Prevalence and Prognostic Significance of Renal Artery Calcification in Patients with Diabetes and Proteinuria

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Background and objectives: Vascular calcification is common and severe in chronic kidney disease. Because the consequences of calcification may differ by vascular beds, we sought to test the hypothesis that patients who have diabetes with proteinuria and have significant renal artery calcification (RAC) have a higher risk for progression to ESRD.

Design, setting, participants, & measurements: Using electron-beam computed tomography, RAC was computed as the sum of Agatston scores at each of the two renal ostia and renal arteries. Time-to-event analysis was conducted to compare the risk in individuals with or without significant RAC (total score >10).

Results: Of 172 patients with type 2 diabetes and overt proteinuria studied (estimated GFR 56 ± 25 ml/min per 1.73 m^2), significant RAC was present in 31%. In 33 ± 21 months, 41 progressed to ESRD and 65 reached a composite outcome (ESRD or death). Serum phosphorus was a significant predictor of progression to ESRD but was replaced by the significant RAC in multivariate models that included the latter. Individuals with significant RAC had a higher risk for reaching the composite outcome. In contrast, there was no association between coronary artery calcification scores and progression to ESRD.

Conclusions: Significant RAC was an independent predictor of progression to ESRD as well as reaching the composite outcome. Understanding the pathogenesis of RAC would allow determination of whether this risk is potentially modifiable.

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Advancing chronic kidney disease (CKD) is characterized by a progressive inability to excrete phosphorus and is associated with worsening abnormalities in mineral metabolism. Changes such as an increase in serum parathyroid hormone and fibroblast growth factor 23 begin early during the course of CKD and serve to maintain serum phosphorus within the reference range in most patients until late in the course of the disease (1–3). In addition to inducing renal osteodystrophy, higher serum phosphorus levels within the reference range are associated with higher risk for all-cause mortality in individuals with and without CKD (4,5). Furthermore, epidemiologic studies of patients with CKD have shown a graded relationship between serum phosphorus levels and rate of loss of GFR or progression to ESRD (6–8). The biological basis of this association in humans has not been well studied; however, CKD is associated with intrarenal calcification in animal models, which is ameliorated with dietary phosphorus restriction (9–12). Furthermore, vascular calcification is an active cell-mediated process, and phosphorus has been shown to be an important mediator for the induction and progression of vascular calcification in cell culture and animal studies (13,14), so it seems reasonable to postulate that extraskeletal calcification may be a biological basis for the association that is seen between serum phosphorus and progression of CKD.

Vascular calcification begins early and is often severe early during the course of CKD, particularly among those with diabetes. Most of the studies in CKD have focused on either coronary or peripheral arterial calcification. The prognostic value of coronary artery calcification (CAC) has been established in many populations—our group has extended these findings to patients with diabetes and proteinuria (15)—however, calcification occurs in many vascular beds, including the renal arteries (16–20). The clinical relevance of renal artery calcification (RAC) has heretofore not been studied. We undertook this study to test the hypothesis that among patients with diabetes and proteinuria, the presence of significant RAC is associated with a higher risk for progression to ESRD and a composite outcome of either progression to ESRD or all-cause mortality.

Materials and Methods

Patients and Baseline Assessment

For this analysis, we pooled the data from participants who were enrolled in two prospective study cohorts; the primary purpose of each of the two studies was to evaluate racial/ethnic differences in the severity of CAC in patients with type 2 diabetes and proteinuria. Some of the results from these cohorts have been published previously (15,21–24). Among 195 eligible patients from the two cohort studies, renal artery images were available for 172. The individuals for whom the renal artery images were not available ($n = 23$) were more likely to

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be Latino (87 *versus* 66%; $P = 0.05$) and had lower median body mass index (26 ± 8 *versus* 30 ± 9 kg/m^2, $P = 0.01$) and higher mean estimated GFR (eGFR; 65 ± 20 *versus* 56 ± 25 ml/min per 1.73 m^2; $P = 0.08$). Of these 23 participants, five progressed to ESRD and three died. There was no significant difference between the time to event between the 172 individuals who were included in the analysis when compared with those who were excluded (by log rank test, $P = 0.94$ and 0.62 for progression to ESRD and composite outcome, respectively).

