Association of Race/Ethnicity, Inflammation, and Albuminuria in Patients With Diabetes and Early Chronic Kidney Disease

Satyesh K. Sinha,[1] Magda Shaheen,[1] Tripathi B. Rajavashisth,[1,2] Deyu Pan,[1] Keith C. Norris,[1,2] and Susanne B. Nicholas[1,2]

OBJECTIVE

African Americans (AAs) and Hispanics have higher diabetes and end-stage renal disease but similar or lower early chronic kidney disease (CKD) compared with whites. Inflammation plays a critical role in the pathogenesis of diabetes-related CKD. We postulated that in contrast to the general population, AAs and Hispanics have a higher prevalence of early diabetic CKD and systemic inflammatory markers compared with whites.

RESEARCH DESIGN AND METHODS

We analyzed the National Health and Nutrition Examination Survey 1999–2008 of 2,310 diabetic patients aged ≥20 years with fasting plasma glucose (FPG) ≥126 mg/dL. We performed multiple linear regression among patients with early CKD (urinary albumin excretion [UAE] ≥30 μg/mL and estimated glomerular filtration rate ≥60 mL/min/1.73 m^2) to test the relationship between UAE and C-reactive protein (CRP) by race/ethnicity, adjusting for demographics, diabetes duration, FPG, hemoglobin A_{1c}, uric acid, white blood cell count, medication use, cardiovascular disease, and related parameters.

RESULTS

In patients with diabetes, the prevalence of early CKD was greater among Hispanics and AAs than whites ($P < 0.0001$). AAs had higher adjusted odds ratio (AOR) for CRP ≥0.2 mg/dL (AOR 1.81 [95% CI 1.19–2.78]), and Hispanics had higher AOR for UAE ≥30 μg/mL (AOR 1.65 [1.07–2.54]). In a regression model adjusted for confounding variables, there was a significant association between UAE and CRP in the mid-CRP tertile (CRP 0.20–0.56 mg/dL, $P = 0.001$) and highest CRP tertile (CRP ≥0.57 mg/dL, $P = 0.01$) for Hispanics, but only in the mid-CRP tertile ($P = 0.04$) for AAs, compared with whites.

CONCLUSIONS

AAs and Hispanics with diabetes have a higher prevalence of early CKD compared with whites, which is significantly associated with UAE and/or CRP.

Diabetes Care 2014;37:1060–1068 | DOI: 10.2337/dc13-0013

[1]Department of Research, Charles R. Drew University of Medicine and Science, Los Angeles, CA
[2]Department of Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA

Corresponding author: Satyesh K. Sinha, satyeshsinha@cdrewu.edu.

Received 2 January 2013 and accepted 18 December 2013.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-0013/-/DC1.

Rapidly increasing rates of diabetes mellitus (DM) throughout the developed world represent an emerging epidemic with profound consequences. Approximately 30% of patients with DM develop chronic kidney disease (CKD), accounting for ~45% of end-stage renal disease (ESRD) cases in the U.S. (1). Racial/ethnic minority populations are disproportionately affected by DM and its complications (2). The 2012 United States Renal Data System report showed the incidence of new ESRD cases in African Americans (AAs) and Hispanics was, respectively, 3.4 and 1.8 times higher than whites (1). Further, the incidence of ESRD attributed to DM or hypertension was found to be 12 times higher among AAs compared with whites in a 12-year follow-up cohort study of 9,082 AA and white adults between 30 and 74 years of age (3). However, in the general population, the prevalence of early CKD was not found to be elevated in minorities, suggesting a racial/ethnic difference in CKD progression (4). Although the etiologic causes for the increased rate of progression of CKD- and DM-related ESRD in AAs and Hispanics compared with whites remains unclear, it appears to involve both sociocultural and biologic factors (5).

Inflammation plays a central role in the pathogenesis of many renal diseases (6,7). Studies suggest that inflammatory mechanisms significantly contribute to the development and progression of CKD (8,9). Epidemiological studies have shown that C-reactive protein (CRP), the most extensively studied inflammatory marker, is associated with microalbuminuria in diabetic patients and in the general population (10–13). Inflammation has been reported in the early stages of CKD (estimated glomerular filtration rate [eGFR] >90 mL/min/1.73 m^2 and microalbuminuria) in patients with type 1 DM (14,15). Despite the knowledge that AAs and Hispanics are disproportionately affected by CKD, and the potential role of inflammation in the pathophysiology of early CKD, little is known about the potential contribution that inflammation may play in racial/ethnic disparities when the eGFR is still preserved. We postulated that in contrast to the general population, the prevalence of early CKD in patients with primarily type 2 DM would be higher in AAs and Hispanics than in whites. In the current study, we tested this hypothesis in the National Health and Nutrition Examination Survey (NHANES) 1999–2008 and speculated that elevated levels of systemic inflammatory markers in general, and CRP in particular, may be associated with the posited increase in early CKD (eGFR ≥60 mL/min/1.73 m^2 and urinary albumin excretion [UAE] ≥ 30 μg/mL) in racial/ethnic minorities.

RESEARCH DESIGN AND METHODS

Study Population

The study included participants of the NHANES 1999–2008, conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). NHANES used a highly stratified multistage probability sampling (total *N* = 51,623) and used oversampling of the elderly (*n* = 7,094), non-Hispanic blacks (*n* = 7,765), and Hispanics (*n* = 8,688). Descriptions of the survey, sampling procedures, and details of the laboratory tests evaluated can be found on the CDC website (http://www.cdc.gov/nchs/nhanes/nh3rrm.htm#refman).

