### Title

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

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## Abstract

Renal artery calcium (RAC) has been shown to be associated with a 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 1226 participants underwent computed tomography (CT) 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: eGFR, urinary albumin-to-creatinine ratio (UACR) and CKD stage. The analyses were adjusted for age, gender, race, height, visceral fat, dyslipidemia, diabetes, cigarette smoking, hypertension, interleukin-6 (IL-6) and abdominal aortic calcium (AAC). The average age of this cohort was 66.1 years (SD 9.7), 44.8% (549 of 1226) were male, and nearly 30% had RAC > 0. Compared to those with no RAC, those with RAC > 0 were significantly older but not different by gender or race. After adjustment for age, sex and race, those with RAC > 0 had significantly higher visceral fat, were more likely to have dyslipidemia, diabetes and hypertension, had a higher IL-6, and a higher prevalence of AAC > 0. The mean eGFR and UACR among those without RAC were 80 mL/min/1.73m$^2$ and 21 mg/g, while these values were 78 mL/min/1.73m$^2$ 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

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with increased odds of being in a worse CKD category (OR = 1.14, p = 0.05). When measured by eGFR and CKD stage, there is a modest relationship 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.

**Index Words**

Renal artery calcium (RAC); Kidney function; estimated glomerular filtration rate (eGFR); urinary albumin-to-creatinine ratio (UACR)

## Introduction

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 relationship between subclinical atherosclerosis in the renal arteries and kidney function. While 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 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 relationship 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 relationship 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 6814 men and women between the ages of 45–84 who were free of clinically apparent cardiovascular disease and came from six 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 four subsequent examinations (visits 2, 3, 4 and 5) at approximately 18–24-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 1970 participants from five of the six 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 = 1226) 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. Resting blood pressure was measured three times in seated participants with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL, USA). The average of the second and third readings was used to calculate blood pressure. Hypertension (HTN) was defined as systolic blood pressure ≥ 140mm Hg, diastolic blood pressure ≥ 90mmHg 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, IL-6) and insulin concentration.[18] Serum creatinine was assayed by isotope dilution mass spectrometry (IDMS).

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 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 males and > 350 mg/g in females.

Stored fasting blood samples obtained at clinic visits 2 and 3 were analyzed to provide serum concentrations of renin (PRA), aldosterone and cystatin-C. All assays were performed at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT, USA). PRA was measured using the GammaCoat Plasma Renin Activity 125I radioimmunoassay Kit (DiaSorin; Stillwater, MN, USA), while 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, IL) 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, CA, USA) or prospective electrocardiogram-triggered scanners (Siemens S4þ Volume Zoom; Siemens, Erlanger, Germany; and General Electric Hi Speed LX, GE Medical Systems, Milwaukee, WI, USA). The distal 15cm 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, CA, USA). 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 semi-automated segmentation of the body compartments using the Medical Image Processing, Analysis, and Visualization (MIPAV) 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 (ANCOVA).

We examined RAC both as a dichotomous variable (RAC > 0 versus RAC = 0) and, among those with RAC > 0, as a continuous variable. We computed regression models to assess the relationship between RAC and three primary outcome variables: eGFR, log transformed UACR, and CKD stage. CKD stage was divided into the following eGFR groups (in $mL/min/1.73m^2$): > 90, 60–89, 30–59 and < 30. In supplementary analyses, we also evaluated the following outcomes: serum creatinine, cystatin-C, urine albumin, eGFR (> 60 versus < 60) and micro/macroalbuminuria. We evaluated a sequence of models. Our initial model (model 1) included RAC and adjusted for age, gender and race/ethnicity; model 2 adjusted for model 1 plus height and visceral fat; model 3 adjusted for model 2 plus traditional CVD risk factors (dyslipidemia, diabetes, smoking and hypertension); model 4 adjusted for model 3 plus interleukin 6 (IL-6) and abdominal aortic calcium (AAC); model 5 adjusted for model 4 plus aldosterone and renin.

The analysis was conducted using Stata version 13 (College Station, TX, USA). P-values < 0.05 were considered statistically significant for all analyses, including interaction terms. We explored interactions between RAC and diabetes for eGFR and UACR (separately). Neither of these was significant (p = 0.16 and p = 0.12, respectively). We also assessed interactions

between race/ethnicity and RAC in predicting various measures of kidney function and found these to be non-significant.

