Relation Between Calcified Atherosclerosis in the Renal Arteries and Kidney Function (from the Multi-Ethnic Study of Atherosclerosis)

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Renal artery calcium (RAC) has been shown to be associated with higher odds of hypertension (HTN). The purpose of this study was to determine if the presence and extent of RAC is associated with renal function. We analyzed cross-sectional data from the Multi-Ethnic Study of Atherosclerosis (MESA). A subsample of 1,226 participants underwent computed tomography of the abdomen and also had venous blood samples measured for kidney function. RAC was the primary predictor variable and the following measures of kidney function were the outcome variables: estimated glomerular filtration rate (eGFR), urinary albumin-to-creatinine ratio (UACR), and chronic kidney disease (CKD) stage. The analyses were adjusted for age, gender, race, height, visceral fat, dyslipidemia, diabetes, cigarette smoking, hypertension, interleukin-6 and abdominal aortic calcium (AAC). The average age of this cohort was 66.1 years (SD 9.7), 44.8% (549 of 1,226) were men, and nearly 30% had RAC >0. Compared with those with no RAC, those with RAC >0 were significantly older but not different by gender or race. After adjustment for age, gender, and race, those with RAC >0 had significantly higher visceral fat, were more likely to have dyslipidemia, diabetes, and hypertension, had a higher interleukin-6, and a higher prevalence of AAC >0. The mean eGFR and UACR among those without RAC were 80 ml/min/1.73 m^2 and 21 mg/g, whereas these values were 78 ml/min/1.73 m^2 and 55 mg/g among those with RAC. In fully adjusted multivariable linear regression models, the presence of RAC was associated with a lower eGFR ($\beta = -2.21$, $p = 0.06$) but not with UACR ($\beta = 0.02$, $p = 0.79$). In fully adjusted ordinal logistic regression, RAC as a continuous variable was associated with increased odds of being in a worse CKD category (odds ratio 1.14, $p = 0.05$). When measured by eGFR and CKD stage, there is a modest relation between RAC and kidney function. Further studies might involve clinical trials to assess the role of intensive cardiovascular disease risk factor management in patients with subclinical RAC to determine if this may prevent or delay the development and progression of CKD. **(Am J Cardiol 2017;120:1434–1439)**

Renal mechanisms play a primary role in blood pressure regulation,[1,2] with microvascular disease being central to this hypothesis. Indeed, some have proposed that renal microvascular disease is the unifying pathophysiologic mechanism in the development of hypertension.[1,3] In this regard, there have been several studies showing an association between renal artery calcium (RAC), as measured by computed tomography (CT), and hypertension.[4–7] RAC has also been shown to be associated with cardiovascular and all-cause mortality.[8–10] However, little is known about the relation between subclinical atherosclerosis in the renal arteries and kidney function. Although risk factors such as diabetes and hypertension clearly impact renal filtration capacity, it is unclear if RAC impacts this function independently or in concert with these other factors. Importantly, there are hypothesized mechanisms by which RAC may impact kidney filtration. RAC and subclinical luminal stenosis in the renal artery may decrease microvascular renal blood flow and lead to a decrement in glomerular filtration rate (GFR).[5] Another possible mechanism is that increased plaque burden leads to renal artery stiffness, and the transmission of elevated pulse pressures leads to downstream glomerular damage.[11,12] Finally, activation of the renin-aldosterone-angiotensin system (RAAS), which is known to be associated with atherosclerosis,[13] may result in decreased kidney filtration.[14] Studies to date of the relation

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between RAC and kidney function have been limited by ethnically homogenous, primarily diabetic cohorts.[5,11,15] As such, there is a need to further examine the relation between RAC and multiple measures of renal function within an ethnically diverse, community-based population that includes diabetic patients.

Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal cohort study of African, Chinese, and Hispanic Americans, as well as non-Hispanic Whites. Details on this study design are available elsewhere.[16] In brief, between July 2000 and August 2002 (visit 1), MESA enrolled 6,814 men and women between the ages of 45 to 84 who were free of clinically apparent cardiovascular disease and came from 6 communities throughout the United States. Exclusion criteria included current dialysis, a history of physician-diagnosed heart attack, angina, heart failure, stroke or transient ischemic attack, or having undergone an invasive procedure for cardiovascular disease (coronary artery bypass graft, angioplasty, valve replacement, or pacemaker placement). Enrolled participants returned for follow-up clinic examinations on 4 subsequent examinations (visits 2, 3, 4, and 5) at approximately 18- to 24-month intervals. All participants provided written informed consent, and the institutional review boards at the participating universities approved the study.