Analysis was limited to adults ≥20 years of age, because those <20 years of age did not have plasma glucose tested. Patients with missing race/ethnicity or classified as "other" (*n* = 117) and those with missing laboratory data (*n* = 335) were excluded. The total analytic sample was 2,310 adults with DM (early CKD [*n* = 693] and those with no CKD [*n* = 1,459]). Patients with late CKD (eGFR <60/mL/min/1.73 m^2) were also excluded from the analysis (Supplementary Fig. 1).

Study Variables

Data on race/ethnicity were collected by self-report. Subjects were classified as AA (*n* = 647), Hispanic (*n* = 799), white (*n* = 864), and Asian/other (*n* = 91). Subjects were defined as having DM if they answered "yes" to the question "Have you ever been told you have sugar/diabetes?" (*n* = 2,038) or had a fasting plasma glucose (FPG) level ≥126 mg/dL (*n* = 1,508). Of the 2,310 participants with DM, 2,292 participants answered the question regarding the use of insulin, and of these, 462 participants said they take insulin. Of those, one participant said he began using insulin before 20 years of age, the majority being likely to have type 2 DM, although a few may have type 1 DM. Thus, 0.03% participants with DM (unadjusted) have type 1 DM and because of this low number, all subjects with DM were analyzed together. There was no difference in any of our analyses if the one participant <20 years of age was excluded.

Data were analyzed for age, sex, race/ethnicity, history of hypertension, cardiovascular disease (CVD), smoking, use of metformin, pioglitazone, statin, ACE inhibitors (ACEIs), and angiotensin receptor blockers (ARBs), systolic and diastolic blood pressure (SBP and DBP), BMI, duration of DM, FPG, hemoglobin A_{1c} (HbA_{1c}), serum albumin, total cholesterol, HDL cholesterol (HDL-C), triglyceride, inflammatory markers (CRP, uric acid, fibrinogen, and white blood cell counts [WBCs]), UAE, serum creatinine, and eGFR.

For categorical analyses, subjects were classified as obese/nonobese according to the BMI level using a cutoff of 30 kg/m^2. Similarly, based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines, a cutoff for hypertension of ≥140/90 mmHg was used. Cutoffs for total cholesterol ≥240 mg/dL and triglyceride ≥200 mg/dL were used. CRP was categorized according to the distribution of the variables into tertiles (<0.2 mg/dL, 0.20–0.56 mg/dL, and ≥0.57 mg/dL). UAE was classified into two groups using the cutoff point 30 μg/mL. Subjects were classified according to the eGFR level and UAE level as follows: subjects with eGFR ≥60 mL/min/1.73 m^2 and UAE <30 μg/mL were considered as having no CKD (*n* = 1,459). Subjects with eGFR ≥60 mL/min/1.73 m^2 and UAE ≥30 μg/mL were considered as having early CKD (*n* = 693). Prior to the use of select continuous variables in multiple linear regression analyses, the following variables were log transformed because their distribution was skewed: duration of DM and laboratory variables (UAE,

CRP, total cholesterol, HDL-C, eGFR, FPG, HbA_{1c}, uric acid, and WBC).

Prevalent CVD was defined as a stated history of physician-diagnosed myocardial infarction or stroke, electrocardiographic evidence of myocardial infarction, or history of a revascularization procedure. Smoking status was defined as any participant who had smoked at least 400 cigarettes in their lifetime and was currently smoking at their baseline examination. Uric acid was classified into two groups using the cutoff point 7 mg/dL.

Statistical Analysis

Descriptive statistics were used to characterize the subjects (mean ± SD for continuous variables and weighted percentages for categorical variables). To test the statistical differences between the groups, χ^2 test for categorical variables and two-sided Student *t* tests for continuous variables were used, and $P < 0.05$ was considered significant. Linear regression analysis (for the continuous outcome, UAE) was used to determine the relationship between CRP and the level of UAE. Multiple linear regression models were used to adjust for confounding variables, and the adjusted regression coefficient, standard error, and *P* value were reported. The β-coefficient represented the rate of change in the outcome variable (UAE) brought about by the main independent variable (CRP) and each of the other independent variables (confounders). Two sets of multiple linear regression models were examined. In the first set, CRP was log transformed and used as the continuous variable. In the second set, CRP was divided into tertiles (normal, mid-, and highest CRP tertiles) representing normal, moderate, and elevated CRP levels. Variables considered as confounders in the multivariate analysis were age, sex, BMI, duration of DM, smoking status, SBP and DBP, use of medications (oral hypoglycemic, statin, and ACEI or ARB), total cholesterol, HDL-C, triglyceride, HbA_{1c}, FPG, comorbidity (hypertension and CVD), and additional postulated inflammatory markers (uric acid and WBC). Fibrinogen was available in only 945 subjects and thus was excluded from multivariate analyses. The effect of each of the confounding variables was tested on the change of the coefficient of the linear regression of UAE and CRP. Significant variables in the linear regression were included in the final multivariate model as follows: model 1, adjusted for social variables (age, sex, race/ethnicity, BMI, duration of DM, and smoking); model 2, adjusted for variables as in model 1 plus log-transformed laboratory variables (total cholesterol, HDL-C, FPG, HbA_{1c}, uric acid, and WBC); model 3, adjusted for variables as in model 2 plus medication use (statin and ACEI) and comorbidity (hypertension and CVD).

