Asymmetric Dimethylarginine, Race, and Mortality in Hemodialysis Patients

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Abstract

Background and objectives Levels of asymmetric dimethylarginine, an inhibitor of nitric oxide synthase, are elevated in kidney disease and associated with mortality in white European hemodialysis populations. Nitric oxide production and degradation are partially genetically determined and differ by racial background. No studies have measured asymmetric dimethylarginine in African Americans on dialysis and assessed whether differences exist in its association with mortality by race.

Design, setting, participants, & measurements Asymmetric dimethylarginine was measured in 259 patients on maintenance hemodialysis assembled from 2004 to 2012 in Boston area outpatient centers. Cox proportional hazards models were used to determine the association between asymmetric dimethylarginine and all-cause mortality, and an interaction with race was tested.

Results Mean (SD) age was 63 (17) years, 46% were women, and 22% were African American. Mean asymmetric dimethylarginine in non–African Americans was 0.79 μmol/L (0.16) versus 0.70 μmol/L (0.11) in African Americans ($P<0.001$); 130 patients died over a median follow-up of 2.3 years. African Americans had lower mortality risk than non–African Americans (hazard ratio, 0.27; 95% confidence interval, 0.15 to 0.50) that was robust to adjustment for age, comorbidity, and asymmetric dimethylarginine (hazard ratio, 0.35; 95% confidence interval, 0.17 to 0.69). An interaction was noted between race and asymmetric dimethylarginine ($P=0.03$), such that asymmetric dimethylarginine was associated with higher mortality in non–African Americans (adjusted hazard ratio, 1.29; 95% confidence interval, 1.06 to 1.57 per 1 SD higher asymmetric dimethylarginine) but not in African Americans (adjusted hazard ratio, 0.57; 95% confidence interval, 0.28 to 1.18). Additional adjustment for fibroblast growth factor 23 partially attenuated the association for non–African Americans (adjusted hazard ratio, 1.22; 95% confidence interval, 0.98 to 1.50).

Conclusions African Americans have lower asymmetric dimethylarginine levels and lower hazard for mortality compared with non–African Americans. Levels of asymmetric dimethylarginine did not explain lower hazard for mortality in non–African American patients. High asymmetric dimethylarginine was a risk factor for mortality exclusively in non–African Americans. Mechanisms explaining these relationships need to be evaluated.

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Introduction

Levels of asymmetric dimethylarginine (ADMA), an inhibitor of nitric oxide synthase, are known to be elevated in patients with kidney disease (1,2). ADMA decreases blood vessel compliance and promotes atherogenesis (3). High ADMA levels have previously been shown to be an independent risk factor for mortality in both patients with CKD and patients on hemodialysis (4–6). However, these previous studies have predominantly been conducted in Europe, resulting in findings that are only generalizable to Caucasian patients.

Multiple reports have shown that African American patients on hemodialysis have better survival than non–African American patients on hemodialysis (7–10). Although it has been suggested that younger age, faster progression toward ESRD, and a lower prevalence of comorbidity may result in overall healthier African American patients on dialysis, these factors do not fully explain the magnitude of this phenomenon. Nitric oxide generation and degradation are strongly influenced by gene polymorphisms, which may be conserved by racial background (11–13). African Americans are more likely to benefit from treatments for heart failure that target nitric oxide pathways, with genetic differences perhaps explaining this treatment effect (14,15). Despite these findings, levels of ADMA in patients on hemodialysis have not been previously evaluated as a potential mechanism for different mortality rates by race. We, therefore, measured baseline ADMA and L-arginine, a precursor of nitric oxide, in a cohort of patients on prevalent hemodialysis. We then evaluated the baseline factors associated with ADMA levels, evaluated whether ADMA explained any of the difference in mortality rates between African American and non–African

American patients, and explored its association with mortality in African Americans and non–African Americans.

Materials and Methods

Study Population

This study is a secondary analysis of data from the Cognition and Dialysis study cohort, the details of which have been described in greater detail elsewhere (16). Briefly, patients receiving chronic in-center hemodialysis at five Dialysis Clinic Inc. (DCI) units or one hospital-based unit (St. Elizabeth's Medical Center) in the greater Boston area were evaluated for study enrollment from January 28, 2004, to May 31, 2012. Reflecting the primary study goal of assessing cognitive performance, eligibility criteria included English fluency as well as sufficient visual and hearing acuity to complete cognitive testing. Individuals with advanced dementia on the basis of medical record review were excluded. Nonvascular access–related hospitalization within 1 month, delirium, receipt of hemodialysis for <1 month, and single-pool Kt/V<1.0 were temporary exclusion criteria. The Tufts Medical Center/Tufts University Institutional Review Board approved the study, and all participants who underwent cognitive testing signed informed consent forms. The clinical and research activities being reported are consistent with the Declaration of Helsinki.