## Results

Overall, the mean (SD) age was 66.1 years (9.7) and 44.8% were male (Table 1). The racial distribution was 36.3% Caucasian, 14.1% Chinese-American, 21.6% African-American and 28.0% Hispanic-American. The average BMI was 28 (5.3) kg/m$^2$, while the prevalence of diabetes was 15.1% and the prevalence of hypertension was 50.5%. Approximately 30% of participants had RAC > 0 and 73.1% of participants had AAC > 0. The mean (SD) creatinine, cystatin-C and eGFR were 0.9 mg/dL (0.3), 0.9 mg/dL (0.2) and 78.1 mL/min/1.73m$^2$ (17.6). The median (IQR) UACR was 5.9 mg/g (3.6 to 11.9).

Among those without RAC, the mean eGFR and UACR were 80 mL/min/1.73m$^2$ and 21 mg/g, while among those with RAC these values were 78 mL/min/1.73m$^2$ and 55 mg/g (Figure 1). Compared with those with no RAC, those with RAC > 0 were significantly older but not significantly different by gender or race (Table 2). After adjustment for these demographic variables, those with RAC > 0 had significantly higher visceral fat, were more likely to have dyslipidemia, diabetes and hypertension, had a higher IL-6, and a higher prevalence of CAC and AAC > 0. Compared with those with eGFR≥60, participants with eGFR < 60 were significantly older. After adjustment for age, sex and race, those with eGFR < 60 had a significantly higher BMI and visceral fat, were more likely to have dyslipidemia, and higher aldosterone and renin levels. Compared to those without microalbuminuria, participants with microalbuminuria were significantly older and more likely to be male. After adjustment for age, sex and race, those with microalbuminuria had a significantly higher BMI and visceral fat, were more likely to have dyslipidemia, had higher IL-6 and aldosterone levels, and were more likely to have AAC > 0.

In fully adjusted linear regression models (Table 3), RAC > 0 was associated with a 2.21 mL/min/1.73m$^2$ lower eGFR ($p = 0.06$), but not with UACR ($\beta = 0.02$, $p = 0.79$). In fully adjusted ordinal regression models (Table 4), RAC > 0 was not significantly associated with being in a higher CKD stage (OR = 1.33, $p = 0.11$). When analyzed as a continuous variable (Table 3), a 1-SD increment of RAC (152 Agatston units) was also associated with a 0.10 mg/g higher UACR ($p < 0.01$) but after adjustment for height, visceral fat, dyslipidemia, diabetes, smoking and hypertension, this association was no longer significant ($\beta = 0.03$, $p = 0.38$). Using ordinal logistic regression (Table 4), when measured as a continuous variable, a 1-SD increase in RAC was associated with a 14% higher odds of being in a worse CKD category ($p = 0.05$).

We conducted additional sensitivity analyses with the following outcomes: serum creatinine, cystatin-C, urine albumin, eGFR (> 60 versus < 60) and micro/macroalbuminuria (Supplementary Tables 1–2). In fully adjusted models (Table S1), RAC > 0 was associated with a higher serum creatinine (0.05 mg/dL, $p = 0.01$) and cystatin-C (0.05 mg/L, $p < 0.01$). Using logistic regression, and after adjustment for age, gender and race, RAC > 0 was borderline significantly associated with the presence of microalbuminuria, defined as urine albumin > 3 mg/dL (OR = 1.4, $p = 0.08$; Table S2). However, this association became non-

significant after adjustment for height and visceral fat (OR = 1.3, p = 0.16), and remained non-significant after adjustment for cardiovascular risk factors including dyslipidemia, diabetes, smoking and hypertension (OR = 0.82, p = 0.44). The results for the association between RAC as a continuous variable and albuminuria (UACR > 250 mg/g in males and > 350 mg/g in females) were similar to the findings for RAC > 0 and microalbuminuria (Table S2).

