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Prevalence and correlates of mitral annular calcification in adults with chronic kidney disease: Results from CRIC study

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ABSTRACT

Background: Risk factors for mitral annular calcification (MAC) and cardiovascular disease (CVD) demonstrate significant overlap in the general population. The aim of this paper is to determine whether there are independent relationships between MAC and demographics, traditional and novel CVD risk factors using cardiac CT in the Chronic Renal Insufficiency Cohort (CRIC) in a cross-sectional study.
Methods: A sample of 2070 subjects underwent coronary calcium scanning during the CRIC study. Data were obtained for each participant at time of scan.
Subjects: were dichotomized into the presence and absence of MAC. Differences in baseline demographic and transitional risk factor data were evaluated across groups. Covariates used in multivariable adjustment were age, gender, BMI, HDL, LDL, lipid lowering medications, smoking status, family history of heart attack, hypertension, diabetes mellitus, phosphate, PTH, albuminuria, and calcium.
Results: Our study consisted of 2070 subjects, of which 331 had MAC (prevalence of 16.0%). The mean MAC score was 511.98 (SD 1368.76). Age and white race remained independently associated with presence of MAC. Decreased GFR was also a risk factor. African American and Hispanic race, as well as former smoking status were protective against MAC. In multivariable adjusted analyses, the remaining covariates were not significantly associated with MAC. Among renal covariates, elevated phosphate was significant.
Conclusion: In the CRIC population, presence of MAC was independently associated with age, Caucasian race, decreased GFR, and elevated phosphate. These results are suggested by mechanisms of dysregulation of inflammation, hormones, and electrolytes in subjects with renal disease.

1. Introduction

A high degree of correlation between risk factors for mitral annular calcification (MAC) and cardiovascular disease (CVD) has been previously shown in the general population [1–3] including age, female gender, diabetes mellitus (DM), and obesity. In these studies, however, the patient population included few subjects with chronic kidney disease (CKD) [3,4]. Among this group, cardiovascular disease is one of the most common causes of increased mortality [5,6]. Patients with renal disease suffer from dysregulation of inflammation, hormones, and electrolytes resulting in significant relative increases in calcium deposits of the coronary arteries and cardiac valves [6–11]. Additionally, an association exists between MAC and coronary artery calcification (CAC) and coronary artery disease (CAD) [12,13]. However, not all CKD patients have MAC. It is still unknown whether these increased calcium deposits are associated with traditional risk factors in the CKD population. Prior studies either lacked sufficient subjects or used echocardiography, which has low specificity in distinguishing dense collagen from calcification and leads to wide variation in MAC prevalence when compared to computed tomography (CT) [1,2]. No previous study has examined the relationship between multiple traditional risk factors and MAC using Cardiac Computed Tomography (CCT) in the Chronic Renal Insufficiency Cohort (CRIC).

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Therefore, the aim of this paper is to determine whether there are independent relationships between MAC and gender, race, age, and traditional and novel CVD risk factors, as well as metabolic variables such as calcium, phosphate, parathyroid hormone (PTH), albuminuria, using CCT in CRIC in a cross-sectional study.

2. Methods

This study was approved by the Institutional Review Board at all participating centers and the scientific and data coordinating center. The cohort was established to examine risk factors for progression of chronic renal insufficiency (CRI) and cardiovascular disease (CVD) among patients with CRI and identify high-risk groups, inform future treatment trials, and increase application of preventive therapies. The CRIC Network is composed of a Scientific and Data Coordinating Center as well as seven Clinical Centers across the U.S [14]. The current analysis included 2070 subjects who underwent coronary calcium scanning as part of the multiethnic CRIC study. The CRIC Study was designed to include a racially and ethnically diverse group of adult individuals who were aged 21–74 years and had mild to moderate CKD and approximately half of whom had diabetes. Recruitment strategies varied from center to center and included computerized searches of laboratory databases and medical records, and referrals from health care providers. Recruitment also occurred at clinics enriched with cases of CRI. Securing local physician approval and contacting potential screenees depended on local institutional review boards' guidelines and the requirements of each medical facility. All participants provided written informed consent and HIPAA authorization. All creatinine levels are performed at a central laboratory and GFR is estimated based on the simplified modification of diet in renal disease (MDRD) equation (GFR [mL/min per 1.73 m^2] = 186 × [serum Cr (mg/dL] $^{-1.154}$ × [age] $^{-0.203}$ × [0.742 if female] × [1.212 if black]) [14,15].