Baseline Demographics and Clinical Characteristics

Demographic, clinical, and laboratory characteristics were ascertained at the time of study enrollment. Demographic data (age and sex) were obtained through participant report, review of medical charts, and the DCI and St. Elizabeth's Medical Center databases. Education (<12th grade, high school graduate, or ≥2 years of college) and smoking history (never, current, or past smoker) were obtained through a standardized patient questionnaire. Race assignment was determined by patient self-classification. Medical history, including history of cardiovascular disease (a composite of a history of either coronary artery disease or peripheral vascular disease), stroke, heart failure (HF), and presence of diabetes, was defined by patient history or documentation in the patient's electronic or paper charts. The cause of ESRD, time since start of hemodialysis (dialysis vintage), and any activated vitamin D use within 2 weeks of cognitive testing were obtained from the DCI or St. Elizabeth electronic record along with the mean monthly predialysis systolic and diastolic BPs. Predialysis blood tests, including serum phosphorus, serum albumin, and single-pool Kt/V, were obtained on the day of study enrollment. High-sensitivity C-reactive protein (CRP) and fibroblast growth factor 23 (FGF-23) levels (C-terminal ELISA assay; Immutopics, Inc.) were measured at a later date from stored frozen samples taken at study enrollment. All DCI laboratory tests were measured in a central laboratory in Nashville, Tennessee.

Measurement of ADMA

Samples were available for testing in 259 patients. Each sample was collected predialysis, centrifuged, and frozen at −80°C, and it had not been previously thawed before testing. ADMA and L-arginine were measured by HPLC in batched assays at the University of Padua (17). Control samples were run with each batch to assess the reproducibility of test results. The coefficient of variation for the control samples was 5.5% for ADMA and 7.7% for L-arginine, similar to previously reported results using this method (18).

Outcomes

We obtained survival status on all patients enrolled in the study by review of the electronic medical record and/or contact with each individual dialysis unit. Survival time was defined as the period of time elapsed from initial study enrollment and blood sample measurement to death, receipt of kidney transplantation (censoring event), or end of study follow-up (March 31, 2013).

Statistical Analyses

Descriptive characteristics of the study population were reported as proportions for categorical and binary variables, means with SDs for continuous normally distributed variables, and medians with interquartile ranges for skewed variables. To better assess differences across ADMA level, the study population was divided into quartiles. Linear trends across quartiles were assessed using linear regression for continuous variables and the Cochrane–Armitage test for binary variables.

Baseline Correlates of ADMA Level

The association of baseline characteristics with ADMA level was assessed using univariate and multivariable linear regression. Continuous variables were expressed per SD to better allow for comparison across variables. A history of cardiovascular disease was forced into the multivariable models given its known association with ADMA levels, whereas selection of the remaining terms was on the basis of a P value of <0.10 for linear trend across quartiles of ADMA.

Mortality Analyses

Race and Mortality. The association between race and all-cause mortality was assessed using Cox proportional hazards models; a univariate model explored the association between race and time to all-cause mortality, whereas a parsimonious model adjusted for age and sex. An expanded model also adjusted for dialysis vintage, vascular access type, history of cardiovascular disease, diabetes, and HF, and a final model added adjustment for ADMA.

ADMA and Mortality. A second set of models explored the univariate association between ADMA level and all-cause mortality, whereas sequentially adjusted multivariable models first evaluated the addition of age and sex, and an expanded model included additional adjustment for dialysis-specific factors potentially associated with mortality, including diabetes, dialysis vintage, vascular access type, history of cardiovascular disease, and HF. Hazard ratios (HRs) are presented per 1 SD-higher ADMA. To assess for differences by race, we included an interaction term for race and ADMA level in the final multivariable model. Using this model, an interaction plot was created to show the predicted HR for mortality by level of continuous ADMA compared with the reference value of mean ADMA

level and non–African American stratified by African American and non–African American.