The inclusion and exclusion criteria and the methods were almost identical for both studies. The definitions for type 2 diabetes and diabetic nephropathy were adapted from those used by the National Institutes of Health–sponsored Family Investigation of Nephropathy in Diabetes (FIND) with minor modifications (25). Patients were deemed to have type 2 diabetes when the disease was diagnosed at ≥30 years of age and the patient had been treated with either diet or oral hypoglycemic agents for at least 6 months. Diabetic nephropathy was diagnosed either by the presence of typical histologic changes on renal biopsy or by clinical criteria: Urine protein-creatinine ratio ≥0.5 mg/mg either at the time of enrollment or in the preceding 12 months in individuals with diabetes duration of ≥10 years or of ≥5 years in the presence of retinopathy. Dialysis-dependent patients or those with a previous renal transplant were excluded.

All eligible patients who consented to participate in the study were scheduled for an outpatient clinic visit at the General Clinical Research Center at the Los Angeles Biomedical Institute at Harbor-UCLA Medical Center. The patients were asked to fast and bring all of the prescribed medication on the scheduled day. All of the data collected were used to determine the prevalence and/or severity of traditional, renal-related, and diabetes-related risk factors. Intact parathyroid hormone concentrations were measured using an immunochemiluminometric assay (Quest Diagnostic Nichols Institute, San Juan Capistrano, CA; reference range 10 to 65 pg/ml), 25-hydroxyvitamin D [25(OH)D] levels using liquid chromatography and tandem mass spectroscopy (Quest Diagnostic Laboratory; analytic sensitivity 4 ng/ml), and albumin using the bromocresol purple method. Clinical evidence of cardiovascular disease was defined as the presence of one of the following: Angina on the Rose questionnaire, a history of either myocardial infarction or previous revascularization, or stroke. GFR was estimated using the four-variable equation from the Modification of Diet in Renal Disease (MDRD) study (26,27). The study was approved by the institutional review board at the Los Angeles Biomedical Research Institute.

Measurement of RAC

Electron-beam computed tomographic scans were performed for the measurement of CAC; the scans were extended to image the upper abdomen to include the entire length of both kidneys. The scans were acquired using 2.5-mm collimation and 5-mm slices that provided overlapping images, including the renal arteries. The severity of RAC was scored using the Agatston method, as has been used in the Multi-Ethnic Study of Atherosclerosis (MESA) for measurement of coronary calcium (28,29). Calcified foci were defined as regions with a density of >130 Hounsfield units and an area of ≥3 contiguous pixels (1.0 mm^2). Both the renal artery and ostia were evaluated by a reader who was blind to the clinical conditions of the study participants. RAC score in this study represents the sum of the calcium score at both the renal artery and the ostia bilaterally. A patient was categorized as having significant RAC when the total score was >10, as is often used in the studies of CAC (30–32). Representative images from two of the study participants are presented in Figure 1.