Data for the unadjusted as well as the adjusted models were reported for the total sample as well as by race/ethnicity. β-Coefficients and standard errors were presented. *P* value <0.05 was considered significant.

Multiple logistic regression was used to determine the association between race/ethnicity and both CRP (≥0.2 mg/dL) and UAE (≥30 μg/mL), adjusting for the previously mentioned confounding variables. Data were presented as adjusted odds ratio (AOR) and 95% CI for CRP (≥0.2 mg/dL) and UAE (≥30 μg/mL), comparing AAs and Hispanics to whites (as reference).

The data were analyzed using SAS and the survey module of STATA (Release 10, 1984–2007 Statistics/Data Analysis; StataCorp, College Station, TX). Sample weights (a value assigned to each case in the data file so that the statistics computed from the data were more representative of the population) provided by the NCHS were used to correct for differential selection probabilities (i.e., oversampling of elderly and minorities) and to adjust for noncoverage (i.e., inadequacies in the sampling frame resulting from omissions of some housing units in the listing of area segments and omissions of people with no fixed address) and nonresponse. For the subpopulation analysis (i.e., data for each race/ethnic group), there were multiple sampling units with a single observation. To accommodate for this, several replacement approaches were used where *1*) the single unit contributed nothing to the standard error, *2*) it was replaced with the average of the variance, or *3*) it was centered at the grand population mean. Then results of the models were compared. All analyses with the different replacement strategies yielded similar results.

RESULTS

Overall Study Population Characteristics

Of the 2,310 subjects with primarily type 2 DM and complete data, 864 were white, 647 were AA, and 799 were Hispanic (Table 1). Overall, 65% had hypertension, 19% had prevalent CVD, and 27% were smokers. Collectively, 30% used metformin and 6% used pioglitazone as the hypoglycemic agent, and their use did not differ between racial/ethnic groups. Statin and ACEI therapies were used by 29 and 31% of the patients, respectively, and only Hispanic patients had significantly less ($P < 0.01$) use of these medications compared with whites. ARBs were used by 6% of patients, and their use among all ethnic groups did not differ. AAs had higher levels of SBP, DBP, BMI, HbA_{1c}, and HDL-C, but lower serum triglyceride levels, compared with whites and Hispanics ($P < 0.01$). Relative to white subjects, Hispanics had higher levels of total cholesterol, FPG, triglycerides, and DM duration and lower BMI ($P < 0.05$). Relative to whites and AAs, Hispanics had a lower prevalence of CVD, uric acid, and history of smoking ($P < 0.01$). AAs had higher CRP and fibrinogen levels ($P < 0.01$ and $P < 0.05$, respectively) and lower WBC levels ($P < 0.01$) relative to whites and Hispanics. Importantly, AAs had higher serum creatinine compared with Hispanics or whites, but both AAs and Hispanics had higher eGFR (which is adjusted for age and sex) compared with whites ($P < 0.01$). In addition, AAs and Hispanics had higher UAE relative to whites ($P < 0.01$). Of the study population with early CKD (*n* = 693), 59% were white, 21% were AA, and 20% were Hispanic. AAs (36%) and Hispanics (34%) had a higher prevalence of early CKD relative to whites (26%, $P < 0.001$) and the total population (29%).

Study Population Characteristics Stratified by Albuminuria

Table 2 shows the population characteristics by absence or presence of albuminuria defined as UAE <30 μg/mL