Medical history, anthropometric measurements, and laboratory data were obtained for each participant at baseline and each annual in-person visit. Questionnaires supplied information about age, gender, race/ethnicity, and medical history. Current smoking was defined as having smoked a cigarette in the last 30 days. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dl or on hypoglycemic medication. Use of antihypertensive and other medications were based on clinic staff entry of prescribed and over-the-counter medications. Resting blood pressure was measured three times in the seated position using a manual blood pressure cuff and the average of the 2nd and 3rd readings was recorded. Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of medication prescribed for hypertension. Body mass index (BMI) was calculated from the equation weight (kg)/height (m^2). Total and HDL cholesterol were measured from blood samples obtained after a 12-h fast. LDL cholesterol was calculated with the Friedewald equation. CRP was measured using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, IL) at the University of Vermont Laboratory for Clinical Biochemistry Research. Analytical intra-assay CVs ranged from 2.3 to 4.4% and inter-assay CVs ranged from 2.1 to 5.7%. The presence and number of risk factors for each subject was calculated based on the Adult Treatment Panel III (ATP III) guidelines. Risk factors included: age (>45 years for men, >55 years for women), current cigarette smoking, diabetes mellitus, history of premature coronary artery disease in first-degree relatives (<55 years in men, < 65 years in women), hypertension, and hypercholesterolemia. Hypercholesterolemia was defined as use of cholesterol lowering medications or, in the absence of use of cholesterol lowering medications, a total serum cholesterol >200 mg/dL.

After signing informed consent, the majority of participants underwent two CT scans at year 1 for evaluation of CAC. Risk factors were assessed at time of scan. CT scans were obtained using either an Imatron C-300 Electron Beam computed tomography scanner or multi-detector CT scanner [16]. Thirty to forty contiguous tomographic slices were obtained at 3 mm intervals beginning 1 cm below the carina and progressing caudally to include the entire coronary tree [17]. Methods for CAC scanning have previously been published [15]. All scans were analyzed by Neo Imagery Technologies software package (City of Industry, California). Calcific lesions were identified by an attenuation threshold of 130 Hounsfield units and a minimum of 3 contiguous pixels, then was scored using Agatston's algorithm. A density factor was assigned based on the following: 1 for lesions with peak attenuation of 130–199 Hu, 2 for lesions with peak attenuation of 200–299 Hu, 3 for lesions with peak attenuation of 300–399 Hu, and 4 for lesions with peak attenuation >400 Hu. The total CAC score was determined by summing individual lesion scores from each of four anatomical sites (left main, left anterior descending, left circumflex, and right coronary artery). The average of the two scores was used in the analysis.

Initially, MAC was dichotomized into the presence and absence of MAC defined as those with MAC = 0 versus those with score >0 [3,4]. Differences in baseline demographic and transitional risk factor data were evaluated across MAC groups using t-test for continuous variables and the Chi-Square test or Fisher's exact test for categorical variables, as appropriate. We described differences in demographics and risk factors between those with positive MAC scores and those with a 0 score. Then, we looked at only those who have positive MAC scores and assessed whether there were differences in age, gender, race and other risk factors.

We used logistic regression models to assess the relationship between each risk factor and the presence of calcium and adjusted for all other risk factors in the model. The odds ratios we estimate approximate relative risks because our endpoint is rare. The following covariates were used in the multivariable adjustment: age, gender, race, ethnicity, body mass index, HDL, LDL, lipid lowering medications, smoking status, family history of heart attack, hypertension, and diabetes mellitus. Statistical analyses were performed with SAS version 9.3 (Cary, NC) and a p-value <0.05 was considered statistically significant.