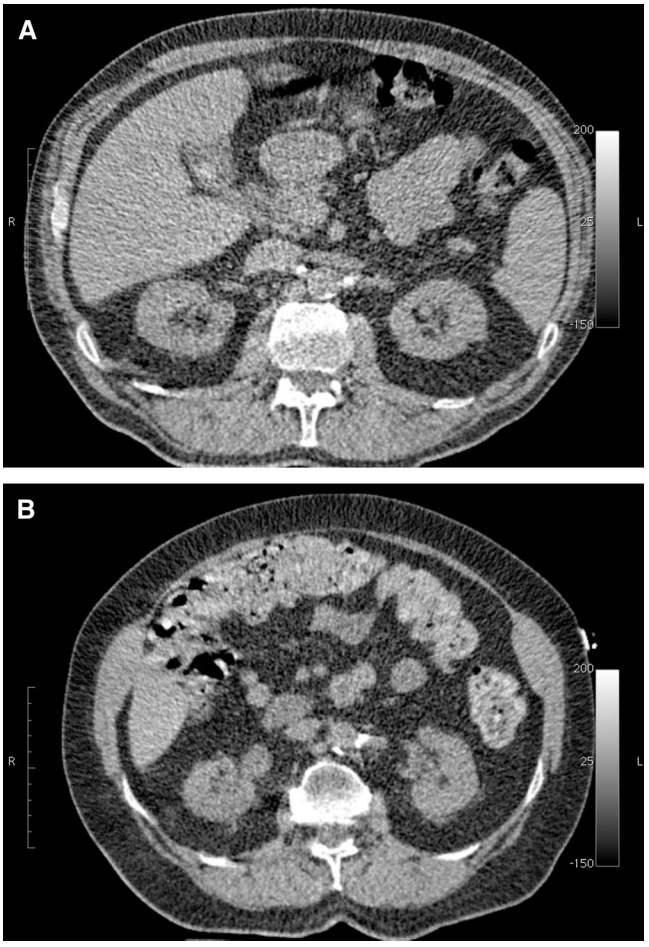

Figure 1. Representative images of RAC in two study participants. The total RAC score in these patients were 424 (A) and 447 (B), respectively.

Patient Follow-up and Ascertainment of Outcomes

Two primary end points were used in this study: Progression to ESRD and a composite outcome of either progression to ESRD or all-cause mortality. As per the study protocol, patients and/or their next of kin were contacted by telephone at 6-month intervals to ascertain the occurrence of either progression to ESRD or death, up until November 1, 2009. For patients who could not be contacted by telephone, at least two certified letters were sent followed by a home visit by one of the members of the study staff. This information was supplemented by merging the data from this study with that available from the US Renal Data System (USRDS, data available through December 31, 2008) and screening the National Death Index (NDI; data available through December 31, 2007).

Statistical Analysis

Continuous variables are expressed as mean ± SD or as median (interquartile range), as appropriate, and categorical variables are expressed as percentages. The significance of difference of continuous variables between individuals with and without significant RAC was tested using either *t* test or Mann-Whitney rank-sum test, as appropriate. The difference in the distribution of categorical variables was tested using the χ^2 test. Multivariate, logistic regression analysis was conducted to determine the independent predictors of significant RAC. All predictors with a $P < 0.10$ were considered using forward selection for

inclusion in a final parsimonious model. Two models were run: One that included only demographic and clinical variables and one that also included CAC scores.

Time-to-event survival analysis was used to determine the independent predictors of the risk of progression to ESRD or the composite end point. Univariate analyses to determine the association of each of the variables listed in Table 1 with each of the two outcomes was performed using Cox proportional hazards. The assumption of proportional hazards was confirmed using the Schoenfeld residual test. For avoidance of making the assumption that the risk with various continuous variables was linear, they were transformed into categorical variables (two groups, using the median as a cutoff value; a third category of missing data was created for variables, if indicated). All predictors with a $P < 0.10$ on univariate analyses were considered for inclusion in the multivariate model using forward selection. For each of the two outcomes, four models were built: first, in which the presence of significant RAC was forced into the model, a second in which significant CAC was forced into the model, a third in which both renal and

Table 1. Baseline characteristics of 172 study participants, categorized by the absence or presence of significant RAC

