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Adiponectin and risk of vascular events in the Northern Manhattan Study

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ABSTRACT

Objectives: Despite adiponectin's independent relationship with many markers of vascular disease risk, its association with clinical outcomes is unclear and results of studies have been inconsistent. We examined the association between adiponectin, an adipocytokine secreted by adipose tissue, and vascular events (stroke, myocardial infarction (MI), vascular death) in the multi-ethnic prospective population-based Northern Manhattan Study (NOMAS).
Methods: Adiponectin was measured at baseline among 2900 participants free of MI and stroke (mean age 69 ± 10 years, 37% men, 21% white, 53% Hispanic, 24% black). Over a mean 10 years follow-up, 692 incident vascular events accrued.
Results: The mean adiponectin = 11.4 ± 6.2 μg/ml (median = 9.8, range = 2.1–53.3). In Cox models adjusting for demographics and vascular risk factors, a decreased risk of vascular events was suggested with lower adiponectin. Examination of quartiles suggested a non-linear relationship, with a reduction in risk observed among those in adiponectin quartiles 1–3 vs. 4, and the lowest effect estimates observed in quartile 2. Similar results were found when stroke, MI, and vascular death were examined separately. We saw no effect modification by baseline vascular health profile, but the positive association between adiponectin and vascular events was stronger among those with elevated waist circumference.
Conclusions: In NOMAS, low-moderate adiponectin was associated with a decreased risk of vascular events despite the fact that low adiponectin levels were associated with an elevated vascular risk profile. These counter-intuitive findings underscore the need for further research on adiponectin as a useful biomarker of vascular disease risk and mechanisms explaining the inconsistent observations in the literature.

1. Introduction

Adiponectin is an adipocytokine secreted by adipose tissue, with insulin sensitizing effects as well as effects on triglyceride and high density lipoprotein (HDL) cholesterol metabolism [1]. Recently, adiponectin has received a great deal of attention due to its potential as a biomarker for cardiovascular disease risk, with low levels presumed to confer elevated risk.

In our large race/ethnically diverse population-based adult cohort, the Northern Manhattan Study (NOMAS), we recently confirmed that lower adiponectin levels are independently associated with several important vascular risk factors including smoking, hypertension, diabetes, waist circumference, body mass index (BMI), estimated glomerular filtration rate, high-sensitivity C-reactive protein (hsCRP), triglycerides, low density lipoprotein (LDL) cholesterol, low HDL cholesterol, and the metabolic syndrome [34]. We have also confirmed a now well-established association between greater adiponectin levels and older age, the underlying mechanisms of which have not been elucidated, that is inconsistent with adiponectin's inverse association with many other vascular risk factors. Lastly, we have previously shown in NOMAS that lower adiponectin was associated with greater carotid intima-media thickness, a marker of atherosclerosis and stroke risk factor [2].

Despite mounting evidence of adiponectin's independent relationship with many markers of vascular disease risk, its association with clinical outcomes, including stroke and myocardial infarction (MI), is unclear and the results of published studies to date have been inconsistent. Several epidemiologic studies have shown that adiponectin levels are lower in subjects with cardiovascular events,

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in some cases predicting events independently of established risk factors [3–5]. However, other studies have failed to show an independent association between adiponectin and stroke and MI [6–8], and still others have demonstrated an increased risk of stroke [9], and cardiovascular disease and mortality [10–15] among those with *greater* adiponectin levels. Potential mechanisms underlying the latter positive associations are not well-understood. Nevertheless, adiponectin seems to be an attractive therapeutic target for prevention of CVD and diabetes, as it can be significantly increased by diet, exercise and weight reduction [16].

We examined the relationship between baseline serum adiponectin levels and incident vascular events (stroke, MI, and vascular death) in our prospective NOMAS cohort. Our recent findings that adiponectin levels vary across race-ethnic groups and are lower among non-Hispanic blacks and Hispanics compared to non-Hispanic whites (under review at Metabolic Syndrome and Related Disorders) underscore the importance of examining this relationship in a multi-ethnic community-based sample.

2. Methods

2.1. Study population

NOMAS is a prospective cohort study designed to determine stroke incidence, risk factors, and prognosis in a multi-ethnic urban population. Study details have been published previously [17].