3. Results

Overall, among the 2070 CRIC subjects who underwent CT scanning, there were 1112 men (53.7%) and 958 women (46.3%). The average subject age was 58.0 years. Whites comprised the majority of the cohort (43%) versus black/African Americans (35%), Hispanics (17%), and others (5%). The average BMI of the cohort was 31 kg/m^2, with mean HDL of 49 mg/dL, LDL 103 mg/dL, and estimated GFR 43 ml/min/1.73 m^2.

Among tested patients, 331 had MAC with a prevalence of 16.0%. The mean MAC Agatston score was 511.98 (range 0.31–13,885.00, SD 1368.76). The prevalence of MAC was highest in whites (19.8%), followed by black/African Americans (13.1%), and Hispanics (12.9%). Those classified as "other" demonstrated prevalence of 14.02%. Table 1 demonstrates the baseline characteristics of the study population according to absence and presence of MAC. MAC was more prevalent in women and older participants.

Participants with MAC had a higher prevalence of hypertension and diabetes mellitus (DM) as well as higher average BMI (all $p < 0.001$) when compared with participants who did not have MAC. They also had higher phosphate and PTH levels compared to participants without MAC ($p < 0.01$, Table 1). There were no statistically significant differences in hsCRP levels or mean GFR between those with and without MAC. However, lipid lowering

Table 1
Characteristics among CRIC participants stratified by the absence or presence of MAC.Numbers of patients are indicated for each group and numbers given in parentheses indicate relative percentages. *are given in mean ± SD.

	MAC = 0	MAC > 0	p-value
N	1739 (84)	331 (16)	
Age*	56.7 ± 11.6	64.7 ± 7.7	<0.0001
Men	948 (54.5)	164 (49.6)	0.10
Race			p = 0.0007
White	717 (41.2)	177 (53.5)	
Black/African American	633 (36.4)	95 (28.7)	
Hispanic	297 (17.1)	44 (13.29)	
Other	92 (5.3)	15 (4.5)	
Smoking			p = 0.11
Former	678 (39.0)	144 (43.5)	
Current	183 (10.5)	24 (7.3)	
Never	878 (50.5)	163 (49.2)	
BMI (kg/m^2)*	30.78 ± 6.6	32.76 ± 6.8	<0.0001
Systolic BP (mmHg)*	125.6 ± 20.8	131.7 ± 22.2	<0.0001
Hypertension	1481 (85.3)	319 (96.67)	<0.0001
Diabetes Mellitus	761 (43.8)	211 (63.75)	<0.0001
Family history of CAD	248 (14.3)	57 (17.2)	0.16
Total cholesterol (mg/dl)*	187.9 ± 44.4	178.3 ± 41.1	0.0005
LDL cholesterol (mg/dl)*	104.5 ± 35.3	95.6 ± 31.4	<0.0001
HDL cholesterol (mg/dl)*	49.5 ± 15.9	46.4 ± 14.5	0.0016
Lipid-lowering meds	1010 (58.35)	246 (74.77)	<0.0001
hsCRP (mg/L)*	4.4 ± 6.9	5.7 ± 13.8	0.31
Estimated GFR (ml/min/1.73 m^2)*	44.2 ± 20.3	37.5 ± 12.8	0.07
Calcium (mg/dL)	9.31 ± 0.54	9.33 ± 0.52	0.68
Phosphate (mg/dL)*	3.92 ± 0.71	4.30 ± 0.71	0.0021
PTH (pg/mL)	80.14 ± 71.28	101.6 ± 139.5	0.0081
Use of vitamin D	92 (5.31)	24 (7.29)	0.15
Albumin excretion, ug/mg creatinine	1885.6 ± 2860.8	2671.8 ± 2999.9	0.14

medications were used more in the MAC group. In addition, the MAC group tended to have lower total cholesterol, LDL, and HDL levels ($p < 0.002$ for all).

