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Original Articles

Markers of kidney disease and risk of subclinical and clinical heart failure in African Americans: the Jackson Heart Study

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ABSTRACT

Background. African Americans and patients with chronic kidney disease (CKD) are at high risk for clinical heart failure (HF). In this study, we aimed to determine the association of markers of kidney disease with subclinical HF (by echocardiogram) and risk of clinical HF among a large, well-characterized community-based cohort of African American patients. We also examined whether the association of markers of kidney disease with HF was attenuated with adjustment for echocardiographic measures.

Methods. We studied participants in the Jackson Heart Study, a large community-based cohort of African Americans. Estimated glomerular filtration rate (eGFR) and urine albumin:creatinine ratio (ACR) were measured at baseline. We tested the association of eGFR and urine ACR with left ventricular mass (LVM), left ventricular ejection fraction (LVEF) and physician-adjudicated incident HF.

Results. Among the 3332 participants in the study, 166 (5%) had eGFR <60 mL/min/1.73 m^2 and 405 (12%) had urine ACR ≥30 mg/g. In models adjusted for demographics, comorbidity and the alternative measure of kidney disease, lower eGFR and higher urine ACR were associated with higher LVM {β-coefficient 1.54 [95% confidence interval (CI) 0.78–2.31] per 10 mL/min/1.73 m^2 decrease in eGFR and 2.87 (95% CI 1.85–3.88) per doubling of urine ACR}. There was no association of eGFR and urine ACR with LVEF [β-coefficient −0.12 (95% CI −0.28–0.04) and −0.11 (95% CI −0.35–0.12), respectively]. There was no association of eGFR with the risk of incident HF [HR 1.02 (95% CI 0.91–1.14) per 10 mL/min/1.73 m^2 decrease], while there was a significant association of urine ACR [HR 2.22 (95% CI 1.29–3.84) per doubling of urine ACR]. This association was only modestly attenuated with adjustment for LVM [HR 1.95 (95% CI 1.09–3.49)].

Conclusions. Among a community-based cohort of African Americans, lower eGFR and higher ACR were associated with higher LVM. Furthermore, higher urine ACR was associated with incident HF, which was not entirely explained by the presence of left ventricular disease.

Keywords: African Americans, chronic kidney disease, echocardiogram, heart failure, left ventricular hypertrophy

INTRODUCTION

Chronic kidney disease (CKD), defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or elevated urine albumin:creatinine ratio (ACR), affects 14% of the US population (http://www.usrds.org/adr.htm). The burden of CKD and ESRD is disproportionately high in African Americans compared with other racial/ethnic groups [1, 2]. African Americans have a faster decline in eGFR compared with whites [3–7].

Heart failure (HF) is the leading cause of cardiovascular morbidity and mortality among patients with CKD. Patients with CKD have 3-fold greater risk of HF compared with those without CKD [8], with higher rates of complications such as hospitalizations and death [9–15]. Prior studies have also reported strong associations between CKD and early changes in left ventricular structure and function, specifically elevated left ventricular mass (LVM) and decreased left ventricular ejection fraction (LVEF), even in patients without known clinical HF [16–21]. The risk of HF is particularly high among African Americans [22, 23]. Previous studies of

HF risk in CKD populations have generally had underrepresentation of African Americans or have studied primarily research populations, which may not be generalizable to African Americans with CKD in general. In a previous study of adults in the Health, Aging and Body Composition Study, the association of eGFR with incident HF was stronger in African Americans compared with whites [22]. However, this study included only older adults and did not examine other important markers of kidney damage (urine albuminuria).

Thus, in this study, we determined the association of markers of kidney disease with the risk of subclinical measures of HF (as determined by echocardiography) and the risk of incident HF among participants in the Jackson Heart Study (JHS) without clinical HF at baseline. We also examined whether the association of kidney disease with HF was attenuated with adjustment for echocardiographic measures.