Eligible subjects: a) had never been diagnosed with ischemic stroke; b) were >40 years old; and c) resided in Northern Manhattan for ≥3 months, in a household with a telephone. Subjects were identified by random-digit dialing, and interviews were conducted by trained bilingual research assistants. The telephone response rate was 91%. Subjects were recruited from the telephone sample to have an in-person baseline interview and assessment. The enrollment response rate was 75%, the overall participation rate was 69%, and a total of 3298 subjects were enrolled with an average annual contact rate of 95%. After excluding those participants with an MI prior to baseline and those with missing adiponectin 2900 NOMAS participants were included in the analytic sample. The study was approved by the Columbia University and University of Miami IRBs and all subjects provided informed consent.

2.2. Baseline evaluation

Data were collected through interviews with trained bilingual research assistants in English or Spanish. Physical and neurological examinations were conducted by study neurologists. Race-ethnicity was based upon self-identification through a series of questions modeled after the US census and conforming to standard definitions outlined by Directive 15 [18]. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control regarding hypertension, diabetes, smoking, and cardiac conditions [19]. Smoking was categorized as never smoking, former smoking, and current (within the past year) smoking. Moderate alcohol use was defined as current drinking of >1 drink per month and ≤2 drinks per day. Hypertension was defined as a blood pressure ≥140/90 mmHg (based on the average of two measurements during one sitting), antihypertensive medication use, or the patient's self-reported hypertension. Diabetes mellitus was defined by the patient's self-reported diabetes, use of insulin or oral anti-diabetic medication, or fasting glucose ≥126 mg/dl. Fasting lipid profile was measured at enrollment. Physical activity was defined as the frequency and duration of 14 different recreational activities during the 2-week period before the interview, as described previously [20]. Waist measurements were determined to the nearest inch. Elevated waist circumference was defined as >35.2 inches for women and >40.8 inches for men (the Third Report of the National Cholesterol Education Program: Adult Treatment Panel III (NCEP ATP III)) [21]. hsCRP was collected at baseline from 2091 of the study participants. Carotid plaque presence and carotid intima-media thickness (cIMT), two distinct markers of atherosclerosis, were measured by B-mode ultrasound, as described previously [2].

2.3. Adiponectin

Baseline adiponectin was measured from stored plasma using a commercially available sandwich ELISA (Mercodia, Winston Salem NC; Catalogue No. 10-1193-01). The assay uses standards in the range of 5–300 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.

2.4. Prospective follow-up

Annual telephone screening was conducted to determine changes in vital status, detect neurologic events, document interval hospitalizations, and review risk factor status, medication changes, and changes in functional status. Persons who screened positive had an in-person assessment, including chart review and physician examination. Outcome events were detected through ongoing hospital surveillance of admission and discharge data from all area hospitals, including screening of International Classification of Diseases-9 codes.

2.5. Definition of outcomes

The outcomes were [1] a combined incident vascular event (incident stroke, MI, or vascular death) as well as [2] incident stroke [3], incident MI, and [4] vascular death. Vascular death included death due to stroke, MI, heart failure, pulmonary embolus, cardiac arrhythmia, or other vascular cause. These are ICD-9 codes 390-459. Follow-up procedures and outcome classifications were detailed previously [22,23]. Briefly, all hospitalization medical records were reviewed to confirm the details of suspected events. Outcome events were reviewed by a specially trained research assistant and, when available, medical records were reviewed for all outcome events. Two neurologists independently classified the strokes after review of the data, and one of the principal investigators (RLS, MSVE) adjudicated disagreements.

2.6. Statistical analysis

Cox proportional hazards models were used to examine the association between adiponectin and vascular events, and hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Person-time of follow-up was accrued from baseline to the end of follow-up (March, 2012), outcome event, death or loss to follow-up, whichever came first. Adiponectin was examined continuously and in quartiles, with the fourth quartile as the referent. The following sequence of models was constructed [1]: Univariate [2]; Adjusted for demographics (age, sex, race/ethnicity) [3]; Adjusted for demographics, smoking, hypertension, diabetes, LDL cholesterol, HDL cholesterol, triglycerides, waist circumference, moderate alcohol use, moderate-heavy physical activity, and previous cardiac disease history. We examined possible interactions between adiponectin and age, sex, race/ethnicity, waist circumference, diabetes, hypertension, lipid levels, previous cardiac disease history, plaque,