Subsequently, when stratifying subjects by estimated GFR, progressively worsening GFR was associated with up to 4-fold increase in likelihood of MAC on univariate and multivariate analysis (Table 2).

Tables 2–4 demonstrate the univariate and multivariable adjusted association of risk factors with presence of MAC. Increasing age (per 10 year) was associated with up to an 8-fold increase in the odds of presence of MAC in unadjusted as well as multivariate adjusted analyses. Males had the same likelihood for MAC as females. As compared to whites, all ethnic groups had a lower odds ratio for presence of MAC, and the association was statistically significant for African American and Hispanic ethnicity after multivariate adjustment (Table 2). Among the traditional cardiac risk factors, elevated BMI, HTN, diabetes, and HDL levels <40 were not associated with increased odds of having MAC in unadjusted analysis (all $p < 0.05$). Furthermore, after multivariable adjusted analysis all these associations remained not statistically significant. Interestingly, a former history of smoking was protective of MAC ($p < 0.05$, Table 3). When looking at calcium and related markers including levels of phosphate, PTH, and albuminuria, having elevated serum phosphate levels was associated with increased likelihood of MAC, with the association persisting after multivariate analysis (Table 4).

Table 2
Association of risk factors with presence of MAC using logistic regression in unadjusted and multivariate analyses when adjusting for age, gender, race, and estimated GFR.

	Age and sex adjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Age		
<55	Ref group	Ref group
55–64	3.95 (2.52–6.20)[b]	4.01 (2.55–6.32)[b]
≥65	9.37 (6.06–14.48)[b]	8.05 (5.17–12.53)[b]
Female Gender	1.19 (0.92–1.52)	1.21 (0.94–1.56)
Race		
Caucasian	Ref group	Ref group
African American	0.60 (0.45–0.80)[b]	0.53 (0.40–0.72)[b]
Hispanic	0.71 (0.49–1.04)	0.56 (0.38–0.82)[b]
Other	0.73 (0.40–1.34)	0.70 (0.37–1.29)
Estimated GFR (ml/min/1.73 m^2)[b]		
<30	3.21 (1.99–5.18)[b]	3.78 (2.32–6.17)[b]
30 to <40	2.90 (1.80–4.68)[b]	3.26 (2.01–5.31)[b]
40 to <50	2.10 (1.28–3.45)[b]	2.30 (1.40–3.79)[b]
50 to <60	1.41 (0.82–2.42)	1.50 (0.87–2.59)
≥ 60	Ref group	Ref Group

[a] All variables adjusted simultaneously.
[b] Indicates statistically significant.

4. Discussion

In brief, our study results show that there is an association between MAC and increasing age, white race, and elevated phosphorus in patients with CKD who are not dependent on dialysis and without kidney transplant. This is important due to the association of MAC with CAC and CAD [12].

We found several notable differences when compared to previous analyses from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, which had few CKD subjects (of 6785, 10% had eGFR <60 ml/min/1.73 m^2) [4]. Our study had nearly twice the prevalence of MAC than observed in MESA (16.0% vs. 9%, respectively) [3,4]. Unlike MESA, we did not find an association with use of lipid lowering medications in MAC. Female and obese patients were more likely to have MAC, although neither reached statistical significance in CRIC, which is in contrast to observations in MESA. Increasing age was independently associated with higher odds of MAC in both studies and patients without MAC in the CRIC population were younger by about 8 years compared with those who had MAC. Conversely, in the Penn Diabetes Heart Study (PDHS) of subjects without renal dysfunction, MAC subjects were 10 years

Table 3
Association of risk factors with presence of MAC using logistic regression in unadjusted and multivariate analyses when adjusting for cardiac risk factors.