We performed several sensitivity analyses. First, to assess for any overt deviation from linearity, the association of quartiles of ADMA with mortality was assessed. Second, to explore whether any additional potential confounding variables may affect the relationship between ADMA and mortality in both the overall cohort and the ADMA–race interaction model, we additionally adjusted for variables that showed a trend to being different across quartiles of ADMA ($P<0.10$): FGF-23, phosphorus, diastolic BP, and body mass index. Three additional factors that may be associated with mortality, albumin, high-sensitivity CRP, and activated vitamin D use were also included in these models. Finally, because some have argued that the L-arginine-to-ADMA ratio is better correlated with nitric oxide production capacity (19), we assessed the relationship between the L-arginine-to-ADMA ratio (higher ratio means more nitric oxide production capacity) and all-cause mortality in similar models. We also tested for an interaction between L-arginine-to-ADMA ratio, race, and mortality.

Results

Baseline Characteristics

The mean (SD) age of the study population was 63 (17) years, 118 (46%) patients were women, and 56 (22%) patients were African Americans. Most patients had arteriovenous fistulas as a form of vascular access (66%), and the median (25th–75th) dialysis vintage was 14 (6.4–33.5) months. The mean (SD) ADMA level was 0.77 (0.15) μmol/L, and the mean L-arginine level was 139.0 (44.6) μmol/L, yielding a mean L-arginine-to-ADMA ratio of 189.5 (69.5). ADMA levels were 0.79 (0.16) μmol/L in non–African American patients versus 0.70 (0.11) μmol/L in African American patients ($P<0.001$), whereas L-arginine and the L-arginine-to-ADMA ratio did not differ by race (Supplemental Table 1).

Correlates of ADMA

Patients in the higher quartiles of ADMA were more likely to be non–African American, have a history of HF and a history of diabetes, and have higher levels of phosphorus and FGF-23 levels (Table 1). In a multivariable model adjusting for age, sex, race, history of HF, history of cardiovascular disease, serum phosphorus, and FGF-23, African American race was associated with ADMA; African Americans had a -0.10 μmol/L (95% confidence interval [95% CI], -0.05 to -0.14) lower ADMA level compared with non–African Americans (Table 2). Women had higher ADMA (0.06 μmol/L; 95% CI, 0.02 to 0.09), whereas patients with diabetes, history of HF, and higher FGF-23 level also had higher ADMA levels. Age and history of cardiovascular disease were not associated with ADMA in multivariable analysis.

All-Cause Mortality

There were 130 deaths (118 deaths in non–African Americans and 12 deaths in African Americans) over a median follow-up time of 2.3 (interquartile range=1.2–3.8) years, with death rates of 23.2 and 7.1 per 100 person-years among non–African Americans and African Americans, respectively; 21 (10%) non–African American patients underwent kidney transplantation and were censored, in contrast to 11 (20%) of African American patients. Compared with non–African American patients, African American patients had a significantly lower hazard for mortality (HR, 0.27; 95% CI, 0.15 to 0.50) in unadjusted models (Supplemental Table 2). A model with adjustment for age and sex (HR, 0.42; 95% CI, 0.23 to 0.79) and an expanded model with additional adjustment for cause of ESRD, dialysis vintage, history of cardiovascular disease, and vascular access type (HR, 0.32; 95% CI, 0.16 to 0.62) showed slight attenuation of the relationship between African American race and mortality. Similar results were seen when adjusting for ADMA in the final multivariable model (HR, 0.35; 95% CI, 0.17 to 0.69).

Association of ADMA with Mortality

In univariate analysis, each 1 SD (0.15 μmol/L)-higher ADMA was associated with a 22% higher risk for all-cause mortality for the total cohort. The risk remained relatively unchanged in a parsimonious model adjusting for age and sex as well as in an expanded model adjusting for age, sex, dialysis vintage, vascular access type, history of cardiovascular disease, history of congestive HF, and diabetes (Table 3). There was a significant interaction between race and ADMA level ($P=0.03$) (Figure 1), such that ADMA was associated with mortality in non–African Americans (adjusted HR, 1.29; 95% CI, 1.0 to 1.57 per 1 SD-higher ADMA) but not in African Americans (adjusted HR, 0.57; 95% CI, 0.28 to 1.18 per 1 SD-higher ADMA) (Table 3).