Characteristic	Entire Cohort	RAC		*P*
		Not Significant (≤10)	Significant (>10)	
Sample size (*n*)	172	118	54	
RAC score (median [range])	0 (0 to 1541)	0 (0 to 10)	91 (11 to 1541)	
Demographics				
age (years; mean ± SD)	57 ± 7	56 ± 7	60 ± 7	<0.001
male gender (%)	56	61	46	0.07
race/ethnicity (%)[a]				0.12
non-Latino white	13	11	19	
non-Latino black	17	20	9	
Latino	66	65	69	
other	4	3	4	
Clinical characteristics				
diabetes duration (years; mean ± SD)	15 ± 6	15 ± 6	16 ± 7	0.35
history of cardiovascular disease (%)	42	31	65	<0.001
current smoker (%)	17	18	15	0.61
BMI (kg/m^2; median [IQR])	30 (9)	30 (9)	31 (9)	0.81
SBP (mmHg; mean ± SD)	154 ± 26	156 ± 27	151 ± 25	0.30
DBP (mmHg; mean ± SD)	77 ± 13	77 ± 13	75 ± 12	0.26
ankle brachial index (%)				0.16
<0.9	22	22	21	
0.9 to 1.3	57	60	49	
>1.3	21	17	30	
Laboratory data				
serum creatinine (mg/dl; median [IQR])	1.4 (0.8)	1.5 (0.8)	1.3 (1.0)	0.68
eGFR (ml/min per 1.73 m^2; mean ± SD)	56 ± 25	58 ± 26	51 ± 22	0.11
HbA_{1c} (%; median [IQR])	7.8 (2.7)	7.8 (3.1)	7.8 (2.0)	0.99
total cholesterol (mg/dl; median [IQR])	190 (63)	182 (68)	190 (53)	0.57
LDL cholesterol (mg/dl; median [IQR])	107 (45)	105 (57)	112 (52)	0.58
corrected serum calcium (mg/dl; mean ± SD)	9.8 ± 0.4	9.8 ± 0.4	9.8 ± 0.4	0.33
serum phosphorus (mg/dl; mean ± SD)	4.3 ± 0.7	4.2 ± 0.8	4.3 ± 0.6	0.53
serum PTH (pg/ml; median [IQR]	49 (52)	47 (52)	55 (55)	0.32
serum 25(OH)D (ng/ml; median [IQR])	22 (15)	20 (14)	24 (16)	0.09
C-reactive protein (mg/L: median [IQR])	0.4 (1)	0.4 (0.7)	0.4 (0.7)	0.57
serum albumin (g/dl; mean ± SD)	3.2 ± 0.5	3.2 ± 0.5	3.3 ± 0.5	0.12
urine protein-creatinine ratio (mg/mg; median [IQR])	2.2 (4.2)	2.5 (4.3)	1.8 (3.2)	0.22
Baseline medical therapy[b]				
ACEIs or ARBs (%)	72	72	72	0.68
β blocker (%)	50	46	59	0.11
no. of antihypertensive agents (median [IQR])	3 (1)	3 (1)	2 (2)	0.14
aspirin (%)	45	42	52	0.27
lipid-lowering agents (%)	63	59	74	0.03
phosphate binders (%)	3	2	6	
active vitamin D (%)	1	0	4	
CAC score				
median (IQR)	158 (469)	85 (275)	497 (974)	<0.001
range (%)				<0.001
0 to 10	26	34	9	
11 to 99	16	20	7	
100 to 400	31	31	30	
>400	27	15	54	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic BP; IQR, interquartile range; PTH, parathyroid hormone.

[a]Other not included in χ^2 test.

[b]Data for medications at baseline was missing for 15 patients.

CAC were forced in the model, and a fourth that did not include the presence of either significant renal or CAC. The variables considered for inclusion in the model for risk of progression to ESRD were diabetes duration; systolic BP (SBP); eGFR; glycosylated hemoglobin (HbA_{1c}); serum phosphorus, 25(OH)D, and albumin; urine protein-creatinine ratio; and treatment with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers. The variables considered for inclusion in the model for risk for reaching the composite outcome were SBP; eGFR; HbA_{1c}; serum calcium, phosphorus, and albumin; urine protein-creatinine ratio; and treatment with β blockers.

Sensitivity analysis was performed using alternative cutoff values for RAC score. Because the median RAC score for individuals with nonzero scores was 45, the study cohort was divided into three groups: 0, ≤45, and >45 (n = 109, 31, and 31, respectively). Multivariate models were built for each of the two outcomes using the same variables as identified to be significantly associated with outcome in the primary analysis. All statistical analyses were performed using PASW Statistics 17.0 (SPSS, Chicago, IL) and STATA 11.0 (Stata Corp, College Station, TX).