MATERIALS AND METHODS

Study population

The JHS is a community-based cohort study of African Americans designed to evaluate risk factors for cardiovascular disease (CVD) [24, 25]. A total of 5301 participants ages 21–94 years were recruited from the tri-county region (Hinds, Madison and Rankin) of metropolitan Jackson, MS, USA [26]. Participants were recruited during calendar years 2000–04 and underwent a second and third in-person exam in 2005–08 and 2009–10, respectively. For this study, participants were excluded if they were missing any of our four echocardiographic measures from baseline ($n = 1915$) or serum creatinine ($n = 54$) at baseline, which left a final analytic sample of 3332. Participants who were excluded were more likely to be older and have lower income and higher comorbidity burden compared with those included in the analysis (Supplementary data, Table S1). Institutional review board approval was obtained from all participating institutions.

eGFR and urine ACR

eGFR and ACR were our primary exposures. eGFR was calculated from serum concentration of creatinine measured at baseline using the Chronic Kidney Disease Epidemiology Collaboration equation [27]. CKD was defined as eGFR <60 mL/min/1.73 m^2. Creatinine was measured using the Jaffe method and calibrated to measurements traceable to isotope dilution mass spectrometry (IDMS) [28]. The urine ACR was obtained from either 24-h urine collections or spot urine samples at Exam 1. Urinary albumin was measured by two different methods at Exam 1: a random spot morning urine collection ($n = 1589$) or a timed 24-h urine collection ($n = 570$) [29]. A subset of participants ($n = 223$) collected urine samples using both methods. The urine albumin (nephelometric immunoassay, Dade Behring) to creatinine (enzymatic Jaffe method) ratio (mg/g) was calculated for both sample types and was found to be highly correlated ($r = 0.965$) [30]. For missing ACRs, multiple imputation using chained equations with sex and age as the main predictor variables (but including all the covariates in Model 2: age, sex, education, BMI, tobacco use, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, lipid-lowering medications, history of coronary heart disease (CHD), history of stroke, history of diabetes, hemoglobin and eGFR) was conducted ($n = 1271$).

Echocardiogram measures

Echocardiograms were performed at Examination 1 by certified ultrasonography technicians (Sonos 4500 echocardiograph; Hewlett Packard, Andover, MA, USA) and following American Society of Echocardiography recommendations [29, 31]. The 2D and M-mode examination was similar to typical clinical echocardiography with parasternal, apical and subcostal windows, and assessment of all four cardiac chambers. A single observer who was blinded to participants' clinical data read all measurements. The calculation of left ventricular (LV) mass was based on the standard formula: LV mass (g) = 0.8×1.04 [(LV end diastolic diameter + IVST + PWT)^3 − (LV end diastolic diameter)^3] + 0.6, where IVST is the interventricular septal thickness and PWT is the posterior wall thickness. LV mass was divided by height$^{2.7}$ to calculate the LV mass index. Left ventricular systolic function was described in terms of the LV ejection fraction (LVEF). The LVEF was derived semiquantitatively by the primary cardiologist using a modified Quinones technique and visual assessment of the LV apex. The modified Quinones formula is as follows: LVEF = (left ventricular internal diameter in systole [LVIDS]^2 − LVIDD^2)/LVIDD^2 × 100% [32].

Incident HF

Incident HF was ascertained from Exam 2 to the end of follow-up (through 2010). Participants who died prior to Exam 2 ($n = 223$) or had prevalent HF (by self-report) at Exam 2 ($n = 36$) were excluded. To capture incident cardiovascular events and death, trained interviewers conducted annual telephone follow-up interviews to ascertain any significant health event since the last JHS contact, including diagnostic tests, hospitalizations or death. Information on cohort hospitalizations and deaths was transmitted to the medical record abstraction unit, which reviews death certificates and hospital records to identify cardiovascular events in the cohort. Interviews with the next of kin and completed questionnaires by physicians and medical examiners or coroners were used to obtain information on deaths in the cohort. The first computer-generated diagnosis during the JHS period with follow-up review and adjudication by trained medical personnel completed the final, disease-specific event classification of hospitalized and fatal cardiovascular events [33]. Ascertainment for outcomes of interest began at Exam 2. Participants were censored at death, loss to follow-up or end of the study period.

