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Coronary artery calcium is associated with degree of stenosis and surface irregularity of carotid artery

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ABSTRACT

Objectives: Carotid stenosis and plaque stability are critical determinants of risk for ischemic stroke. The aim of this study is to elucidate the association of CAC with carotid stenosis and plaque characteristics.
Methods: We examined data from the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective cohort study of subclinical cardiovascular disease in multiethnic participants ($N = 6814$). The association between CAC measured by computed tomography and carotid ultrasonography of carotid plaque was examined using multiple logistic linear models adjusting for traditional vascular risk factors including ethnicity. We also developed ethnic specific models to compare the relationship between CAC and carotid disease across the four ethnicities.
Results: Significant carotid stenosis was associated with the presence of CAC (OR 1.73; 95% CI, 1.20–2.49) and log-transformed Agatston score (OR per 1 point increase, 1.18; 95% CI 1.04–1.35). Overt carotid stenosis was also associated with the presence of CAC (OR, 2.34; 95% CI, 1.93–2.83) and log-transformed Agatston score (OR per 1 point increase, 1.53; 95% CI 1.38–1.69). Irregular plaque surface was associated with the presence of CAC (OR, 1.87; 95% CI 1.50–2.32) and the log-transformed Agatston score (OR per 1 point 1 increase, 1.31; 95% CI 1.16–1.48). Associations between CAC and stenosis/stability were not different across ethnicities.
Conclusions: Both the presence of CAC and log-transferred Agatston score are independently associated with significant/overt carotid stenosis and carotid plaque surface irregularity regardless of ethnicity. The subjects with a positive or increased CAC score are more likely to have carotid disease potentially increasing their risk for future ischemic stroke.

1. Introduction

Numerous studies document that measure of coronary calcium offers incremental information beyond traditional risk factors for prediction of coronary heart disease events. For instance, the presence of coronary artery calcium (CAC) score is a predictor of incident cardiovascular disease (CVD) events [1–4], and the addition of CAC score to a prediction model based on traditional risk factors significantly improves net reclassification of risk for coronary heart disease events [3].

In contrast, the relationship between CAC and cerebrovascular disease is less well established. Although CAC has been shown to be related to carotid intima-media thickness (IMT) [5], the relationship between CAC and other anatomic features of carotid disease more strongly associated with atherosclerotic cerebrovascular events, including degree of stenosis and surface irregularities has not been evaluated. Similarly, there are only limited data concerning the prospective relationship between CAC and actual clinical cerebrovascular events [6]. Given the increasingly large number of subjects undergoing coronary artery CT scanning for risk stratification, it would be helpful to know if these data can be used

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to provide more information about risk for anatomic or clinical cerebrovascular disease as well. The considerable ethnic variation in the prevalence of CAC [7] and risks for carotid occlusive lesion [8] suggest that it may be useful to also explore whether any apparent associations between CAC and carotid disease vary by ethnicity.

In the present study, we used the baseline CAC scanning data and carotid ultrasound (US) from the Multi-Ethnic Study of Atherosclerosis (MESA) to: (1) elucidate whether CAC is associated with overt carotid stenosis and carotid plaque characteristics in a prospective cohort free of clinical cardiovascular disease at baseline; and (2) examine ethnic differences among these associations.

2. Methods

2.1. Study participants and risk factor assessments

MESA is a population-based cohort study of men and women from 4 race/ethnic groups (Whites, Blacks, Hispanics, and Chinese). It recruited 6814 participants 45–84 years of age who were free of clinically apparent CVD from the 6 communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St Paul, Minnesota), and initially examined 38% Whites, 28% Blacks, 22% Hispanics, and 12% Chinese participants from July 2000 to September 2002. The research protocols were approved by the participating Institutional Review Boards, and detailed descriptions of the study design and methods have been published previously [9].

Demographic characteristics and information on cardiovascular risk factors were captured by a centrally trained team during an in-person interview using a structured questionnaire. Cigarette smoking status was categorized as never, former, or current smoker. During a standardized clinical examination, height, weight, waist and hip circumferences and resting blood pressure were measured; blood pressure was taken three times in a seated position with the Dinamap model Pro 1000 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida), and the average of the last two measurements were used in analysis. Hypertension was defined according to the sixth report of the Joint National Committee (1997) criteria. Blood samples were collected after a 12 h fast; lipids, lipoprotein and glucose were analyzed by a central laboratory. Diabetes was defined by the 2003 American Diabetes Association fasting criteria algorithm. Hyperlipidemia was defined as use of lipid-lowering drug or low-density lipoprotein cholesterol >160 mg/dL.