Results

Patient Characteristics and Predictors of Significant RAC

Significant RAC was present in 31% of the study participants. In contrast, significant CAC (score >10) was present in 74% of participants. The characteristics of the study cohort, categorized by the absence or presence of significant RAC, are summarized in Table 1; individuals with significant RAC were older, were more likely to have cardiovascular disease, and had higher CAC scores. There was no significant difference in eGFR, CKD stage, or any measures of mineral metabolism between individuals in the two groups. Using multivariate logistic regression models, increasing age, female gender, history of cardiovascular disease, and higher CAC scores were identified as independent predictors of significant RAC (Table 2).

Association of RAC with Progression to ESRD

During a mean observation period of 33 ± 21 months, 41 individuals progressed to ESRD, 33 died, and 65 reached the composite outcome of either progression to ESRD or death; the numbers among those with significant RAC for each of the three outcomes were 13, 13, and 22, respectively. Of the 35 patients who reached ESRD before December 31, 2008 (cutoff date for data from USRDS), 31 were identified by both the USRDS search and our contact with the study participant or next of kin, three were identified by USRDS search alone, and one was identified by contact with the study participant alone. The information on six individuals who progressed to ESRD after December 31, 2008, was ascertained only by contact with study participants or with next of kin.

Serum phosphorus (more than median value of 4.2 mg/dl) was associated with a significantly higher risk for progression to ESRD on both univariate (hazard ratio [HR] 2.56; 95% confidence interval [CI] 1.31 to 5.07) and multivariate (adjusted HR 2.01; 95% CI 1.01 to 3.99) analyses (model without including either renal or CAC). In addition, a lower eGFR (less than median value of 49 ml/min per 1.73 m^2; adjusted HR 5.27; 95% CI 2.55 to 10.88) and a lower serum albumin (less than median value of 3.3 mg/dl; adjusted HR 3.40; 95% CI 1.67 to 6.92) independently predicted the risk for progression to ESRD.

Individuals with significant RAC had a higher risk for progression to ESRD (HR 1.43; 95% CI 0.77 to 2.77; reference was no significant RAC). In multivariate analysis, significant RAC replaced serum phosphorus as an independent predictor of progression to ESRD (adjusted HR 2.20; 95% CI 1.09 to 4.47; Figure 2); lower eGFR and serum albumin continued to be associated with a significantly higher risk for progression to ESRD. Similar results were obtained when the data were further adjusted for age, gender, race/ethnicity, diabetes duration, SBP, HbA_{1c}, serum phosphorus and 25(OH)D, urine protein-creatinine ratio, and treatment with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers (adjusted HR 3.01; 95% CI 1.34 to 6.75). In contrast, neither significant (score >10) nor severe (score >400) CAC was associated with risk for progression to ESRD on either univariate or multivariate analyses.

Finally, when measures of both coronary and RAC were considered together in multivariate analyses, neither the presence of significant (score >10) nor severe (score >400) CAC

Table 2. Logistic regression analysis to determine the independent predictors for the presence of significant RAC

Independent Predictors	Model 1[a]		Model 2[b]	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, every 1-year increase	1.10 (1.04 to 1.16)	0.001	1.09 (1.02 to 1.16)	0.01
Gender (reference male)	–	–	3.02 (1.29 to 7.06)	0.01
History of cardiovascular disease (reference no)[c]	4.49 (2.16 to 9.33)	<0.001	4.38 (1.93 to 9.93)	<0.001
CAC score (reference 0 to 10)				<0.001
11 to 99			1.23 (0.26 to 5.90)	0.79
100 to 399			2.72 (0.78 to 9.44)	0.12
≥400			11.62 (3.35 to 40.39)	<0.001

[a]Variables considered for inclusion in model 1: Age, gender, history of cardiovascular disease, serum phosphorus, serum 25(OH)D, and lipid-lowering agents; c statistic 0.76.
[b]Variables considered for inclusion in model 2: Model 1 plus CAC score; c statistic 0.77.
[c]History of cardiovascular disease was defined as the presence of any one of the following: previous myocardial infarction, stroke, coronary revascularization, or typical angina (based on Rose questionnaire).