Covariates

Baseline covariates were included in the analysis. Demographic characteristics (age, sex and race), education and income were determined by self-report. Hypertension was defined by the use of blood pressure medications or blood pressure >140/90 mmHg. Diabetes was defined as fasting glucose >126 mg/dL or use of oral hypoglycemic medications or insulin. Information on tobacco use was collected from self-reports (never, former or current). Physical examination measures (systolic and diastolic blood pressure, body mass index in kg/m^2) and laboratory values (total cholesterol, LDL cholesterol,

HDL cholesterol) were obtained at each study visit. Medication use was determined by the evaluation of participant pill bottles and recorded by study personnel.

Statistical methods

We compared baseline characteristics of the study population across categories of eGFR at baseline. We reported means of our echocardiographic variables of interest across categories of eGFR and urine ACR. Urine ACR was log-transformed given the skewed distribution.

We used cubic splines to assess the function form of the unadjusted association of each kidney measure with each echocardiogram measure. In cross-sectional analyses, we used linear regression to examine the association of eGFR (per 10 mL/min/1.73 m^2 decrease and <60 versus ≥60 mL/min/1.73 m^2) and urine ACR (per doubling as a continuous variable and in >30 g/mg versus ≤30 g/mg) with LVM, left ventricular mass index (LVMI) and LVEF (all continuous). We adjusted for (i) age, sex and education; (ii) age, sex, education and other possible confounders, including BMI, tobacco use, HDL, LDL, lipid-lowering medications, history of CHD, history of stroke, history of diabetes, hemoglobin, eGFR and urine ACR and (iii) possible mediators, including systolic blood pressure, diastolic blood pressure and anti-hypertensive medications. We also tested for interaction by age and gender.

In longitudinal analyses, we calculated rates and cumulative incidence of HF per year across categories of baseline eGFR and urine ACR. We confirmed that the Cox proportional hazards assumption was not violated. We then utilized Cox proportional hazards model to examine the association of baseline eGFR and urine ACR with the risk of incident HF. We adjusted for age, sex, systolic blood pressure and the alternative measure of kidney disease in these models. In a series of 'mediation' analyses, we adjusted (individually) for LVM, LVMI and LVEF. The rationale for these models was to determine if the associations of markers of kidney disease with incident HF were attenuated with adjustment of subclinical HF at baseline.

All analyses were conducted in STATA version 13 (StataCorp, College Station, TX, USA) and P-values <0.05 were considered statistically significant.

RESULTS

Characteristics of the study population

Among the 3332 participants in the study, 166 (5%) had eGFR <60 mL/min/1.73 m^2 at baseline. Overall, participants

Table 1. Baseline characteristics of participants in the Jackson Heart Study by level of eGFR (*N* = 3332)

	eGFR (mL/min/1.73 m^2)		
	≥60	<60	Total
n	3166	166	3332
Age, years, mean (SD)	52 (12)	66 (10)	53 (13)
Male	1174 (37)	52 (31)	1226 (37)
Income			
Poor	360 (14)	41 (31)	401 (14)
Lower-middle	597 (22)	32 (24)	629 (22)
Upper-middle	814 (31)	44 (33)	858 (31)
Affluent	902 (34)	17 (13)	919 (33)
Education			
<High school	481 (15)	60 (36)	541 (16)
High school graduate	558 (18)	35 (21)	593 (18)
≥GED	730 (23)	30 (18)	760 (23)
College degree	1384 (44)	41 (25)	1425 (43)
Body mass index, kg/m^2, mean (SD)	31.4 (6.9)	31.2 (6.7)	31.3 (6.9)
Systolic blood pressure, mmHg, mean (SD)	125 (18)	132 (21)	125 (18)
Diastolic blood pressure, mmHg, mean (SD)	79 (10)	76 (12)	79 (10)
Smoking			
Never	2208 (70)	105 (64)	2313 (70)
Former	521 (17)	45 (27)	566 (17)
Current	408 (13)	14 (9)	422 (13)
Diabetes mellitus	549 (17)	77 (46)	626 (19)
Hypertension	1725 (55)	155 (93)	1880 (56)
Use of hypertension medications	1362 (55)	147 (92)	1509 (57)
Use of RAAS inhibitors	650 (21)	91 (55)	741 (22)
Use of β-blockers	266 (11)	39 (24)	305 (12)
Prevalent coronary heart disease	153 (5)	41 (25)	194 (6)
Prevalent stroke	98 (3)	20 (12)	118 (4)
Total cholesterol, mg/dL, mean (SD)	198 (39)	213 (47)	198 (40)
LDL, mg/dL, mean (SD)	126 (36)	137 (43)	126 (36)
HDL, mg/dL, mean (SD	51 (14)	52 (15)	52 (14)
Triglycerides, mg/dL, median (IQR)	87 (62–121)	108 (77–148)	87 (63–122)
Statins	287 (12)	38 (24)	325 (12)
HbA1c, %, mean (SD)	5.8 (1.2)	6.5 (1.5)	5.9 (1.2)