	Age and sex adjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Smoking		
Never	Ref group	Ref group
Former	0.47 (0.20–1.09)	0.42 (0.19–0.95)[b]
Current	0.32 (0.04–2.62)	0.25 (0.03–2.03)
BMI		
18.5–24.99 (Normal)	Ref group	Ref group
25–29.99 (Overweight)	1.88 (0.39–9.16)	1.87 (0.37–9.48)
30–39.99 (Obese)	2.09 (0.45–9.77)	2.09 (0.41–10.51)
≥40 (Morbidly obese)	2.58 (0.43–15.50)	2.13 (0.33–13.89)
Hypertension	0.86 (0.23–3.24)	0.90 (0.24–3.45)
Diabetes Mellitus	2.21 (0.96–5.08)	2.39 (0.95–5.99)
Family History of CAD	1.16 (0.40–3.40)	0.96 (0.32–2.94)
Lipid lowering meds	1.18 (0.58–2.39)	0.88 (0.39–2.04)
LDL (mg/dl)		
<100	Ref group	Ref group
100–129	1.00 (0.46–2.18)	0.99 (0.43–2.28)
130–159	0.16 (0.02–1.28)	0.14 (0.02–1.14)
≥160	1.19 (0.35–4.01)	0.79 (0.19–3.32)
HDL (mg/dl)		
40–59 (average risk of CAD)	Ref group	Ref group
<40 (higher risk of CAD)	1.86 (0.89–3.89)	1.73 (0.79–3.79)
>60 (lower risk of CAD)	0.82 (0.21–3.20)	0.98 (0.24–3.97)

[a] All variables adjusted simultaneously.
[b] Indicates statistically significant.

Table 4
Association of Risk Factors with Presence of MAC using logistic regression in unadjusted and multivariate analyses when adjusting for phosphate, PTH, albuminuria, and calcium.

	Age and sex adjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Phosphate (mg/dL)		
2.4–4.1	Ref group	Ref group
>4.1	3.64 (1.52–8.70)[b]	3.33 (1.37–8.09)[b]
PTH (pg/mL)		
11–55	Ref group	Ref group
>55	2.33 (0.97–5.55)	2.02 (0.83–4.91)
Albuminuria		
<30	Ref group	Ref group
30 to <300	0.94 (0.20–4.34)	0.50 (0.11–2.38)
≥300	5.52 (1.77–17.25)[b]	1.23 (0.39–3.87)
Calcium (mg/dL)		
8.6–10.2	Ref group	Ref group
>10.2	#	#

#Unable to compute due to excess standard error in sample.
[a] All variables adjusted simultaneously.
[b] Indicates statistically significant.

older on average than those without MAC [13]. Former smokers were associated with lower odds of MAC in the CRIC population, but MESA found a higher odds ratio. In our study, we found that this segment of former smokers had lower LDL levels than never-smokers (data not shown). In addition, unmeasured confounders such as lifestyle and environmental factors are plausible explanation of this interesting finding. Current smokers in the MESA population were independently associated with MAC [3]. Similar to findings from MESA, multivariable predictors of MAC in CRIC included older age, and white race, while neither study observed independent associations with MAC for hypertension, family history of heart attack, higher LDL level, lower HDL and higher CRP level [3,4]. These are in agreement with a related study on the PDHS (Diabetics with creatinine ranging 0.7–1.0) population where age and Caucasian race were independently associated with MAC, while hypertension, hyperlipidemia, statin medication use, and increased CRP were not [13]. Unlike MESA and PDHS, we did not find female gender or diabetes independently associated with MAC. Other studies have not looked at calcium and related markers including levels of phosphate, PTH, and albuminuria in relation to MAC, but we found an elevated serum phosphate level to be independently associated with increased likelihood of MAC.