Table 1—Characteristics of study participants by race/ethnicity

	Overall (n = 2,310)	White (n = 864)	AA (n = 647)	Hispanic (n = 799)
	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)
Age (years)	56 ± 14	57 ± 11	54 ± 16	52 ± 18
Sex				
Male	1,215 (52%)	501 (55%)	317 (43%)	397 (50%)**
Female	1,095 (48%)	363 (45%)	330 (57%)	402 (50%)
History of hypertension (yes)	1,553 (65%)	569 (65%)	493 (76%)	491 (55%)**
Prevalent CVD (yes)	472 (19%)	216 (21%)	141 (20%)	115 (11%)**
Smoking (yes)	535 (27%)	233 (28%)	177 (33%)*	125 (20%)**
Use of metformin (yes)	715 (30%)	267 (31%)	200 (31%)	248 (27%)
Use of pioglitazone (yes)	131 (6%)	49 (7%)	42 (6%)	40 (4%)
Use of statin (yes)	641 (29%)	304 (33%)	164 (23%)	173 (20%)**
Use of ACEI (yes)	749 (31%)	290 (32%)	231 (35%)	228 (21%)**
Use of ARB (yes)	165 (6%)	58 (6%)	57 (8%)	50 (5%)
Blood pressure (mmHg)				
SBP	130 ± 20	130 ± 15	133 ± 26**	129 ± 27
DBP	72 ± 14	71 ± 10	73 ± 20**	72 ± 17**
BMI (kg/m^2)	33 ± 7	33 ± 5	34 ± 10**	31 ± 10*
Duration of DM (years)	10 ± 11	10 ± 9	10 ± 13	10 ± 17*
FPG (mg/dL)	158 ± 73	151 ± 48	168 ± 111	175 ± 121**
HbA_{1c} (%)	7.3 ± 1.9	7.0 ± 1.3	7.7 ± 2.7**	7.9 ± 3.2**
Serum albumin (g/dL)	4.2 ± 0.3	4.2 ± 0.2	4.1 ± 0.4	4.2 ± 0.5
Total cholesterol (mg/dL)	200 ± 53	198 ± 36	200 ± 56	212 ± 107**
HDL-C (mg/dL)	47 ± 14	46 ± 11	52 ± 19**	46 ± 17
Triglyceride (mg/dL)	208 ± 248	216 ± 209	160 ± 175**	226 ± 301*
CRP (mg/dL)	0.66 ± 1.2	0.63 ± 0.86	0.83 ± 1.83**	0.59 ± 1.21
Uric acid (mg/dL)	5.5 ± 1.4	5.5 ± 1.1	5.6 ± 1.9	5.0 ± 1.9**
Fibrinogen (mg/dL)	389 ± 88	384 ± 61	420 ± 136*	378 ± 113
WBC (10^3 cells/μL)	7.7 ± 2.4	7.8 ± 1.7	7.1 ± 3.7**	7.8 ± 2.9
UAE (μg/mL)	95 ± 492	63 ± 185	155 ± 686**	157 ± 1,340**
Creatinine (mg/dL)	0.81 ± 0.18	0.81 ± 0.12	0.88 ± 0.29**	0.73 ± 0.24
eGFR (mL/min/1.73 m^2)	84 ± 19	80 ± 12	90 ± 29**	90 ± 28**
No CKD (eGFR ≥60 mL/min/1.73 m^2 and UAE <30 μg/mL)	1,459 (71%)	590 (74%)	358 (64%)	511 (66%)
Early CKD (eGFR ≥60 mL/min/1.73 m^2 and UAE ≥30 μg/mL)	693 (29%)	223 (26%)	219 (36%)***	251 (34%)***

The data are presented as mean ± SD or unweighted number (n) and weighted percent (%). AAs and Hispanics were compared with whites. *P < 0.05. **P < 0.01. ***P < 0.001.

or UAE ≥30 μg/mL, respectively. Of the 2,152 subjects, 693 had UAE ≥30 μg/mL. Patients with UAE ≥30 μg/mL were further stratified into macro- (UAE ≥300 μg/mL) and microalbuminuria (UAE = 30–299 μg/mL) in order to assess the relationship between these levels of albuminuria and the independent variables. There were statistically significant differences (P < 0.05) between no CKD and early CKD groups in all the variables except smoking, use of DM medications, statin, and ARB, HDL, triglycerides, and eGFR. Diabetic participants with early CKD had a significantly higher history of hypertension, prevalent CVD, use of ACEI, SBP, DBP, BMI, duration of DM, FPG, HbA_{1c}, CRP, uric acid, fibrinogen, WBC, and serum creatinine compared with those with no CKD (P < 0.01). Serum albumin levels were slightly lower in diabetic patients with UAE ≥30 μg/mL, relative to those with UAE <30 μg/mL (P < 0.04).

In the group divided into macro- and microalbuminuria, those with macroalbuminuria had statistically significant higher levels of SBP, HbA_{1c}, and uric acid and higher reported history of hypertension, but lower serum albumin (P < 0.05), reflecting the relationship of some parameters consistent with more advanced disease. Other values did not differ between groups. In addition, in relation to the entire cohort, microalbuminuria was present in 24% of white subjects, 27% of AAs, and 27% of Hispanics, whereas macroalbuminuria was present in only 3% of white subjects, 10% of AAs, and 7% of Hispanics (data not shown).

AOR of CRP and UAE

In the adjusted logistic regression analyses (controlling for age, sex, BMI, smoking, DM duration, total cholesterol, HDL-C, FPG, HbA_{1c}, uric acid, WBC, statin or ACEI use, CVD, and hypertension), relative to whites, AAs had higher adjusted odds of CRP ≥0.2 mg/dL (AOR 1.81, P = 0.007) and

Table 2—Demographic and clinical characteristics of diabetic patients with and without early CKD