Values presented as *n* (%) unless otherwise noted.
GED, General Educational Development test; HbA1c, hemoglobin A1c; RAAS, renin-angiotensin-aldosterone system.

Table 2. Baseline characteristics of participants in the Jackson Heart Study by level of ACR (*N* = 3332)

	ACR	
	<30 mg/g	≥30 mg/g
n	2915	417
Age, years, mean (SD)	52 (13)	57 (13)
Male	1083 (37)	143 (34)
Income		
Poor	335 (14)	66 (18)
Lower-middle	510 (21)	119 (33)
Upper-middle	758 (31)	100 (28)
Affluent	846 (35)	73 (20)
Education		
<High school	433 (15)	109 (26)
High school graduate	510 (18)	85 (20)
≥GED	671 (23)	93 (22)
College degree	1301 (45)	130 (31)
Body mass index, kg/m^2, mean (SD)	31.1 (6.8)	33.2 (7.6)
Systolic blood pressure, mmHg, mean (SD)	124 (17)	133 (20)
Diastolic blood pressure mmHg, mean (SD)	79 (10)	80 (11)
Smoking		
Never	2047 (70)	287 (69)
Former	495 (17)	75 (18)
Current	375 (13)	55 (13)
Diabetes mellitus	451 (16)	175 (42)
Hypertension	1553 (53)	327 (78)
Use of hypertension medications	1229 (54)	280 (76)
Use of RAAS inhibitors	583 (20)	158 (38)
Use of β-blockers	244 (11)	61 (16)
Prevalent coronary heart disease	140 (5)	54 (13)
Prevalent stroke	84 (3)	34 (8)
Total cholesterol, mg/dL, mean (SD)	197 (39)	204 (42)
LDL, mg/dL, mean (SD)	126 (36)	130 (38)
HDL, mg/dL, mean (SD)	52 (14)	51 (15)
Triglycerides, mg/dL, median (IQR)	86 (61–120)	97 (71–145)
Statins	308 (11)	68 (16)
HbA1c, %, mean (SD)	5.8 (1.1)	6.6 (1.7)

Values presented as *n* (%) unless otherwise noted.
GED, General Educational Development test; HbA1c, hemoglobin A1c; RAAS, renin-angiotensin-aldosterone system.

with lower eGFR were older, more likely to be male, had lower income and lower educational attainment. Participants with lower eGFR and higher urine ACR. Also had higher systolic blood pressure, were more likely to be taking blood pressure medications and were more likely to have a history of coronary heart disease or stroke at baseline (Tables 1 and 2).