The difference between other studies and CRIC in MAC prevalence and age of onset is likely related to renal patient's dysregulation of inflammation, hormones, and electrolytes [18]. Secondary hyperparathyroidism, stimulated by decreased active vitamin D and increased phosphorus excretion in CKD, is associated with increased circulating calcium and increased risk of calcification. Hyperphosphatemia, a hallmark of CKD, contributes by depositing in the tunica media or intimal layer and acts as mediator to activate genes leading to transformation of vascular smooth muscle cells (VSMC) and pericytes to osteoblast-like cells. Calcium sensing receptors (Ca-SR) expression is decreased in uremic patients. Ca-SR suppresses PTH and is also present in endothelium, VSMC, and cardiomyocytes where they protect against calcification. Diets high in calcium and drugs designed to suppress Ca-SR have been shown to be cardioprotective [19]. Fibroblast growth factor 23 (FGF23), upregulated in CKD earlier than PTH, has been shown to stimulate vascular calcification and be a strong and independent predictor of the extent of coronary stenosis and number of stenotic vessels [20,21]. A related protein called Kothlo, which is downregulated early in CKD, is cardioprotective. In Kothlo knockout mice, there is increased phosphate transport into VSMC and increased transcription of factors that stimulate local osteoblastic transformation [22]. CKD patients also suffer from vitamin D deficiency, which stimulates vascular calcification and is associated with poor survival in ESRD and CKD [18]. Finally, inflammation is known to accelerate atherosclerosis and vascular calcification. CKD patients show upregulation of pro-inflammatory markers IL-1, IL-6, TNFα while decreased levels of anti-inflammatory proteins such as fetuin A, which prevents precipitation of calcium and phosphate in serum and whose concentration is inversely related to survival [23]. Fortunately, calcific progression, whether by these processes or others, is attenuated after kidney transplantation [24]. In CRIC, MAC subjects tended to have a lower GFR than those without MAC although this difference was not statistically significant (MAC

44.2 ± 20.3 v. 37.5 ± 12.8; p = 0.0706); similar results were found even after excluding diabetics. The finding of association between elevated phosphorus level and MAC supports the above mechanism. The lack of association with an elevated calcium level is consistent with the standard of care to maintain normal calcium intake. It is possible that no relation was found between MAC and PTH due to the well-managed calcium levels (MAC = 0, 9.31 ± 0.54; MAC > 0, 9.33 ± 0.52).

Multiple other risk factors have been associated with MAC in the general population. However, in a population that entirely suffers from CKD, these may not play a significant role. CKD patients suffer from decreased clearance of phosphorus, which is directly toxic to the tissues exposed to the bloodstream. Mechanisms related to other risk factors, such as obesity and body mass index (BMI), low HDL <40, diabetes mellitus, and female gender, may be too far upstream or insufficient in severity. These include inflammatory markers (IL-1, IL-6, TNFα or adipocytokines specific to fatty tissue) [18]; the nuclear factor kβ ligand (RANKL) – receptor activator and nuclear factor kβ (RANK) – osteoprotegerin (OPG) signaling pathway [25–27] inducing osteoclastogenesis [28–34]; cholesterol reducing and anti-inflammatory benefits of HDL [35,36]. Also, we know that the benefits of lipid lowering medications decrease with advancing kidney disease [37].

Our study had several strengths. First, CRIC is one of the largest prospective cohorts of adults with a range of CKD severity that is likely generalizable to most patients with CKD. Second, there was systematic collection of clinical and biomarker candidate predictor data. Additionally, the use of CT scanners to assess MAC diminishes false positive studies as compared to echocardiography. Our study also had several limitations. The absolute number of patients with MAC was modest—even though prevalence was higher than in other studies—and this limited our precision and ability to examine subgroups rigorously. Additionally, it is difficult to prove causation in cross-sectional studies.

This study is clinically relevant because it identifies the risk factors for MAC in patients with CKD who are not dependent on dialysis and without renal transplant. We identify several targets (signaling and inflammatory factors) for future research that have the potential to modify treatment and prevention of MAC. Additionally, if our results are validated, the presence of these risk factors could potentially prompt earlier diagnostic investigations or modification of lifestyle or medicines. It is also possible that earlier screening could discover associated conditions such as CAC prior to symptom onset. Future longitudinal studies are needed to validate these claims.

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