Sensitivity Analyses

The fourth quartile of ADMA was associated with significantly higher risk than the first quartile, with the second and third quartiles also showing higher hazards but not being statistically different from the first quartile (Table 3). A model with additional adjustment for serum phosphorus, albumin, high-sensitivity CRP, diastolic BP, body mass index, and activated vitamin D use revealed similar HRs to the main model. Additional adjustment for FGF-23 partially attenuated the HR for mortality in non–African Americans (adjusted HR per 1 SD-higher ADMA, 1.22; 95% CI, 0.98 to 1.50) but did not change the HR for African Americans (adjusted HR, 0.55; 95% CI, 0.26 to 1.15 per 1 SD-higher ADMA). Notably, the interaction with race remained significant ($P=0.04$).

The L-arginine-to-ADMA ratio was inversely associated with all-cause mortality in univariate analysis (HR, 0.78; 95% CI, 0.66 to 0.93 per 1 SD higher) and a parsimonious model adjusting for age and sex (HR, 0.78; 95% CI, 0.65 to 0.93). The relationship was attenuated and nonsignificant in an expanded model adjusting for age, sex, cause of ESRD, dialysis vintage, history of cardiovascular disease, and vascular access type (HR, 0.85; 95% CI, 0.70 to 1.03). The P value for the interaction of L-arginine-to-ADMA and race was 0.16.

Discussion

In a cohort of patients on maintenance hemodialysis, we noted that ADMA levels were lower in African American than non–African American patients. African American race was strongly associated with a lower hazard for

Table 1. Demographics and clinical characteristics by quartile of asymmetric dimethylarginine

Qs of ADMA (*n*=259)	ADMA Q1 (*n*=66)	ADMA Q2 (*n*=62)	ADMA Q3 (*n*=67)	ADMA Q4 (*n*=64)	Trend *P* Value
ADMA (μmol/L)	0.58±0.06	0.71±0.03	0.80±0.03	0.98±0.08	—
L-Arginine (μmol/L)	127.1±36.3	133.7±41.9	145.7±44.1	149.6±52.0	0.004
L-Arginine-to-ADMA ratio	219.6±60.9	188.8±60.5	181.6±56.3	152.7±49.3	<0.001
Age (yr)	61.7±16.8	60.8±18.5	63.4±16.5	66.6±15.0	0.08
Women	36	47	48	52	0.09
African American	32	26	24	5	<0.001
HF	26	29	37	47	<0.01
Stroke	9	18	25	14	0.26
CVD	41	37	42	47	0.42
Diabetes	39	39	54	55	0.03
Active vitamin D use (%)	58	53	67	60	0.41
Primary cause of ESRD					
Diabetes	35	26	33	39	0.84
Hypertension	15	19	22	17	
Other	15	16	19	9	
Unknown	14	23	15	11	
GN	21	16	10	23	
Smoking history					
Never	32	40	43	41	0.50
Past	61	45	46	52	
Current	8	15	10	6	
Dialysis access					
Fistula	71	55	69	70	0.81
Graft	2	10	9	3	
Catheter	27	35	22	27	
Vintage (mo)	15.0 (5.0–37.5)	13.1 (6.5–35.4)	15.0 (7.8–29.1)	14.0 (4.9–30.9)	0.88
Systolic BP (mmHg)	140±18	143±22	141±20	140±24	0.95
Diastolic BP (mmHg)	74±10.6	75±15	73±11	70±12	0.09
Kt/V	1.54±0.20	1.50±0.25	1.52±0.27	1.49±0.25	0.23
Albumin (g/dl)	3.8±0.3	3.8±0.3	3.8±0.4	3.8±0.3	0.80
Phosphorus (mg/dl)	5.2±1.4	5.7±1.7	5.9±1.4	5.6±1.5	0.03
CRP (mg/L)	4.5 (1.6–16.4)	4.7 (1.8–9.6)	5.0 (2.3–11.9)	7.1 (2.6–16.6)	0.51
FGF-23 (RU)	1750 (931–5660)	1806 (936–7739)	3655 (1333–8682)	4151 (1784–9038)	0.004

Presented as mean±SD, median (interquartile range), or percentage. Q, quartile; ADMA, asymmetric dimethylarginine; HF, heart failure; CVD, cardiovascular disease (composite of history of peripheral vascular disease or coronary artery disease); CRP, high-sensitivity C-reactive protein; FGF-23, fibroblast growth factor 23; RU, relative units.

mortality. This finding was only slightly attenuated in multivariable analyses, including adjustment for ADMA. We also noted an interaction between African American race and ADMA, such that high ADMA was associated with mortality only in non–African American participants, although this finding was partially attenuated after additional adjustment for FGF-23. In contrast to ADMA alone, the L-arginine-to-ADMA ratio was inversely associated with mortality in univariate and demographic-adjusted analyses but not the expanded multivariable analyses.