Association of markers of kidney disease with subclinical HF as determined by echocardiogram measures

In unadjusted models, every 10 mL/min/1.73 m^2 decrease in eGFR, eGFR <60 mL/min/1.73 m^2 and higher urine ACR were associated with higher LVM (Table 3). These associations remained statistically significant with adjustment for demographics, cardiovascular risk factors, eGFR (when urine ACR was predictor) and urine ACR (when eGFR was the predictor). Every 10 mL/min/1.73 m^2 decrease in eGFR was associated with 1.54 g (95% CI 0.78–2.31) higher LVM (Table 3). This association remained statistically significant even with adjustment for blood pressure and blood pressure medications,

Table 3. Cross-sectional association of markers of kidney disease with echocardiographic measures among participants in the Jackson Heart Study

	LVM, β (95% CI)	LVEF, β (95% CI)
eGFR (per 10 mL/min/1.73 m^2 decrease)		
Unadjusted	3.89 (3.17, 4.61)	0.03 (−0.10, 0.17)
Model 1	2.08 (1.67, 2.48)	−0.15 (−0.23, −0.08)
Model 2	1.54 (0.78, 2.31)	−0.12 (−0.28, 0.04)
Model 3 (mediation)	1.26 (0.52, 1.99)	−0.13 (−0.28, 0.03)
eGFR <60 mL/min/1.73 m^2 (ref ≥60 mL/min/1.73 m^2)		
Unadjusted	25.86 (19.22, 32.51)	−0.72 (−1.94, 0.49)
Model 1	18.93 (15.70, 22.16)	−1.51 (−2.13, −0.88)
Model 2	10.62 (4.34, 16.91)	−1.07 (−2.38, 0.23)
Model 3 (mediation)	11.08 (5.03, 17.13)	−1.09 (−2.40, 0.22)
ACR ≥30 g/mg (ref <30 g/mg)		
Unadjusted	22.31 (16.86, 27.77)	−0.46 (−1.60, 0.68)
Model 1	18.74 (13.71, 23.76)	−0.64 (−1.71, 0.43)
Model 2	10.98 (6.20, 15.76)	−0.51 (−1.69, 0.66)
Model 3 (mediation)	7.58 (2.65, 12.51)	−0.57 (−1.77, 0.62)
ACR (per doubling)		
Unadjusted	4.89 (3.78, 6.00)	−0.28 (−0.21, 0.15)
Model 1	4.39 (3.36, 5.42)	−0.14 (−0.35, 0.08)
Model 2	2.87 (1.85, 3.88)	−0.11 (−0.35, 0.12)
Model 3 (mediation)	1.95 (0.96, 2.95)	−0.13 (−0.36, 0.10)

Values presented as mean (95% CI) difference in LVM and LVEF.
Model 1: Adjusted for age, sex and education.
Model 2: Model 1 + BMI, tobacco use, LDL cholesterol, HDL cholesterol, lipid-lowering medications, history of CHD, history of stroke, history of diabetes, hemoglobin and eGFR/ACR (adjusting for the alternative kidney disease marker).
Model 3: Model 2 + systolic blood pressure, diastolic blood pressure and hypertension medications. ref, reference.

possible mediators of this association. In multivariable models, every doubling of urine ACR was associated with 2.87 g (95% CI 1.85–3.88) higher LVM. This association was only partially attenuated with adjustment for blood pressure and blood pressure medications. In multivariable models, there was no association of eGFR or urine ACR with LVEF. Interactions by age and gender were not statistically significant (all P > 0.05).

Association of markers of kidney disease with incident HF

Over a median of 3.36 [interquartile range (IQR) 2.73–4.47] years of follow-up, there were 84 cases of incident HF. The cumulative incidence of HF was higher in those with eGFR <60 mL/min/1.73 m^2 and urine ACR >30 mg/g (Figures 1 and 2). In unadjusted models, every 10 mL/min/1.73 m^2 decrease in eGFR was associated with a 28% higher risk of incident HF. This association was attenuated with adjustment for demographics, systolic blood pressure and urine ACR. Further adjustment for LVM and LVEF did not attenuate the point estimate. Similarly, eGFR <60 mL/min/1.73 m^2 was associated with a >3-fold greater risk of incident HF. This association was attenuated with multivariable adjustment (Table 4). Every doubling of urine ACR was associated with a 26% greater risk of incident HF. This association was attenuated but remained statistically significant with adjustment for demographics, systolic blood pressure and eGFR. Urine ACR ≥30 g/mg was associated with a >3-fold greater risk of incident HF in adjusted models. This association remained robust with multivariable adjustment. While further adjustment for LVM and LVEF somewhat attenuated the association between urine ACR ≥30 g/mg, it remained statistically significant (Table 4).