## Discussion

In a multiethnic cohort of adult men and women from five US locations, our results suggest there is modest relationship between RAC prevalence and lower eGFR. This association was independent of demographics and CKD risk factors. In contrast to prior studies, we did not find that RAC was independently associated with microalbuminuria.[11]

One important question is whether RAC is simply a reflection of systemic vascular disease or whether it exhibits local effects on renal function. In our study, after adjusting for age, sex and race, individuals with RAC > 0 were more likely to have traditional cardiovascular risk factors, including dyslipidemia, diabetes and hypertension. They also had a higher prevalence of systemic atherosclerosis as represented by the presence of calcified atherosclerosis in the abdominal aorta. However, even after adjusting for these risk factors, the relationships between RAC and kidney function, as measured by eGFR, creatinine and cystatin-C, were statistically significant. Moreover, despite sequential adjustment for a broad array of demographic and CKD risk factors, the association of RAC with eGFR was essentially unaltered across the sequence of models. This suggests that RAC, beyond its association with systemic atherosclerosis and cardiovascular disease risk factors, is associated with a modest decrement in kidney function.

Given that renovascular calcium is a marker of atherosclerotic plaque burden and is associated with RAAS up-regulation, some have proposed that RAC indicates a state of RAAS activation.[11] RAAS activation promotes systemic and glomerular capillary hypertension, thereby inducing hemodynamic injury in the glomerular endothelium.[14] Moreover, RAAS activation is associated with inflammation, which has been implicated in the progression of renal diseases.[13] Our results suggest that this is not the case, as the magnitude of the association between RAC as a binary variable and both eGFR and creatinine was not materially changed with adjustment for renin and aldosterone (see Table 3, model 5 and Table S1, model 5). However, it is important to note that serum renin and aldosterone levels are known to be variable during the course of the day and over time. Given that these were measured only at point in our study, it is possible that we were unable to properly capture the mediation by RAAS activation.[22]

There are other possible physiologic mechanisms for our findings. First, glomerular or tubular damage may result from increased stiffness of the renal arteries and the transmission of an elevated pulse pressure, leading to downstream glomerular damage.[12] However, this is unlikely as we found that RAC was not associated with UACR. A second possible explanation is that subclinical luminal stenosis in the renal artery decreases microvascular renal blood flow, leading to a decrement in GFR.[5] However, our results show no association

between RAC and renin and aldosterone, suggesting that the degree of renal ischemia may be low. It is possible that a combination of mechanisms, including both RAAS activation that we were unable to fully capture with our study design and mildly decreased microvascular blood flow, explain our finding of a modest relationship between RAC and decreased kidney function.

Our study adds new information in the area of RAC and kidney function in several important ways. First, our results corroborate other studies that have shown an association between RAC and cardiac risk factors including older age, CAC and AAC.[5,15] In this regard, our study validates these results in a diverse population that includes African Americans, Hispanics and Chinese Americans, in addition to non-Hispanic Whites. Second, unlike other studies that have focused on the relationship between RAC and kidney function in primarily diabetic populations, our study shows a relationship between RAC and renal function in a sample where only 15.1% of patients have diabetes.[5,15] For the first time, we evaluate effect modification by diabetes status, and show that the relationship between RAC and renal function does not differ between diabetic and non-diabetic populations. Therefore, our results are more generalizable to a multi-ethnic, low-diabetes prevalence population. Finally, unlike other studies which have focused only on GFR or only on microalbuminuria,[11,15] our study suggests a modest relationship between RAC and kidney function represented by several different kidney filtration measures.

Limitations of our study include its cross-sectional design, and it is possible that our single time point estimate of RAC is an imprecise estimate of the cumulative burden of RAC over time. Another potential limitation of our study is that a significant proportion of patients without visualization of the renal arteries on abdominal CT were excluded, possibly biasing our results. Additionally, MESA recruited persons aged 45–84 years without clinically apparent CVD, and results from our study may not generalize to different populations in other settings. A strength of our study is its multiethnic sample, making our findings relevant to ethnically diverse populations. Our findings suggest an opportunity for clinical trials assessing intensive risk factor management in patients with subclinical RAC, to determine if this may prevent or slow CKD progression.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References