ADMA, a potent inhibitor of nitric oxide synthase, has been previously shown to adversely affect blood vessel compliance as well as promote atherosclerosis (3,20). ADMA levels are known to increase as kidney function declines because of both decreased renal clearance and impairment of enzymatic breakdown (1). We found several factors associated with high ADMA, including non–African American race, women, diabetes, history of HF, and FGF-23 level. Two prior studies have examined factors associated with ADMA. A study of 820 patients with stages 3 and 4 CKD showed that higher ADMA levels were associated with prevalent cardiovascular disease and reduced GFR (6). A second study of 90 patients on maintenance hemodialysis noted an association between CRP and ADMA (21). In comparison, our study showed no relationship between baseline cardiovascular disease or CRP and ADMA, although the related conditions, diabetes and HF, did show associations, perhaps indicating a shared pathophysiology. The differences in the findings may be because of the differences in the study populations, including different stages of CKD (6), different prevalence of cardiovascular disease and diabetes (4), and different demographics of the study population (4). The association between a history of HF and ADMA may be consistent with a recent study showing that ADMA may be useful in diagnosing acute HF (22). Finally, we noted an association between higher FGF-23 level and higher ADMA, a finding seen in a previous study of patients with stages 3 and 4 CKD (23) but not previously reported in patients on hemodialysis.

Table 2. Association between baseline characteristics and asymmetric dimethylarginine

Baseline Characteristics	Univariate		Multivariable[a]	
	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Age (per 1 SD increase)	0.02 (<−0.01 to 0.03)	0.14	0.01 (−0.01 to 0.03)	0.45
Men versus women	−0.05 (−0.08 to −0.01)	0.02	−0.06 (−0.09 to −0.02)	0.002
African American versus non–African American	−0.09 (−0.04 to −0.13)	<0.001	−0.1 (−0.14 to −0.05)	<0.001
Diabetes	0.05 (0.02 to 0.09)	<0.01	0.06 (0.02 to 0.1)	<0.01
HF	0.06 (0.02 to 0.09)	<0.01	0.04 (0.01 to 0.08)	0.03
History of CVD	0.02 (−0.02 to 0.06)	0.36	−0.01 (−0.06 to 0.03)	0.50
Phosphorus (per 1 SD increase)	0.02 (<−0.01 to 0.03)	0.06	0.01 (−0.01 to 0.03)	0.55
Log FGF-23 (per doubling)	0.01 (<0.01 to 0.02)	0.01	0.02 (0.01 to 0.03)	0.004

CVD, cardiovascular disease (composite of history of peripheral vascular disease or coronary artery disease); 95% CI, 95% confidence interval.
[a]Multivariable model is adjusted for all listed covariates.

Table 3. Association of asymmetric dimethylarginine level and mortality in overall cohort and with interaction with race

Asymmetric Dimethylarginine	Unadjusted HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Total cohort			
Continuous	1.22 (1.03 to 1.44)	1.25 (1.04 to 1.49)	1.22 (1.01 to 1.47)
Quartile 1	Reference	Reference	Reference
Quartile 2	1.23 (0.73 to 2.08)	1.24 (0.73 to 2.10)	1.12 (0.66 to 1.93)
Quartile 3	1.22 (0.73 to 2.04)	1.19 (0.71 to 2.00)	1.12 (0.67 to 1.90)
Quartile 4	1.91 (1.15 to 3.17)	1.97 (1.17 to 3.34)	1.84 (1.08 to 3.12)
Interaction with race			
African American[c]	0.65 (0.30 to 1.44)	0.66 (0.31 to 1.40)	0.57 (0.28 to 1.18)
Non–African American[c]	1.16 (0.98 to 1.38)	1.30 (1.08 to 1.56)	1.29 (1.06 to 1.57)

HR per 1 SD change in asymmetric dimethylarginine (0.15 μmol/L), except for quartile analysis. HR, hazard ratio.
[a]Model 1: adjusted for age and sex.
[b]Model 2: adjusted for age, sex, dialysis vintage, vascular access type, history of cardiovascular disease, history of congestive heart failure, and diabetes.
[c]Models include interaction term between African American race and asymmetric dimethylarginine.