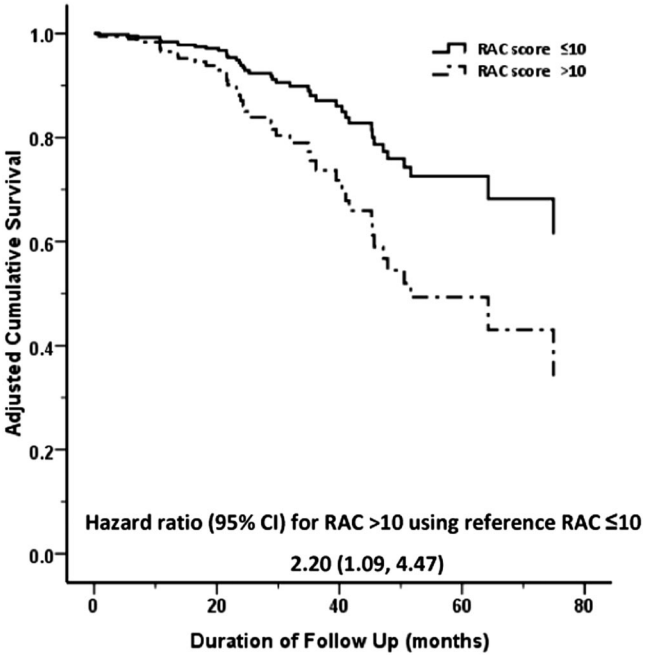

Figure 2. Adjusted accumulative event-free curves stratified by RAC score for progression to ESRD. The event-free curves shown were adjusted for eGFR and serum albumin as binary variables ($P = 0.03$).

predicted risk for progression to ESRD; however, RAC remained an independent predictor of progression to ESRD (adjusted HR for models that included CAC >10 or >400: 2.50 [95% CI 1.18 to 5.31] and 2.22 [95% CI 1.04 to 4.74], respectively).

Association of RAC to ESRD or Death

Of the 33 deaths, 20 occurred on or before December 31, 2007 (cutoff date for data from NDI): 14 were identified by both the NDI search and contact with next of kin, one was identified on NDI data screen only, and five were identified by contact with next of kin only (predominantly because of death occurring outside the United States). All of the deaths after December 31, 2007 ($n = 13$), were ascertained by contact with next of kin. For the composite end point of progression to ESRD or death, 65 events occurred during an observation period of 33 ± 21 months: 43 in individuals without significant RAC and 22 in those with significant disease. In models that did not include the presence of vascular calcification, only lower eGFR (adjusted HR 3.27; 95% CI 1.91 to 5.59) and serum albumin (adjusted HR 2.84; 95% CI 1.68 to 4.80) were associated with a higher risk for reaching the composite end point.

Individuals with significant RAC had a higher risk for reaching the composite outcome (HR 1.46; 95% CI 0.87 to 2.45; reference was no significant RAC). In multivariate analyses, the risk for reaching the composite end point was significantly higher among individuals with significant RAC (adjusted HR 1.92; 95% CI 1.12 to 3.28; Figure 3); lower eGFR and serum albumin remained independent predictors of the risk for reaching the composite end point. Similar results were obtained when the data were further adjusted for age, gender, race/ethnicity, SBP, HbA_{1c}, serum calcium and phosphorus, urine protein-creatinine ratio, and treatment with β blockers (adjusted HR 2.22; 95% CI 1.24 to 3.99). When analyses were performed using coronary artery instead of RAC, severe (score >400) but not significant (score >10) calcification was significantly associated with risk for reaching the composite outcome on both univariate and multivariate analyses (adjusted HR 1.72; 95% CI 1.02 to 2.90).