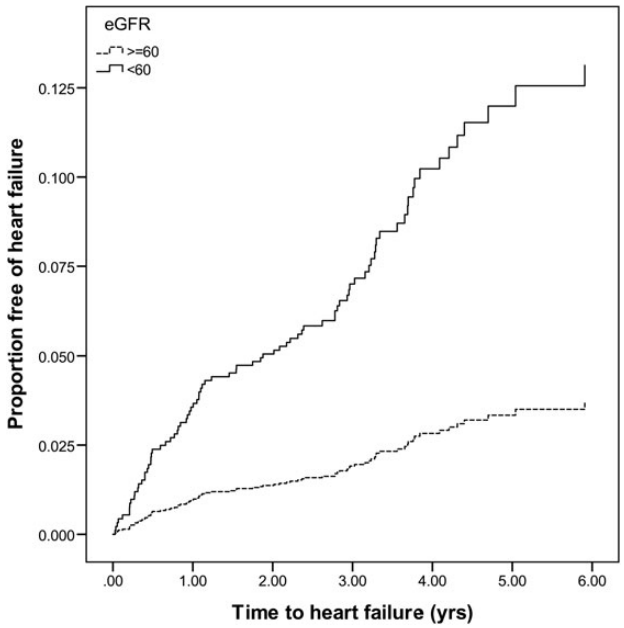

FIGURE 1: Cumulative incidence of HF by eGFR category.

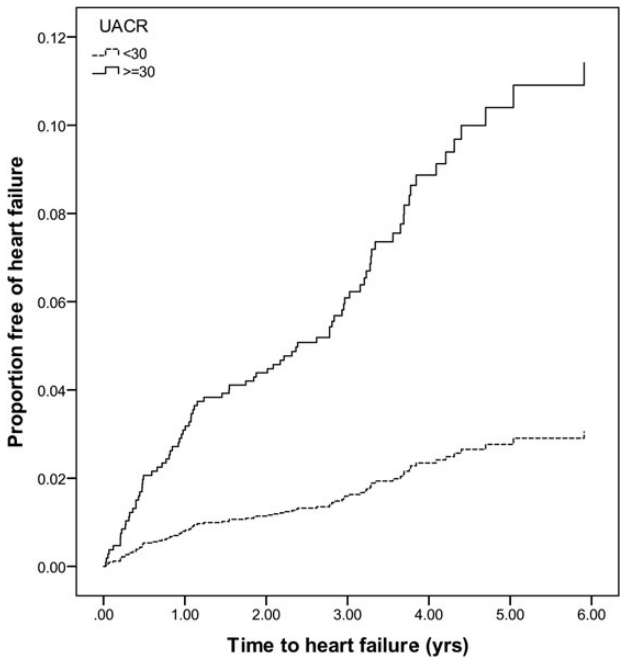

FIGURE 2: Cumulative incidence of HF by urine ACR category.

DISCUSSION

This study of African American participants from a community-based cohort found that lower eGFR and higher urine ACR were significantly associated with higher LVM and LVMI. Furthermore, urine ACR ≥30 mg/g was associated with a >2-fold higher risk of incident HF in multivariable models. This association was only partially attenuated when we adjusted for baseline echocardiographic measures. These data further support the link between kidney disease and HF risk in African Americans. While structural heart disease likely contributes to this risk of HF, our findings suggest that it may not fully explain the entire risk for HF among African Americans with kidney disease.

Our study noted an association between lower eGFR and higher urine ACR with higher LVM and LVMI. Consistent with our findings, prior studies have also noted an association of CKD with higher LVM [16–18, 21, 34]. We also found an association with even mild reductions in eGFR with higher LVM among African Americans. This is similar to the findings in a cross-sectional study of 4971 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) study, where a 1.6 greater odds for LVH was noted among participants with eGFRs between 60 and −75 mL/min/1.73 m^2 [35]. This association was consistent across race/ethnic categories, including African Americans. Interestingly, we found a strong association of urine ACR with higher LVM, independent of eGFR level. A study of young hypertensive African American men also reported an association between urine ACR with elevated LVMI [36]. In previous studies of Caucasian participants, higher urine ACR (even <30 mg/g) was associated with LVH [37, 38]. Our study extends the findings of prior reports that have shown an important link between kidney disease and subclinical HF to a large, community-based cohort of African Americans with a wide range of eGFR.