	DM with no CKD	DM with early CKD		DM with early CKD and macroalbuminuria (UAE ≥300 μg/mL)	DM with early CKD and microalbuminuria (UAE = 30–299 μg/mL)	
	n = 1459	*n* = 693		*n* = 169	*n* = 608	
	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	*P* value	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	*P* value
Age (years)	55 ± 13	56 ± 15	0.02	55 ± 16	57 ± 13	0.9
Sex						
Male	726 (51%)	428 (63%)	0.001	103 (63%)	359 (61%)	0.7
Female	733 (49%)	265 (37%)		66 (37%)	249 (39%)	
Race/ethnicity						
White	590 (69%)	223 (59%)	0.0002	38 (42%)	216 (62%)	0.001
AA	358 (15%)	219 (21%)		65 (34%)	188 (20%)	
Hispanic	511 (16%)	251 (20%)		66 (24%)	204 (18%)	
History of hypertension (yes)	924 (61%)	508 (73%)	0.0001	140 (85%)	437 (72%)	0.02
Prevalent CVD (yes)	245 (16%)	168 (21%)	0.04	48 (24%)	157 (23%)	0.77
Smoking (yes)	342 (26%)	192 (31%)	0.07	42 (34%)	150 (30%)	0.59
Use of metformin (yes)	431 (29%)	234 (33%)	0.15	52 (30%)	204 (34%)	0.47
Use of pioglitazone (yes)	71 (6%)	49 (7%)	0.67	6 (3%)	50 (8%)	0.05
Use of statin (yes)	410 (29%)	167 (27%)	0.55	47 (28%)	154 (29%)	0.93
Use of ACEI (yes)	445 (28%)	238 (35%)	0.003	66 (45%)	210 (35%)	0.08
Use of ARB (yes)	88 (5%)	57 (7%)	0.20	20 (10%)	48 (7%)	0.41
Blood pressure (mmHg)						
SBP	127 ± 18	135 ± 21	0.0001	143 ± 26	134 ± 19	0.0003
DBP	71 ± 13	73 ± 15	0.005	75 ± 18	72 ± 14	0.14
BMI (kg/m^2)	32 ± 7	33 ± 8	0.008	34 ± 9	33 ± 7	0.35
Duration of DM (years)	9 ± 11	11 ± 12	0.03	14 ± 14	11 ± 11	0.08
FPG (mg/dL)	153 ± 70	170 ± 78	0.0002	180 ± 81	168 ± 73	0.13
HbA_{1c} (%)	7.1 ± 1.8	7.8 ± 2.1	0.0001	8.4 ± 3.0	7.6 ± 2.0	0.002
Serum albumin (g/dL)	4.19 ± 0.3	4.15 ± 0.4	0.04	4.0 ± 0.4	4.2 ± 0.3	0.0001
Total cholesterol (mg/dL)	198 ± 43	208 ± 74	0.04	207 ± 55	208 ± 72	0.91
HDL-C (mg/dL)	47.3 ± 13	46.5 ± 15	0.41	48.6 ± 15	46.1 ± 14	0.13
Triglyceride (mg/dL)	191 ± 16	237 ± 36	0.10	234 ± 19	246 ± 39	0.75
CRP (mg/dL)	0.61 ± 0.95	0.77 ± 1.58	0.03	1.1 ± 2.80	0.72 ± 1.20	0.24
Uric acid (mg/dL)	5.4 ± 1.4	5.7 ± 1.6	0.0003	6.1 ± 1.5	5.6 ± 1.5	0.02
Fibrinogen (mg/dL)	380 ± 83	406 ± 94	0.0002	420 ± 13	404 ± 84	0.51
WBC (10^3 cells/μL)	7.6 ± 2.0	7.9 ± 2.9	0.02	7.9 ± 2.5	8.0 ± 3.0	0.62
Serum creatinine (mg/dL)	0.80 ± 0.17	0.84 ± 0.20	0.0001	0.88 ± 0.25	0.83 ± 0.18	0.12
eGFR (mL/min/1.73 m^2)	83.7 ± 18	83.9 ± 20	0.85	85.5 ± 27	83.6 ± 17	0.51

The data are presented as mean ± SD or unweighted number (*n*) and weighted percent (%).

Hispanics had higher odds of having UAE ≥30 μg/mL (AOR 1.65, *P* = 0.03) (Fig. 1).

Multiple Linear Regression Analyses to Assess the Independent Association Between CRP and UAE

In the first set of the multiple linear regression analyses, the CRP data were transformed into log CRP to achieve normal distribution and used in unadjusted and adjusted analyses with log UAE for the total sample (*n* = 693) and for each racial/ethnic group. In the unadjusted model for the overall sample population, CRP was not a predictor of UAE. However, in the adjusted model, CRP was a strong predictor for UAE for the total sample as well as for whites and Hispanics (Table 3*A*).

In the second set of the multiple linear regression models, CRP was divided into tertiles in order to provide more sensitivity between CRP and UAE (i.e., comparing UAE in the presence of normal, moderate, and very elevated CRP levels). The CRP tertiles were as follows: first tertile, which was used as the reference, <0.2 mg/dL; mid- or second tertile, 0.20–0.56 mg/dL; and highest or third tertile, ≥57 mg/dL. In an unadjusted linear regression analysis, an association between UAE and the second CRP tertile was found among Hispanics (*P* = 0.04). In model 1, which was adjusted for social variables, Hispanics in the second CRP tertile had significant associations with higher UAE relative to those in the reference tertile. In model 2, adjusted for model 1 plus laboratory variables, Hispanics had significant associations with UAE in both the second and third CRP tertiles. However, in model 3, adjusted for model 2 plus medication use and comorbidity, both AAs and Hispanics had a significant association with higher