Finally, when measures of both coronary and RAC were considered together in multivariate analyses, neither the presence of significant (score >10) nor severe (score >400) CAC predicted risk for the composite outcome. The same trend for a higher risk for reaching the composite outcome was seen in patients with significant RAC (adjusted HR for models that included CAC >10 or >400: 1.92 [95% CI 1.09 to 3.35] and 1.68 [95% CI 0.94 to 3.00], respectively).

Sensitivity Analysis

Similar results were obtained when the severity of RAC was classified differently (0, ≤45, and >45; Table 3).

Discussion

To our knowledge, this is the first study to evaluate the relationship between the presence of significant RAC and clinically relevant outcomes. Patients who had diabetes with proteinuria and significant RAC had a twofold higher adjusted risk for progression to ESRD or reaching a composite outcome of progression to ESRD or death. In contrast, no such association was seen with significant CAC: Severe CAC was associated

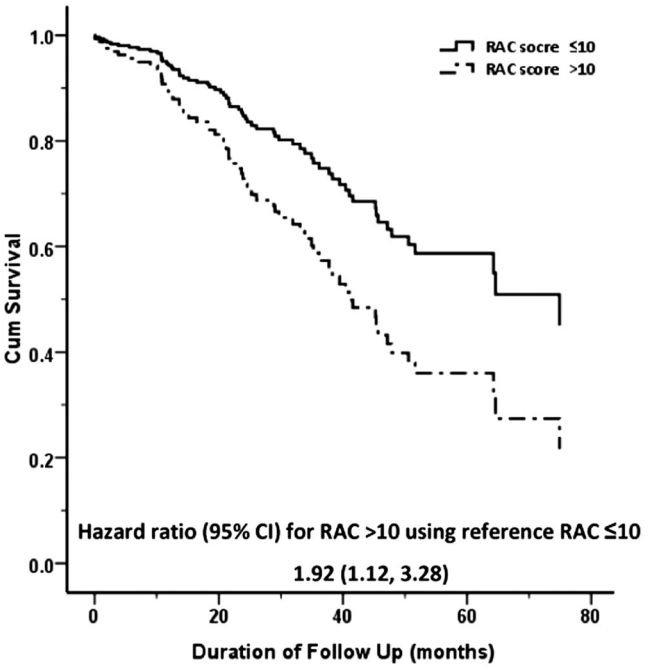

Figure 3. Adjusted accumulative event-free curves stratified by RAC score for progression to ESRD or all-cause mortality The event-free curves shown were adjusted for eGFR and serum albumin as binary variables ($P = 0.02$).

Table 3. Sensitivity analyses performed by using an alternative method of classifying the severity of RAC

RAC Score (Reference 0)[a]	Progression to ESRD (HR [95% CI])[b]	Progression to ESRD or Death (HR [95% CI])[b]
1 to 45	0.79 (0.30 to 2.05)	1.15 (0.59 to 2.24)
>45	2.38 (1.03 to 5.52)	2.28 (1.20 to 4.32)

[a]The median score for individuals with total RAC score >0 was 45 and hence was used to group patients.
[b]Adjusted for eGFR and serum albumin.

only with the composite outcome, which included the risk for death. Finally, our analyses confirm the previous findings of an association of serum phosphorus with progression to ESRD. Our analysis allows us to generate a hypothesis that induction and/or progression of RAC may be one of the mechanisms whereby higher serum phosphorus levels may contribute to progressive loss of renal function.