We did not find an association of lower eGFR or higher urine ACR with LVEF. This is consistent with a previous study that did not show an association between CKD and LVEF in a large CKD population [34]. In contrast, a community-based cohort of Caucasian participants found an association between eGFR and LVEF [39]. In a study of patients with HF with preserved ejection fraction, higher urine ACR was associated with greater LVEF [40]. Our study differed from these previous studies in that we included a large, relatively healthy cohort of African American participants, many of them younger in age and largely with preserved kidney function, which may explain the difference in findings. It is plausible that at this range of kidney disease, development of LVH may precede reductions in LVEF.

There was a significant association of higher urine ACR with the risk of incident HF in our study. However, the association of lower eGFR with incident HF was attenuated with multivariable adjustment. It is possible that we did not have adequate power to detect an association between eGFR and incident HF, as our results differ from prior studies. A previous study of young African American participants noted that CKD was one of the strongest predictors of incident HF [23]. Among older participants, the association of eGFR with the risk of incident HF was stronger in blacks compared with whites [22]. Similar to our findings, among clinical trial participants at high risk for incident HF, urine ACR was identified as a novel predictor of HF [41]. Another analysis noted that any level of measurable urine ACR was associated with a greater risk of CVD (including HF) [42]. These studies and ours highlight the importance of comprehensive measurement of kidney disease, which includes testing of urine ACR, in high-risk patient populations. Even in the absence of reduced eGFR, high urine albumin excretion may have important cardiovascular pathological consequences, including endothelial damage and inflammation, which may contribute to the risk of HF. This hypothesis is supported in part by clinical trials, which have shown that renin–

Table 4. Association of markers of kidney disease with risk of incident HF among participants in the Jackson Heart Study

	n	With HF, *n*	Rate/ year	Unadjusted, HR (95% CI)	Model 1,[a] HR (95% CI)	M1[a] + LVM, HR (95% CI)	M1[a] + LVMI, HR (95% CI)	M1[a] + LVEF, HR (95% CI)
eGFR (per 10 mL/min/1.73 m^2 decrease)	3073	84	0.75	1.28 (1.17–1.39)	1.02 (0.91–1.14)	0.99 (0.89–1.11)	1.01 (0.91–1.12)	1.00 (0.89–1.12)
eGFR								
≥60	2939	71	0.66	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
<60	134	13	2.51	3.78 (2.09–6.84)	1.37 (0.71–2.66)	1.09 (0.55–2.15)	1.19 (0.61–2.32)	1.24 (0.63–2.43)
ACR (per doubling)	3073	84	0.75	1.26 (1.15–1.39)	1.18 (1.06–1.32)	1.12 (1.01–1.26)	1.13 (1.01–1.26)	1.18 (1.06–1.32)
ACR								
<30	2745	61	0.60	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
≥30	328	23	2.01	3.16 (1.86–5.35)	2.22 (1.29–3.84)	1.95 (1.09–3.49)	1.98 (1.12–3.50)	2.28 (1.24–4.20)

ref, reference.
[a]Adjusted for age, sex, systolic blood pressure, ACR (for eGFR) or eGFR (for ACR).

angiotensin–aldosterone system inhibitors decrease the risk of subclinical and clinical HF across many populations [43–46].

Adjusting for echocardiographic variables from baseline only partially attenuated the association between higher urine ACR and incident HF. While structural heart disease is an important risk factor for the development of clinical HF, the pathogenesis of HF is likely very complex and multifactorial, particularly in the setting of kidney disease. Kidney disease is associated with retention of uremic toxins, impaired sodium handling, deranged mineral metabolism, inflammation and other processes, which may contribute to altered biological pathways that lead to HF. For example, alterations in FGF-23 and parathyroid hormone, which are common in the setting of kidney disease, have been linked to the development of HF [47–50]. Further understanding of the mechanisms linking kidney disease with HF may lead to effective targeted primary and secondary therapies.