2.2. Evaluation of CAC and carotid USG

CAC was measured by certified technologist using cardiac-gated electron-beam computed tomography (EBT; Imatron C-150; Imatron, San Francisco, California) or multidetector computed tomography (MDCT; Lightspeed, General Electric Medical System, Waukesha, Wisconsin; or Volume Zoom, Siemens, Erlanger, Germany), prospectively triggered at 50% of the R–R interval acquiring a block of four axial 2.5 mm slices per cardiac cycle. The radiation exposure time was 100 ms/tomographic slice (total 30–40 contiguous slice), and total irradiation dose was 0.6 mSv/scan. All scans incorporated a calcium phantom. The phantom contained 4 bars of known physical calcium concentration, and provided a way of calibrating the degree of brightness between sites and participants allowing high rescan reproducibility with both EBT and MDCT scanners [10]. Participants were scanned twice consecutively, and these scans were read independently at a central center (Los Angelis Biomedical Research Institute at Harbor-UCLA Medical Center in Torrance, California). The results were averaged and quantified with the Agatston scoring method [11] which is a pseudo-continuous variable derived from plaque densities. Calcium scores were adjusted with the mean value of the calcium phantom from each field of view [12]. Kappa statistics for Inter- and intra-observer agreement were found to be very high ($k = 0.93$ and 0.90, respectively) (Tables 1 and 2).

Carotid US images were captured in the right and left common carotid and internal carotid arteries using the Logiq 700 ultrasound machine (General Electric Medical Systems) at all centers. Interpretations of the degree of stenosis and the surface characteristics were performed centrally at the Department of Radiology, Tufts Medical Center (more than 5 years of reader's experience). The extent of atherosclerosis was determined from the Doppler spectra and the peak-systolic velocities (PSV) measured in the internal carotid artery. PSV of 150–250 cm/s were considered to represent 50–74% stenosis, whereas PSV greater than 250 cm/s correspond to 75–99% stenosis. If PSV were less than 150 cm/s, the reader evaluated the lesion on the gray-scale image, categorizing the percentage of stenosis into one of three remaining categories: 0%, 1–24% and 25–49% stenosis. The appearance of the largest focal lesion, if present, was classified by surface characteristics, echogenicity, and texture. The maximum surface characteristics were categorized as: no lesion, smooth, mildly irregular (height variations ≤0.4 mm along the contour of the lesion), or markedly irregular (height variations 0.4 mm) or ulcerated (a discrete depression of more than 2 mm in width extended into the media) [13].

2.3. Statistical analysis

CAC scores were available in all 6814 MESA participants, but 99 (1.45%) subjects were excluded from these analyses due to missing in carotid US data (either stenosis degree or surface characteristics) at baseline. Data are presented as mean ± standard deviation (SD) for continuous variables and percentage for dichotomous variables. The degree of stenosis and surface characteristics are determined according to the area of maximal abnormality. Vessels with more

Table 1
Distribution of the degrees of stenosis and surface characteristics of the internal carotid artery by patterns of CAC.

Maximum stenosis	No stenosis ($N = 3927$)	1–24% ($N = 1914$)	25–49% ($N = 821$)	50–100% ($N = 51$)	P-value
CAC = 0 ($N = 3366$)	72.8%	21.6%	5.4%	0.2%	<0.001
CAC = Non-zero ($N = 3349$)	44.1%	35.4%	19.2%	1.3%	
ln[a](CAC + 1)	1.47 ± 2.1[b]	2.81 ± 2.6	4.02 ± 2.6	4.22 ± 2.5	<0.001

Maximum surface	No lesion ($N = 3922$)	Smooth ($N = 2217$)	Mildly irregular ($N = 501$)	Markedly irregular or ulcerated ($N = 75$)	P-value
CAC = 0 ($N = 3366$)	72.8%	22.3%	4.5%	0.3%	<0.001
CAC = Non-zero ($N = 3349$)	43.9%	43.7%	10.4%	1.9%	
ln(CAC + 1)	1.47 ± 2.1	3.11 ± 2.6	3.42 ± 2.7	4.51 ± 26	<0.001

[a] In: Natural logarithm transformation.
[b] Mean ± SD.