1. Abe K, Abe M, Ito S. Pathogenesis of hypertension. Nihon Rinsho. 1997; 55:1889–1894. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9284398. [PubMed: 9284398]
2. Guyton AC. Blood pressure control--special role of the kidneys and body fluids. Science. 1991; 252:1813–1816. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2063193. [PubMed: 2063193]
3. Goldblatt H. The renal origin of hypertension. Physiol Rev. 1947; 27:120–165. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20282156. [PubMed: 20282156]
4. Allison MA, Lillie EO, DiTomasso D, Wright CM, Criqui MH. Renal artery calcium is independently associated with hypertension. J Am Coll Cardiol. 2007; 50:1578–1583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17936157. [PubMed: 17936157]
5. Freedman BI, Hsu FC, Langefeld CD, Bowden DW, Moossavi S, Dryman BN, Carr JJ. Renal artery calcified plaque associations with subclinical renal and cardiovascular disease. Kidney Int. 2004; 65:2262–2267. [PubMed: 15149339]
6. Thomas IC, Ratigan AR, Rifkin DE, Ix JH, Criqui MH, Budoff MJ, Allison MA. The association of renal artery calcification with hypertension in community-living individuals: the multiethnic study of atherosclerosis. J Am Soc Hypertens. 2016; 10:167–174. [PubMed: 26796664]
7. Tolkin L, Bursztyn M, Ben-Dov IZ, Simanovsky N, Hiller N. Incidental renal artery calcifications: A study of 350 consecutive abdominal computed tomography scans. Nephrol Dial Transplant. 2009; 24:2170–2175. [PubMed: 19225015]
8. Rifkin DE, Ix JH, Wassel CL, Criqui MH, Allison MA. Renal artery calcification and mortality among clinically asymptomatic adults. J Am Coll Cardiol. 2012; 60:1079–1085. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22939556. [PubMed: 22939556]
9. London GM, Guérin AP, Marchais SJ, Métivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant. 2003; 18:1731–1740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12937218. [PubMed: 12937218]
10. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000; 342:1478–1483. [PubMed: 10816185]
11. Roseman DA, Hwang S-J, Manders ES, O'Donnell CJ, Upadhyay A, Hoffmann U, Fox CS. Renal artery calcium, cardiovascular risk factors, and indexes of renal function. Am J Cardiol. 2014; 113:156–161. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3882167&tool=pmcentrez&rendertype=abstract. [PubMed: 24210678]
12. Safar ME, London GM, Plante GE. Arterial Stiffness and Kidney Function. Hypertension. 2004; 43:163–168. [PubMed: 14732732]
13. Ferrario CM, Strawn WB. Role of the renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. Am J Cardiol. 2006; 98:121–128. Available at: http://linkinghub.elsevier.com/retrieve/pii/S000291490600573X. [PubMed: 16784934]
14. Brewster UC, Perazella MA. The renin-angiotensin-aldosterone system and the kidney: effects on kidney disease. Am J Med. 2004; 116:263–272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14969655. [PubMed: 14969655]
15. Chiu Y-W, Adler S, Budoff M, Takasu J, Ashai J, Mehrotra R. Prevalence and prognostic significance of renal artery calcification in patients with diabetes and proteinuria. Clin J Am Soc Nephrol. 2010; 5:2093–2100. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3001764&tool=pmcentrez&rendertype=abstract. [PubMed: 20705966]
16. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol. 2002; 156:871–881. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12397006. [PubMed: 12397006]
17. Criqui MH, Kamineni A, Allison MA, Ix JH, Carr JJ, Cushman M, Detrano R, Post W, Wong ND. Risk factor differences for aortic versus coronary calcified atherosclerosis: The multiethnic study of atherosclerosis. Arterioscler Thromb Vasc Biol. 2010; 30:2289–2296. [PubMed: 20814018]

18. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18:499–502. [PubMed: 4337382]

19. Manuscript A, Predictions BR. NIH Public Access. NIH Public Access. 2011; 55:622–627.

20. Stevens LA, Schmid CH, Greene T, Zhang Y, Beck GJ, Froissart M, Hamm LL, Lewis JB, Mauer M, Navis GJ, Steffes MW, Eggers PW, Coresh J, Levey AS. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1. 73 m2. Am J Kidney Dis. 2010; 56:486–495. [PubMed: 20557989]

21. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990; 15:827–832. [PubMed: 2407762]

22. Hurwitz S, Cohen RJ, Williams GH. Diurnal variation of aldosterone and plasma renin activity: timing relation to melatonin and cortisol and consistency after prolonged bed rest. J Appl Physiol. 2004; 96:1406–1414. Available at: http://jap.physiology.org/cgi/content/abstract/96/4/1406. [PubMed: 14660513]

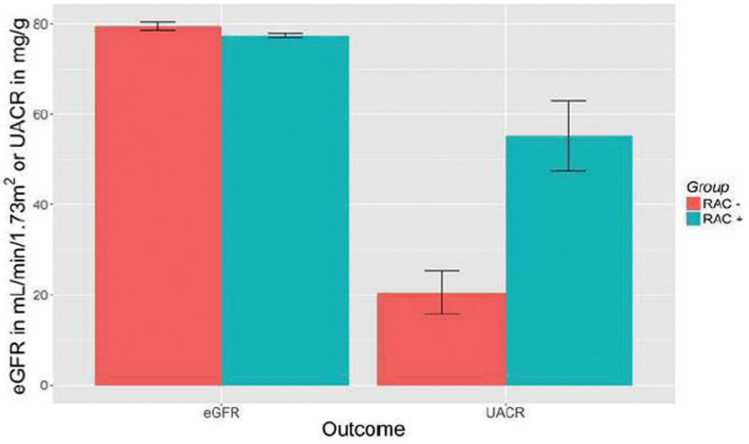


**Figure 1.**
Mean eGFR and UACR by RAC Status

## Table 1

Cohort Characteristics (n = 1226)

| Variable | Mean ± SD or Frequency (%) |
|---|---|
| Age (years) | 66.1 ± 9.7 |
| Men | 549 (44.8) |
| Non-Hispanic White | 445 (36.3) |
| Chinese American | 173 (14.1) |
| Black | 265 (21.6) |
| Hispanic | 343 (28.0) |
| Body Mass Index ($kg/m^2$) | 28 ± 5.3 |
| Visceral Fat ($cm^2$) | 146.8 ± 69.8 |
| Dyslipidemia | 461 (38.5) |
| Diabetes Mellitus | 184 (15.1) |
| Ever Smoke | 649 (53.1) |
| Hypertension | 611 (50.5) |
| Interleukin-6 (pg/mL) | 2.4 ± 1.8 |
| Aldosterone (pg/mL) | 149.0 ± 86.2 |
| Plasma Renin Activity (ng/mL) | 1.4 ± 3.6 |
| Coronary Artery Calcium > 0 | 694 (58.1) |
| Abdominal Aorta Calcium > 0 | 898 (73.5) |
| Renal Artery Calcium > 0 | 363 (29.6) |
| Creatinine (mg/dL) | 0.9 ± 0.3 |
| Cystatin-C (mg/dL) | 0.9 ± 0.2 |
| Calculated Creatinine (mg/dL) | 1.0 ± 0.3 |
| Estimated Glomerular Filtration Rate by CKD Epi ($mL/min/1.73m^2$) | 78.1 ± 17.6 |
| Urine Albumin (mg/dL) | 3.0 ± 13.0 |

**Table 2**

Cohort Characteristics by Renal Artery Calcium Status and Kidney Function (n = 1226)