There are no previously published data on the prevalence of RAC in individuals with CKD. In this study, we enrolled patients who had CKD and probably were at the highest risk for vascular disease: Patients with type 2 diabetes with overt proteinuria. Almost one third of this high-risk group had demonstrable RAC. Vascular calcification can occur in either the intima or the media of the blood vessels. Intimal calcification involves atherosclerotic plaques, and it is substantially more severe in patients with CKD (33). Medial calcification is generally present in the elderly or those with diabetes or CKD. None of the noninvasive methods that are used to detect vascular calcification can distinguish intimal from medial calcification (34). The relative contribution of intimal and medial calcification to the composite assessment of RAC with electron-beam computed tomography is not known. At least two studies have demonstrated an association between RAC and renal artery stenosis; the latter is generally atherosclerotic in origin and hence, intimal (16,20). The association between the severity of RAC with luminal narrowing was modest, however. These findings are consistent with what has previously been demonstrated for CAC: Although the calcification score correlates well with total plaque burden, the severity of luminal narrowing is often modified by vascular remodeling. Histologic studies of peripheral arteries have demonstrated the presence of medial calcification, and it is possible that some of the total calcification measured herein involves the tunica media (35,36). Studies in the future would be needed to clarify the relative contribution of intimal and medial calcification to the total RAC burden ascertained by noninvasive ante mortem imaging studies.

The most important finding of our study is the demonstration of an association between significant RAC and progression to ESRD. Even though there was a strong relationship between the presence of significant RAC and vascular disease at other sites in this and other studies (CAC scores or history of cardiovascular disease), the association with progression to ESRD was specific to the renal vascular disease (17–19). We were unable to demonstrate any relationship between the severity of CAC and progression to ESRD. This suggests either that the severity of RAC is the proximate cause (causal) for the worsening of renal function or that it serves as a sensitive marker for intrarenal processes (*viz.*, intrarenal calcification, downstream ischemia) that eventually lead to ESRD. This raises the question of whether RAC is a modifiable risk factor for the progression of CKD or a marker that could help to identify the patients with the highest risk for progressive loss of renal function. Our study is insufficient to answer this question, and this needs to be addressed in future studies. In this context, it is important to acknowledge that recent clinical trial data indicated that renal revascularization offers no significant clinical advantage over medical therapy for the treatment of significant renal artery stenosis, either for the decline in GFR or control of BP (37); however, escalation of medical therapy (control of BP, lipids, and abnormalities in mineral metabolism) may be an effective strategy in patients with CKD and significant RAC.

Finally, our study confirms the previous direct association of serum phosphorus levels with progression to ESRD (6–8). Animal studies have demonstrated the presence of significant intrarenal parenchymal calcification that seems to contribute to progressive renal injury (9–12). It is interesting that the intrarenal calcification and the consequent renal injury were ameliorated by dietary phosphorus restriction. Our study extends the findings of these previous studies: Serum phosphorus was no longer a significant predictor when RAC was included in the multivariate model. One has to be cautious in making strong deductions about causal pathways from such observations; however, this does allow us to generate a biologically plausible hypothesis: Calcification of the renal arteries may be one of the mechanisms whereby higher serum phosphorus leads to a faster progression of CKD. This raises the hope that aggressive management of abnormalities in mineral metabolism may slow the rate of loss of GFR. This hypothesis needs to be tested directly in future investigations.

Our study is not without its limitations. First, our study population consisted predominantly of minorities, particularly Latinos, and was limited to patients with type 2 diabetes and proteinuria. Second, the number of events of interest, particularly death, was limited. In building our multivariate models, we were careful to include only a limited number of important covariates so that we could obtain stable estimates of risk. Nevertheless, our findings need to be confirmed in larger cohorts with a longer follow-up period that would allow for a larger number of events. Third, we used only the baseline data for risk prediction. Fourth, the inter- and intraobserver variabilities specifically for the measurement of RAC were not determined and need to be studied to determine the reproducibility of the measurement. Finally, patients with CKD have two competing risks: Progression to ESRD and death. Individuals with

the most severe vascular disease may die before they progress to ESRD. To minimize the bias introduced by this competing risk, we also analyzed the risk for reaching a composite outcome.

Conclusions

We report a novel finding of the association between the presence of significant RAC with risk of progression to ESRD or reaching a composite outcome of progression to ESRD or death. The processes and possibly even the triggers that lead to RAC may be the same as for calcification at other sites; however, the consequences seem to be unique to the affected vascular bed. Future studies need to determine whether altering the natural history of vascular calcification in early CKD will translate into a reduction in progression to ESRD and mortality in this high-risk population.

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Disclosures

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