findings suggest that low adiponectin is associated with increased IMT in a multi-ethnic cohort and support a protective role for adiponectin in atherosclerosis.

### Keywords

Adiponectin; carotid artery; intima-media thickness; atherosclerosis; epidemiology

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## Introduction

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]. Since stroke affects Hispanics and blacks more than whites[4] we aimed to investigate the association between adiponectin and IMT in a multi-ethnic urban population. Consistent with the observations in predominantly white populations, we hypothesized that adiponectin and IMT would be inversely associated in our multi-ethnic 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 multi-ethnic urban population. The methods of subject recruitment and enrollment were previously described[5]. Baseline data were collected from 1993-2001 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 IRBs and all subjects provided written informed consent.

### Adiponectin

Adiponectin in stored frozen baseline plasma was measured using a commercially available double antibody radioimmunoassay (Linco Research, Millipore, Billerica, MA; Cat # HADP-61HK). The assay utilizes standards in the range of 1-100 ng/ml; since human sera adiponectin levels are in the μg/ml range, samples were diluted (approximately 1:5000) prior to assay. The intra- and inter-assay coefficient of variation were < 6% and <10 %, 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 combining near and far walls of the CCA IMT, bifurcation IMT and ICA 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 standard deviation (SD) increase) and in quartiles. A sequence of regression models was used: (1) adjusted for demographics only (age, sex, and race/ethnicity), (2) adjusted for demographics, body mass index (BMI), diabetes, never/former/current smoking, moderate alcohol consumption, moderate-heavy physical activity, HDL and LDL cholesterol, triglycerides, hypertension, and carotid plaque. We examined potential interactions between adiponectin and demographics, BMI and diabetes in relation to IMT.

## Results

The mean age at baseline was 66±9 years, 60% female, 20% black, 18% white, 60% Hispanic, mean BMI 28±5, mean IMT 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 1, 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 HOMA insulin resistance (not shown). There was no significant interaction between adiponectin and age, sex, race/ethnicity or BMI 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 (supplementary Table 1).

The findings were consistent in a sensitivity analysis restricted to 944 participants whose IMT was measured over two 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 multi-ethnic cohort. Our results are consistent with previous reports of an inverse association between adiponectin and atherosclerosis in primarily Caucasian 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 pro-atherogenic 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. Multi-collinearity 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], though 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## Table 1

Association between adiponectin and IMT

| Adiponectin | mm difference in IMT (p-value) | | Odds ratio (95% confidence interval) of being in the top quartile of IMT (0.96-1.41 mm) | |
|---|---|---|---|---|
| | Model 1* | Model 2† | Model 1* | Model 2† |
| **Quartile 1** (2.25-6.99 μg/ml) | 0.020 (0.002) | 0.020 (0.005) | 1.60 (1.11-2.32) | 1.50 (0.98-2.30)‡ |
| **Quartile 2** (7.00-9.87 μg/ml) | 0.009 (0.16) | 0.008 (0.21) | 1.25 (0.86-1.81) | 1.16 (0.78-1.75) |
| **Quartile 3** (9.87-13.83 μg/ml) | -0.0003 (0.97) | -0.0002 (0.97) | 1.08 (0.74-1.57) | 1.04 (0.70-1.55) |
| **Quartile 4** (13.83-53.26 μg/ml) | ref | ref | ref | ref |
| **Trend p-value** | 0.0004 | 0.001 | 0.01 | 0.04 |
| **Continuous 1 SD increase** | -0.007 (0.001) | -0.006 (0.01) | 0.82 (0.72-0.94) | 0.85 (0.73-0.99) |

*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

‡p=0.06