We noted lower levels of ADMA in African Americans versus non–African Americans in univariate and multivariable analyses. Among patients with normal kidney function, there are conflicting reports about racial differences in ADMA level. A study of 30 healthy black Africans and 28 age-matched white Europeans showed higher ADMA in black versus white patients (0.34 versus 0.25 μmol/L) (24), whereas a significantly larger study of over 900 older United States residents showed that black patients had modestly but statistically significant lower ADMA levels compared with white patients (0.60 versus 0.63 μmol/L) (25). We are not aware of prior studies of ADMA that have formally reported racial differences in patients with kidney disease, because most prior studies were conducted in Europe or Japan and did not include participants of African ancestry (4,26,27).

We confirmed that African American race was associated with a lower risk for mortality compared with non–African American race. Although the African American group was younger and had a lower prevalence of cardiovascular disease, adjustment for these differences did not change the risk for mortality. Furthermore, adjustment for ADMA level only slightly attenuated this association, suggesting that the lower ADMA levels in African Americans do not significantly explain this mortality difference. African American race has been associated with longer survival on dialysis in multiple previous studies (7–10). Several possible mechanisms have been proposed for this phenomenon, including a younger average age at start of dialysis, fewer comorbid conditions, and, perhaps, a more rapid decline in kidney function and, therefore, survivor bias in those patients who reach ESRD. However, even when these factors are considered, there still seems to be a survival benefit of being African American, indicating that additional research is needed. In support of this finding, a recent study of patients with CKD also showed improved survival in African Americans, even after adjusting for case-mix differences, suggesting that a survival advantage may exist even before the onset of ESRD (28).

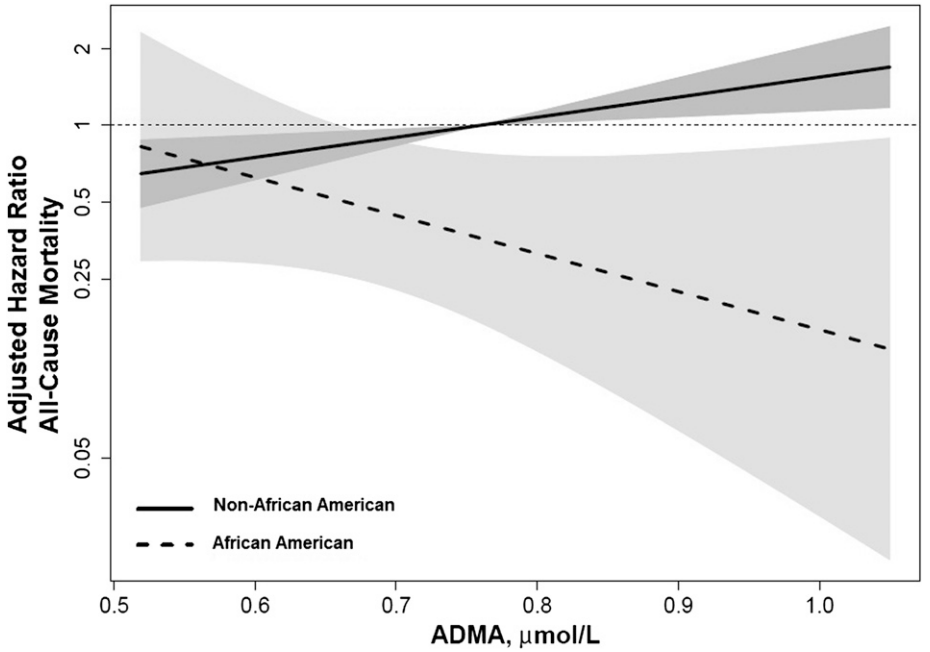

Figure 1. | **Interaction plot between ADMA, all-cause mortality, and race.** Final multivariable model was adjusted for age, sex, dialysis vintage, vascular access type, history of cardiovascular disease, history of heart failure, and diabetes. Hazard ratios are compared with a reference mean ADMA level in non–African Americans (0.79 μmol/L). Shading represents the 95% confidence interval for each race. AMDA, asymmetric dimethylarginine.