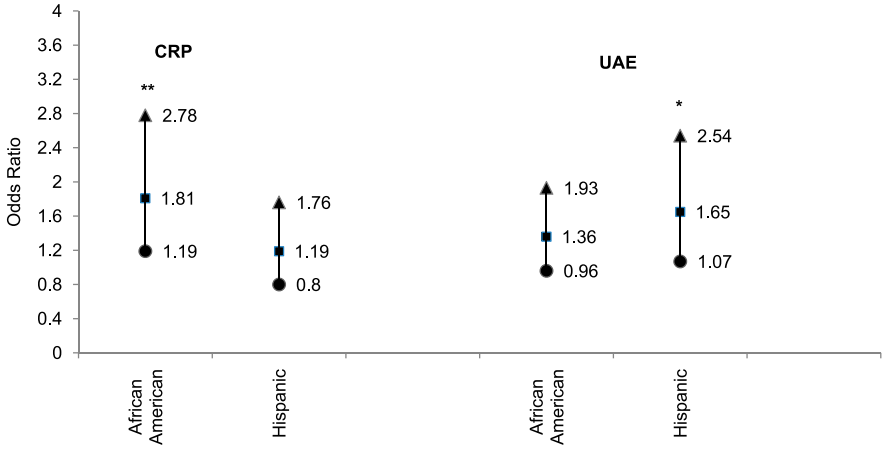

Figure 1—AOR for CRP (≥0.2 mg/dL) and UAE (≥30 μg/mL) among diabetic patients comparing AAs and Hispanics to whites (as reference). CRP and UAE are adjusted for age, sex, BMI, smoking, DM duration, total cholesterol, HDL-C, FPG, HbA_{1c}, uric acid, WBC, medication use (statin and ACEI), CVD, and hypertension. *P = 0.03; **P = 0.007. ■, AOR; ●, lower CI; ▲, upper CI.

UAE in the second CRP tertile, but only Hispanics had an association with higher UAE in the third CRP tertile (Table 3*B*).

Furthermore, in the adjusted model for the total sample, uric acid, but not WBC, was a significant predictor of UAE in both the total sample (adjusted β = 0.74 ± 0.24, P = 0.003) and in AAs (adjusted β = 1.50 ± 0.35, P = 0.001; data not shown).

CONCLUSIONS

In our study of a nationally representative sample of the noninstitutionalized U.S. population, we found an increased percentage of AAs and Hispanics with type 2 DM and early CKD associated with both CRP and UAE. Our analyses of the adjusted models indicate that UAE among people with early CKD was significantly elevated in Hispanics compared with whites, and CRP was significantly elevated in AAs compared with whites. Our findings of elevated CRP in AAs are consistent with previous reports, such as the Midlife in the United States (MIDUS) study (16). However, the MIDUS study was limited to investigating the association between ethnicity and CRP in a biomarker substudy group of pooled patients, a portion from a random national sample and a portion from an enriched group of AA participants from Milwaukee (16), which may confound both the findings and the generalizability. Despite these limitations, the MIDUS study found that early life adversities (e.g., school failure, relation with parents, parental unemployment, or alcohol problem) correlated with high concentrations of inflammatory markers (CRP, interleukin-6 [IL-6], fibrinogen, and E-selectin) at midlife for AAs, but not for whites. This pattern may be associated with the development of an accelerated course of age-related chronic diseases, including DM and its complications in AAs (16).

In our study, Hispanics had higher adjusted odds of UAE ≥30 μg/mL compared with whites, whereas the trend toward higher odds for UAE ≥30 μg/mL among AAs did not reach statistical significance. This trend among AAs compared with whites is consistent with the NHANES III population where the prevalence of albuminuria (albumin-to-creatinine ratio ≥30 mg/g) was 12% among AAs and 8% among whites (17). Further, in the Kidney Early Evaluation Program, albuminuria was prevalent in 11% of AAs and 8% of whites (18).

In the fully adjusted multiple linear regression model, we found a modest association between UAE and CRP for AAs (second tertile only) and more robust for Hispanics (both second and third tertile) in comparison with whites. Our finding of an association between CRP and UAE is also consistent with earlier reports supporting an association between CRP and micro/macroalbuminuria in high-risk populations such as those with DM (10,19), although none of these studies had reported ethnic differences in the level of inflammation and UAE in the setting of early CKD. Others have also demonstrated that CRP is associated with microalbuminuria in the general population (12,13), and in the Multi-Ethnic Study of Atherosclerosis cohort, this association was found to be stronger in nonwhite men and AA women (20). Indeed, in our study, the relationship between CRP and UAE with early CKD was most robust in Hispanics, less so in AAs, and not significant in whites. The weaker association of CRP and UAE in AAs is consistent with two recent studies of patients treated with maintenance hemodialysis (21,22) that found higher CRP and IL-6 levels were less predictive of mortality in AAs than whites, suggesting that although CRP levels are generally higher in AAs, clinical outcomes in AAs may be less dependent on the level of CRP.

We also considered WBC and uric acid, which were previously used as inflammatory markers in an NHANES III analysis (23). The multiple linear regression models indicated that uric acid, and not WBC, was a significant predictor of UAE. Studies suggest that uric acid may cause microvascular complications through endothelial dysfunction, increased activity of the renin angiotensin aldosterone system, and induction of the inflammatory cascade including increased CRP levels (24). However, due to the paradoxical pro- and antioxidant properties of uric acid (25), we limited our discussion

Table 3—Multiple linear regression models for the association between log-transformed UAE and CRP in patients with early CKD, *n* = 693

