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The relationship between carotid intima-media thickness and carotid plaque in the Northern Manhattan Study

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ABSTRACT

Objective: Carotid intima-media thickness (cIMT) and carotid plaque (CP) are proposed biomarkers of subclinical atherosclerosis associated with stroke risk. Whether cIMT and CP are distinct phenotypes or single traits at different stages of atherosclerotic development is unclear. We explored the relationship between these markers in the population-based Northern Manhattan Study.

Methods: We used high-resolution ultrasound and validated imaging protocols to study the cross-sectional (N = 1788 stroke-free participants) and prospective relationship (N = 768 with follow-up scan; mean years between examinations = 3.5) between CP and cIMT measured in plaque-free areas.

Results: The mean age was 66 ± 9 (40% male, 19% black, 17% white, 61% Hispanic). The mean baseline cIMT was 0.92 ± 0.09 mm, 0.94 ± 0.09 mm among the 58% with prevalent plaque, 0.90 ± 0.08 mm among the 42% without prevalent plaque ($p < 0.0001$). Each 0.1 mm increase in baseline cIMT was associated with a 1.72-fold increased odds of plaque presence (95%CI = 1.50–1.97), increased plaque thickness (effect on the median = 0.46 mm, $p < 0.0001$), and increased plaque area (effect on the median = 3.45 mm^2, $p < 0.0001$), adjusting for demographics and vascular risk factors. Elevated baseline cIMT was associated with an increased risk of new plaque in any location at follow-up, but after adjusting for demographics and vascular risk factors this association was no longer present. No association was observed in carotid segment-specific analyses.

Conclusion: Increased cIMT was associated with baseline prevalent plaque but did not predict incident plaque independent of other vascular risk factors. This finding suggests that increased cIMT is not an independent predictor of plaque development although these atherosclerotic phenotypes often coexist and share some common vascular determinants.

1. Introduction

Carotid atherosclerosis plays a large role in the etiology of stroke and cardiovascular disease (CVD). B-mode carotid ultrasound has been widely used to detect subclinical carotid atherosclerosis by quantifying carotid intima-media thickness (cIMT) and carotid plaque (CP). Both cIMT and CP have been proposed surrogate

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imaging biomarkers of subclinical atherosclerosis [1,2] until recently, when it became increasingly clear that cIMT and CP may be genetically and biologically distinct atherosclerotic phenotypes with evidence of heterogeneous etiology [3,4]. In addition, carotid atherosclerotic plaque burden, defined as the two-dimensional total plaque area (TPA) or three-dimensional total plaque volume, may be a powerful non-invasive imaging tool for vascular risk estimation, and stronger predictor for future ischemic stroke (IS) than cIMT [5–8].

cIMT and CP have been associated with prevalent and incident atherosclerotic disease with variable effects [9–11]. Whether cIMT and CP are distinct phenotypes or represent a single trait at a different stage of atherosclerotic development is unclear. Recent studies have suggested that increased cIMT more likely represents adaptive changes to increased shear stress with aging and less likely atherosclerotic changes [12]. The biological mechanism by which increased arterial wall thickening initiates focal plaque formation is poorly understood. Therefore, a greater understanding of adaptive changes in the arterial wall with aging and of how these changes relate to the development of atherosclerosis in various populations is needed.

In the current study, we sought to examine the cross-sectional and prospective relationships between cIMT and carotid plaque phenotypes in a multi-ethnic population of northern Manhattan. We hypothesized that increased cIMT was not related to presence of carotid plaque and to development of new carotid plaque over time.

2. Material and methods

2.1. Study participants

Subjects were participants in the Northern Manhattan Study (NOMAS), an ongoing, prospective, population-based study of stroke incidence and vascular risk factors, and were concurrently enrolled in the Oral Infections and Vascular Disease Epidemiology Study (INVEST). The details of the NOMAS and INVEST designs, methods and populations have been described previously [13,14].

Eligible subjects were those who 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. Subjects were recruited from the telephone sample (telephone response rate was 91%) 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%. Of the 3298 subjects, ultrasound measurements of cIMT and CP were performed for 1,788, and of those, 768 had multiple ultrasound measurements over time as a part of INVEST [14]. NOMAS and INVEST are approved by the Institutional Review Boards of the Columbia University Medical Center and the University of Miami. All subjects signed written consent for participation.

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 [15]. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control regarding hypertension, diabetes, smoking, and cardiac conditions [16]. Blood pressure (BP) was measured with mercury sphygmomanometers and appropriately-sized cuffs. Hypertension was defined as a BP ≥140/90 mmHg (based on the average of two measurements during one sitting), the patient's self-reported hypertension, or use of antihypertensive medications. Diabetes mellitus was defined by the patient's self-reported diabetes, use of insulin or oral anti-diabetic medications, or fasting glucose ≥126 mg/dl. The fasting lipid profile was measured at enrollment. Body mass index (BMI) was calculated in kg/m^2.

2.3. Carotid ultrasound

High-resolution B-mode ultrasound imaging (GE LogIQ 700, 9- to 13-MHz linear-array transducer) was performed by trained and certified sonographers as previously described [17–19]. Presence of plaque was defined as a focal wall thickening or protrusion in the lumen more than 50% greater than the surrounding thickness. Carotid plaque area (mm^2) and maximum thickness (mm) were measured with the automated computerized edge tracking software program M'Ath (M'Ath Inc, Paris, France) [20]. TPA was defined as the sum of all plaque areas measured in any of the carotid artery segments within an individual. cIMT was measured in areas without plaque. cIMT was calculated as a composite measure of the near and the far walls of the common carotid artery (CCA) IMT, bifurcation (bif) IMT, and internal carotid artery (ICA) IMT of both sides of the neck, and examined continuously as a mean of the maximum measurements of the 12 carotid sites. We also examined cIMT in the Bifurcation and ICA exclusively and cIMT in the CCA exclusively. Likewise, we examined plaque phenotypes in the Bifurcation and ICA exclusively. Fig. 1 is a representation of cIMT and carotid plaque using high-resolution B-mode ultrasound.

2.4. Statistical analysis

The cross-sectional association between cIMT and plaque presence was examined with logistic regression models, where cIMT was the independent variable and plaque presence was the dependent variable. Due to the non-normal distribution of plaque thickness and area with a large percentage of the study population having no plaque, we used quantile regression to examine plaque thickness and area as continuous outcomes. For individuals without plaque, a value of 0 was assigned for plaque thickness and area. We chose the median (50th percentile) and 75th percentile as our outcome variables of interest. A three model sequence was constructed: univariate (model 1); adjusted for demographics (age, sex, race-ethnicity; model 2); and adjusted for demographics and systolic blood pressure, diastolic blood pressure, antihypertensive medication use, diabetes, low-density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, statin use, and BMI (model 3). A subset of the study population had data on left ventricular mass measured using transthoracic echocardiography, and a subset had data on diastolic intraluminal CCA diameter measured using M mode ultrasound with M'Ath software. Sensitivity analyses were conducted within these subsamples adding these two variables separately to model 3.

Next, we performed segment specific analyses as secondary exploratory analyses. We examined cIMT in the Bifurcation and ICA only in relation to plaque presence, thickness, and area in these segments only. For the latter analysis the left and right sides were examined separately. We examined cIMT in the CCA only in relation to plaque presence in any location.

Next, we used logistic regression to conduct a prospective analysis of baseline cIMT as a predictor of incident plaque from