In this study, high ADMA was associated with a higher risk of mortality in non–African American patients. ADMA levels have been previously associated with a higher risk for mortality in both patients with CKD and patients on hemodialysis. Two previous studies in cohorts of patients with CKD showed that high ADMA was associated with a modestly higher risk for mortality (5,6). Notably, this association remained unchanged in each study after adjustment for a history of cardiovascular disease and vascular disease risk factors. Extending this finding to hemodialysis, a study of 225 patients also showed that high ADMA was an independent risk factor for mortality (4). Finally, ADMA has been shown to be independently associated with a higher risk for mortality in a cohort of community-dwelling participants without evident kidney disease (29). In our cohort, we also found that the association between ADMA and mortality in non–African American patients persisted even after adjustment for multiple comorbid conditions and laboratory values. Additional adjustment for FGF-23, however, partially attenuated the relationship. One prior study found an association between ADMA and FGF-23 and reported that ADMA attenuated the relationship between FGF-23 and flow-mediated dilation of the forearm (23). It was suggested by Yilmaz *et al.* (23) that ADMA and FGF-23 may share a common pathway for inducing vascular dysfunction. Therefore, it remains unclear whether the attenuation seen in our findings is caused by either a shared pathway (where one would not want to adjust for the FGF-23) or true confounding (where adjustment is appropriate).

We also found an inverse relationship between the L-arginine-to-ADMA ratio and all-cause mortality in our univariate and parsimonious models, although the association was attenuated when adjusting for comorbid conditions. Although no studies have previously assessed this relationship in patients with kidney disease, a previous study of patients with HF noted that the L-arginine-to-ADMA ratio was independently associated with mortality (30). L-Arginine acts as a substrate for nitric oxide synthase in the production of nitric oxide; thus, it has been argued that the ratio of L-arginine to ADMA may be reflective of nitric oxide production capacity (19).

We noted a significant interaction of ADMA with race, such that ADMA was only associated with mortality within non–African American patients. High ADMA within African American patients was associated with lower risk for mortality, although this result was not statistically significant. Potential mechanisms for these differences by race could reflect the mechanism of the action of ADMA as an inhibitor of nitric oxide. Racial differences in nitric oxide production have been described in patients without kidney disease that have been attributed to gene polymorphisms that alter the function nitric oxide synthase (11,31,32). Additionally, ADMA level is strongly influenced by dimethylarginine dimethylaminhydrolase (DDAH), an enzyme responsible for ≤80% of the metabolism of ADMA (33). Genetic polymorphisms in DDAH genes have been associated with variation in ADMA levels in humans (12), and animal studies involving knockout/gain of function of DDAH have raised/lowered ADMA levels with a subsequent effect on vascular health. There is additional evidence that, in addition to influencing ADMA levels, DDAH may also directly influence vascular health, independent of ADMA (34). We hypothesize that

DDAH polymorphisms may be responsible for both the lower ADMA levels that we observed in African American patients and, possibly, the lack of association between ADMA and mortality. Perhaps reflecting these findings, African Americans also seem to have a different response than other races to nitric oxide–related treatments (14).

There are several limitations to our study. First, the patient population in our cohort was selected as part of a study evaluating cognition, which may have resulted in a population that is not fully generalizable. Our cohort, by design, excluded patients acutely ill as well as patients with severe cognitive impairment, which may bias to a healthier population. However, we note that our cohort is comparable in terms of demographics (age, sex, and race) and vascular disease prevalence with the overall hemodialysis population in the United States (35). Second, the statistical power to detect an association between ADMA and mortality within African Americans is limited by a smaller number of outcomes in this subgroup. As a result, we are limited to stating that an association with ADMA was detected only within non–African American patients. In addition, we do not have a direct measure of residual renal function, which may partially affect ADMA levels. To partially address this limitation, we included dialysis vintage in the adjusted analyses, because those patients with longer vintage are likely have less residual kidney function. Third, we acknowledge that, given the observational nature of the study, both residual and unmeasured confounding are possible. This study also has several strengths, including a detailed ascertainment of medical history and comprehensive laboratory testing on all cohort patients. Given the design of the study, we also have detailed follow-up of participants, allowing for accurate ascertainment of the time of death and censoring events.

In conclusion, we showed lower levels of ADMA in African American versus non–African American patients on hemodialysis. ADMA level was associated with all-cause mortality, a finding that was exclusive to non–African American patients on hemodialysis. We also confirmed a lower hazard for mortality in African American patients versus non–African American patients, and this difference was not explained by ADMA levels. Given the modest sample size, these exploratory findings should be replicated in larger cohorts of patients on hemodialysis with diverse racial/ethnic backgrounds. The mechanism underlying our results should also be further evaluated.

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Disclosures

None.

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