Total sample

	Total (*n* = 693)		White (*n* = 223)		AA (*n* = 219)		Hispanic (*n* = 251)	
Outcome: log UAE	β ± SE*	*P* value	β ± SE*	*P* value	β ± SE*	*P* value	β ± SE*	*P* value
A. Simple linear regression								
Unadjusted	0.08 ± 0.04	0.050	0.50 ± 0.06	0.400	0.11 ± 0.06	0.05	0.10 ± 0.06	0.120
Adjusted	0.16 ± 0.05	0.006	0.19 ± 0.06	0.007	0.06 ± 0.05	0.24	0.23 ± 0.07	0.002
B. Total sample with CRP tertiles								
Unadjusted								
CRP <0.20 mg/dL	Reference		Reference		Reference		Reference	
CRP = 0.20–0.56 mg/dL	0.06 ± 0.05	0.24	0.02 ± 0.06	0.76	0.06 ± 0.08	0.48	0.19 ± 0.09	0.04
CRP ≥57 mg/dL	0.07 ± 0.05	0.16	0.06 ± 0.08	0.41	0.07 ± 0.07	0.30	0.06 ± 0.08	0.44
Model 1: adjusted for social variables								
CRP <0.20 mg/dL	Reference		Reference		Reference		Reference	
CRP = 0.20–0.56 mg/dL	0.13 ± 0.06	0.02	0.09 ± 0.07	0.25	0.13 ± 0.10	0.18	0.25 ± 0.08	0.006
CRP ≥57 mg/dL	0.12 ± 0.08	0.12	0.16 ± 0.11	0.16	−0.05 ± 0.09	0.60	0.26 ± 0.12	0.380
Model 2: model 1 plus laboratory variables								
CRP <0.20 mg/dL	Reference		Reference		Reference		Reference	
CRP = 0.20–0.56 mg/dL	0.15 ± 0.06	0.01	0.12 ± 0.08	0.15	0.11 ± 0.07	0.15	0.32 ± 0.08	0.001
CRP ≥57 mg/dL	0.14 ± 0.08	0.08	0.20 ± 0.12	0.13	0.10 ± 0.07$	0.15	0.27 ± 0.11	0.030
Model 3: model 2 plus medication use and comorbidity								
CRP <0.20 mg/dL	Reference		Reference		Reference		Reference	
CRP = 0.20–0.56 mg/dL	0.15 ± 0.06	0.02	0.11 ± 0.08	0.20	0.13 ± 0.06	0.04	0.28 ± 0.07	0.001
CRP ≥57 mg/dL	0.13 ± 0.08	0.10	0.18 ± 0.11	0.13	0.08 ± 0.06$	0.22	0.28 ± 0.11	0.010

Model 1, adjusted for social variables (age, sex, race/ethnicity, BMI, DM duration, and smoking); model 2, adjusted for variables as in model 1 plus log-transformed laboratory variables (total cholesterol, HDL-C, FPG, HbA_{1c}, uric acid, and WBC); model 3, adjusted for variables as in model 2 plus medication use (statin and ACEI) and comorbidity (hypertension and CVD). *Adjusted β-coefficient = expected change in the log UAE for subjects with CRP = 0.20–0.56 mg/dL or CRP ≥57 mg/dL relative to subjects with CRP <0.2 mg/dL when other variables in the model are held constant; SE = linearized standard error. $Unstable unreliable estimate, small sample size.

mainly to CRP as a marker of inflammation and adjusted the data for both uric acid and WBC in multivariate analyses. Even after this adjustment, AAs still had significantly higher AOR for having elevated CRP levels, suggesting that the presence of systemic inflammation in AAs may occur at a very early stage in CKD, while eGFR is still preserved. We speculate that this relationship may ultimately contribute to their accelerated and disparate disease progression, which is observed later in the course of CKD.

Recent investigations support the mechanistic notion that type 2 DM includes an inflammatory component that significantly contributes to the genesis and progression of CKD (26). Several clinical and experimental studies have shown that a variety of inflammatory molecules, such as CRP, IL-6, and monocyte chemoattractant protein-1, are involved in the setting of diabetic nephropathy (27,28). In addition, studies show that CRP is not only a prototypic marker of inflammation but may directly influence CKD. Using a mouse model of type 1 DM, Liu et al. (29) showed that CRP promotes CKD by enhanced activation of transforming growth factor-β (TGF-β)/SMAD and nuclear factor-κB (NF-κB) signaling pathways. CRP also induced IL-6 and thrombospondin (TSP-1) mRNA and protein expression in human renal tubular epithelial HK-2 cells via activation of the p38 mitogen-activated protein kinase and NF-κB signaling pathways as well as TGF-β1 expression, suggesting that CRP plays an important role in the propagation and prolongation of inflammation in renal fibrosis (30). Most importantly, in the current context, CRP also promotes proinflammatory cytokine production (31), leading to mesangial cell proliferation, matrix overproduction, and increased vascular permeability resulting in albuminuria (32). Human and murine macrophages exposed to high glucose concentrations show increased levels of CRP mRNA and protein biosynthesis and secretion, suggesting that CRP-mediated proinflammatory effects could be triggered locally by macrophage-produced CRP in addition to the effect of

circulating and liver-derived CRP (33). It has also been demonstrated that CRP promotes the differentiation of human monocytes toward a proinflammatory phenotype (34) and induces macrophage colony–stimulating factor release via upregulation of NF-κB, resulting in increased macrophage recruitment and proliferation (35). It is well known that macrophages infiltrate the glomeruli and/or interstitium in the kidney tissue in diabetic patients with nephropathy, and the intensity of the interstitial infiltrate is proportional to the rate of subsequent decline in renal function (36). These findings support a pivotal role of CRP in inflammation during early CKD. Our finding of an association between CRP and UAE at early CKD seems to be logical as vascular (and possibly microvascular) endothelial damage begins before it becomes clinically apparent even when GFR >90 mL/min/1.73 m^2 (37).