| | RAC > 0 | | eGFR < 60 | | Microalbuminuria* | |
|---|---|---|---|---|---|---|
| **Variable** | **Yes (n=363)** | **p-value** | **Yes (n=174)** | **p-value** | **Yes (n=184)** | **p-value** |
| Age | 72.3 | 0.01 | 74.7 | 0.01 | 67.3 | 0.08 |
| Men | 57.6 | 0.28 | 40.2 | 0.18 | 61.3 | 0.01 |
| *Adjusted for Age, Sex and Race* | | | | | | |
| Body Mass Index (kg/m$^2$) | 28.0 | 0.14 | 28.8 | 0.01 | 29.0 | 0.01 |
| Visceral Fat (cm$^2$) | 150.5 | 0.03 | 150.8 | 0.02 | 165.2 | 0.01 |
| Dyslipidemia | 44.6 | 0.01 | 45.0 | 0.03 | 49.0 | 0.01 |
| Diabetes Mellitus | 20.7 | 0.01 | 19.1 | 0.14 | 34.0 | 0.01 |
| Ever Smoke | 55.8 | 0.06 | 46.1 | 0.22 | 54.1 | 0.16 |
| Hypertension | 63.9 | 0.01 | 50.1 | 0.06 | 68.7 | 0.01 |
| Interleukin-6 (pg/mL) | 2.7 | 0.01 | 2.4 | 0.51 | 2.8 | 0.01 |
| Aldosterone (pg/mL) | 153.2 | 0.13 | 167.0 | 0.01 | 177.0 | 0.01 |
| Plasma Renin Activity (ng/mL) | 1.6 | 0.15 | 2.2 | 0.01 | 1.8 | 0.08 |
| Coronary Artery Calcium > 0 | 75.7 | 0.01 | 57.1 | 0.59 | 61.8 | 0.10 |
| Abdominal Aortic Calcium > 0 | 83.5 | 0.01 | 71.8 | 0.69 | 76.2 | 0.03 |

Data are listed as mean for continuous variables and percentage for binary variables

*Microalbuminuria was defined as urine albumin > 3 mg/dL

## Table 3

The Association Between Prevalent Renal Artery Calcium as a Binary and as a Continuous Variable and Selected Measures of Renal Function

| **RAC +/− (n = 1226)** | | | | |
|---|---|---|---|---|
| | **eGFR (mg/mL/1.73m$^2$)** | | **Urine Albumin/Creatinine Ratio (mg/g)** | |
| **Model** | **β** | **p-value** | **β** | **p-value** |
| 1 | −2.05 | 0.05 | 0.24 | 0.002 |
| 2 | −2.05 | 0.05 | 0.19 | 0.016 |
| 3 | −1.62 | 0.13 | 0.71 | 0.365 |
| 4 | −2.04 | 0.07 | 0.02 | 0.792 |
| 5 | −2.21 | 0.06 | 0.02 | 0.788 |
| RAC Continuous (1-SD Increments of 152 Agatston units) (n = 363) | | | | |
| | eGFR (mg/mL/1.73m$^2$) | | Albumin/Creatinine Ratio | |
| Model | β | p-value | β | p-value |
| 1 | −0.77 | 0.08 | 0.10 | 0.01 |
| 2 | −0.65 | 0.14 | 0.08 | 0.02 |
| 3 | −0.57 | 0.19 | 0.05 | 0.13 |
| 4 | −0.81 | 0.10 | 0.04 | 0.29 |
| 5 | −0.81 | 0.10 | 0.03 | 0.38 |

Model 1: RAC, age, gender, race. Model 2: Model 1 + height, visceral fat. Model 3: Model 2 + dyslipidemia, diabetes, smoking, hypertension. Model 4: Model 3 + IL-6, AAC. Model 5: Model 4 + aldosterone, PRA.

## Table 4

Ordinal Logistic Regression Analysis of Renal Artery Calcium versus Odds of Being in a Higher Chronic Kidney Disease Stage

| **RAC +/− (n = 1226)** | | |
|---|---|---|
| **Model** | **OR** | **p-value** |
| 1 | 1.26 | 0.12 |
| 2 | 1.29 | 0.10 |
| 3 | 1.25 | 0.16 |
| 4 | 1.26 | 0.17 |
| 5 | 1.33 | 0.11 |
| RAC Continuous (1-SD Increments of 152 Agatston units) (n = 363) | | |
| Model | OR | p-value |
| 1 | 1.14 | 0.03 |
| 2 | 1.13 | 0.05 |
| 3 | 1.12 | 0.06 |
| 4 | 1.14 | 0.05 |
| 5 | 1.14 | 0.05 |

Model 1: RAC, age, gender, race. Model 2: Model 1 + height, visceral fat. Model 3: Model 2 + dyslipidemia, diabetes, smoking, hypertension. Model 4: Model 3 + IL-6, AAC. Model 5: Model 4 + aldosterone, PRA.