Our study had several strengths. We studied a large, well-characterized community-based African American population. We had standardized echocardiogram data available that were centrally quantified. HF events were ascertained by central physician adjudication. We recognize a few limitations as well. Determination of prevalent HF (by self-report) and HF adjudication did not begin until Exam 2. Only one serum creatinine value was available and a large proportion of participants were missing urine ACR measures. Although we used multiple imputation to address the issue of missing data, we do recognize that missing data were likely accrued in a nonrandom fashion. Exposures and covariates were modeled as a single measure (rather than time-varying) due to limited availability of repeat measures of some covariates. There were relatively few participants with CKD (either by reduced eGFR or high urine ACR) at baseline, and the number of HF events was low. We had only baseline measures of our echocardiographic measures of interest. The variables diastolic dysfunction and left atrial diameter were not quantified from JHS echocardiograms. We were unable to make comparisons with other patient populations such as white Americans. The study was conducted among a community-based African American population in the South, and thus results may not be generalizable to all African American populations.

In conclusion, among participants in a community-based cohort of African Americans, lower eGFR and higher urine ACR were significantly associated with higher LVM. Additionally, there was an independent association of higher urine ACR with the risk of incident HF, which may identify urine ACR as an important modifiable risk factor in this high-risk patient population. Further studies are needed to understand the mechanisms linking early signs of kidney damage with the risk of HF in high-risk patient populations.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflicts of interest to disclose. The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health or the U.S. Department of Health and Human Services. The US Department of Veterans Affairs does not endorse any of the statements or opinions advocated by this article.

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ORIGINAL ARTICLE

Impaired vascular function contributes to exercise intolerance in chronic kidney disease

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ABSTRACT

Background. Exercise intolerance is an important feature in patients with chronic kidney disease (CKD) and is prognostic for both increased morbidity and mortality. Little is known about the underlying mechanisms in predialysis CKD. This study aimed to gain more insight into the role of vascular dysfunction in the exercise intolerance of predialysis CKD. In addition, vascular-related microRNAs (miRNAs)—as epigenetic regulators of exercise capacity—were analysed.

Methods. Sixty-three patients with CKD stages 1–5 and 18 healthy controls were included. Peak oxygen consumption (VO_2peak) was determined by cardiopulmonary exercise testing, endothelial function by flow-mediated dilation (FMD) and arterial stiffness by carotid-femoral pulse wave velocity (PWV). Plasma miRNA levels (miR-21, miR-126, miR-146a, miR-150 and miR-210) were quantified by quantitative RT-PCR.

Results. VO_2peak was already impaired in mild CKD (stages 1–3A) and significantly correlated with estimated glomerular filtration rate (eGFR; $r = 0.525$, $P < 0.001$). Likewise, both FMD and PWV were significantly correlated with eGFR ($r = 0.319$, $P = 0.007$ and $r = -0.365$, $P = 0.001$, respectively). In multiple regression analysis, PWV remained one of the strongest independent determinants of VO_2peak ($\beta = -0.301$, $P = 0.01$). Of the studied miRNA, circulating levels of miR-146a and miR-150 correlated with eGFR, PWV and VO_2peak, but the association with the latter was lost when correcting for PWV.

Conclusions. Arterial stiffness contributes to the observed reduced aerobic capacity in predialysis CKD, independent of age, haemoglobin levels and endothelial function and represents a promising therapeutic target for improving exercise capacity in this population. Future work is required to elucidate why higher circulating levels of miR-146a and miR-150 are associated with impaired renal function and increased arterial stiffness.

Keywords: arterial stiffness, chronic kidney disease, endothelial dysfunction, exercise intolerance, microRNA

INTRODUCTION

Cardiovascular disease is the main cause of morbidity and mortality in patients with chronic kidney disease (CKD) [1]. The