At clinic visits 2 and 3, a random subsample of 1,970 participants from 5 of the 6 MESA field centers enrolled in an ancillary study to determine the presence and extent of calcified atherosclerosis in the abdominal aorta using CT scans.[17] Only a subset of these patients (n = 1,226) had imaging that showed the entire renal arteries. This subset comprises the analytic sample for our current study. Venous blood samples taken contemporaneously to the CT scans at visit 2 or 3 were subsequently analyzed for selected measures of kidney function, as outlined below.

At all clinic visits, standardized questionnaires were used to obtain information on patient demographics and health history. Cigarette smoking was defined as current, former, or never. Height and weight were measured with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist and hip circumferences were measured using a standard flexible tape measure. Blood pressure at rest was measured 3 times in seated participants with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida). The average of the second and third readings was used to calculate blood pressure. Hypertension (HTN) was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the current use of an antihypertensive medication. At all clinic examinations, blood samples obtained in the sitting position were obtained after a 12-hour fast. Blood was drawn after the participants had been resting in the sitting position for about 1 hour. The blood samples were assayed for total and high-density lipoprotein cholesterol, triglycerides, glucose, and creatinine levels, as well as measures of systemic inflammation (C-reactive protein, fibrinogen, interleukin-6 [IL-6]) and insulin concentration.[18] Serum creatinine was assayed by isotope dilution mass spectrometry.

Dyslipidemia was defined as total cholesterol-to-high-density lipoprotein ratio >5 or use of a lipid-lowering medication. Diabetes was defined as fasting glucose ≥126 mg/dl or current insulin or oral hypoglycemic medication usage. Estimated glomerular filtration rate (eGFR) was computed using the chronic kidney disease (CKD)-Epi equation that is based on creatinine and demographic information.[19,20] Urine was collected for albumin and creatinine, which were used to calculate the urinary albumin to creatinine ratio (UACR). Microalbuminuria was defined as urine albumin >3 mg/dl and albuminuria was defined as UACR >250 mg/g in men and >350 mg/g in women.

Stored fasting blood samples obtained at clinic visits 2 and 3 were analyzed to provide serum concentrations of renin (plasma renin acitivity [PRA]), aldosterone, and cystatin-C. All assays were performed at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, Vermont). PRA was measured using the GammaCoat Plasma Renin Activity 125I radioimmunoassay Kit (DiaSorin, Stillwater, Minnesota), whereas aldosterone was measured using a competition-based radioimmunoassay (ALDOCTK-2, Diasorin). The intra-assay coefficients of variation for PRA ranged from 6.9% to 18.4% and 6.3% to 8.9% for aldosterone, respectively. Cystatin-C was measured using the BNII nephelometer (Dade Behring Inc., Deerfield, Illinois) utilizing a particle-enhanced immunonepholometric assay (N Latex Cystatin C). Intra- and inter-assay coefficients of variation were <5%.

The presence and extent of calcification in the abdominal aorta and the left and right renal arteries were measured from abdominal CT scans conducted using electron-beam CT scanners (Imatron C-150, Imatron, Inc, San Francisco, California) or prospective electrocardiogram-triggered scanners (Siemens S4þ Volume Zoom, Siemens, Erlanger, Germany; and General Electric Hi Speed LX, GE Medical Systems, Milwaukee, Wisconsin). The distal 15 cm of the abdominal aorta terminating at the aortic bifurcation was scanned.

CT images were centrally reviewed by trained study technologists at the MESA CT Reading Center (Los Angeles, California). Calcified foci were defined as those regions with a density of >130 Hounsfield units and an area of ≥3 contiguous pixels (1.0 mm^2). Total RAC scores were calculated by summing left and right renal ostia Agatston scores and left and right renal artery Agatston scores. All calcium scores were quantified using Agatston methodology.[21] The CT scans of the abdomen were also used to measure visceral and subcutaneous fat mass by semiautomated segmentation of the body compartments using the Medical Image Processing, Analysis, and Visualization software program from the National Institutes of Health.

We computed descriptive statistics for all variables, as mean and standard deviation (SD) or median and interquartile range for continuous measures and frequency and percentage for categorical measures, respectively. We described differences in the distributions of baseline characteristics between those with and without RAC using chi-square tests for categorical variables or parametric *t* tests or nonparametric Wilcoxon rank-sum tests for continuous variables. We adjusted mean risk factor values by RAC group for age, gender, and race using analysis of covariance.

We examined RAC both as a dichotomous variable (RAC >0 vs RAC = 0) and, among those with RAC >0, as a