Improving our understanding of the mechanism(s) by which inflammatory molecules such as CRP may contribute to the development of albuminuria can help direct new interventions. For example, oxidative stress modulators that could potentially activate Keap1-Nrf2 and suppress inflammation in CKD (38) may be effective for counteracting CRP activation of TGF-β/SMAD and NF-kB signaling pathways (29,30). Unfortunately, the recent clinical trial using bardoxylone methyl, one such oxidative stress modulator, was stopped prematurely (39), possibly secondary to the detrimental effects of degradation products (40). However, modified analogs addressing this pathway and others outlined above may open doors for developing new therapeutic targets, especially in ethnic minorities.

Limitations and Strengths of the Study

Our study had several limitations. First, it is a cross-sectional study and can provide only associations and not causation. Despite the efforts of NHANES to enroll a random representative noninstitutionalized sample of the U.S. population, people attending the study visits may differ from those not attending in subtle ways that may affect the results of this study. Although we tried to control for the potentially confounding variables, there is still a possibility of residual confounding. In addition, data on race/ethnicity was self-reported. Further, data on risk factors were ascertained only at baseline; therefore, we could not systematically control for differences in the severity of risk factors or perform time-dependent analyses. Although CRP is a widely used marker of inflammation, the test is not established to be highly sensitive or specific to CKD, and the lack of data on other inflammatory markers such as interleukins and TNF-α may limit our ability to interpret a broader assignment of inflammation to the observed racial/ethnic differences in CKD. Balanced against these limitations, the strength of this study lies in the analysis for CRP and covariates in a large, nationwide, population-based sample that includes a well-validated approach to interviews, laboratory, and physical examination.

In summary, we showed here that patients with DM and early CKD had increased CRP levels compared with those with DM and no CKD. We also showed that diabetic AAs and Hispanics had a higher prevalence of early CKD compared with whites, and we found higher levels of UAE in AAs and Hispanics, higher absolute CRP levels in AAs, and an association between CRP and UAE in AAs and Hispanics (stronger in Hispanics), providing additional evidence for a role of inflammation in the increased prevalence of early diabetic CKD in both ethnic groups. The association between UAE and CRP in AAs and Hispanics may impact CKD progression, accounting in part for the exceptionally high rates of DM-related ESRD in minorities. Prospective studies are required to assess whether a targeted intervention to reduce the level of inflammation is an effective strategy to prevent or slow the progression of CKD in DM and whether there is particular efficacy for select interventions across racial/ethnic groups.

Funding. This research project was supported in part by U54-MD-007598 from the National Institute on Minority Health and Health Disparities (S.K.S., M.S., D.P., K.C.N., and S.B.N.), P20-MD-000182 and UL1-TR-000124 (M.S. and K.C.N.), P30-AG-021684 (K.C.N.), and S21-MD-000103 (S.K.S., M.S., and S.B.N.). T.B.R. was supported by a Ramalingaswami Fellowship from the Department of Biotechnology, Government of India.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. S.K.S. researched data and wrote the manuscript. M.S. contributed to data management, data analysis, data interpretation, and manuscript development. T.B.R. and K.C.N. edited the manuscript and contributed to discussion. D.P. contributed to data extraction and analysis. S.B.N. reviewed and edited the manuscript and contributed to discussion and data interpretation. S.K.S. and M.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. This study was presented in abstract form at the American Society of Nephrology Kidney Week, Philadelphia, PA, 10–13 November 2011, and the Western Society for Clinical Investigation Western Regional Meeting, Carmel, CA, 25–28 January 2012.

References

1. U.S. Renal Data System. National Institutes of Health. Bethesda, MD, National Institute of Diabetes and Digestive and Kidney Diseases, 2012
2. Carter JS, Pugh JA, Monterrosa A. Non-insulin-dependent diabetes mellitus in minorities in the United States. Ann Intern Med 1996;125:221–232
3. Tarver-Carr ME, Powe NR, Eberhardt MS, et al. Excess risk of chronic kidney disease among African-American versus white subjects in the United States: a population-based study of potential explanatory factors. J Am Soc Nephrol 2002;13:2363–2370
4. Hsu CY, Lin F, Vittinghoff E, Shlipak MG. Racial differences in the progression from chronic renal insufficiency to end-stage renal disease in the United States. J Am Soc Nephrol 2003;14:2902–2907
5. Young BA, Maynard C, Boyko EJ. Racial differences in diabetic nephropathy, cardiovascular disease, and mortality in a national population of veterans. Diabetes Care 2003;26:2392–2399
6. Erlinger TP, Tarver-Carr ME, Powe NR, et al. Leukocytosis, hypoalbuminemia, and the risk for chronic kidney disease in US adults. Am J Kidney Dis 2003;42:256–263
7. Fried L, Solomon C, Shlipak M, et al. Inflammatory and prothrombotic markers and the progression of renal disease in elderly individuals. J Am Soc Nephrol 2004; 15:3184–3191
8. Tuttle KR. Linking metabolism and immunology: diabetic nephropathy is an inflammatory disease. J Am Soc Nephrol 2005;16:1537–1538
9. Mora C, Navarro JF. Inflammation and diabetic nephropathy. Curr Diab Rep 2006; 6:463–468

10. Navarro JF, Mora C, Maca M, Garca J. Inflammatory parameters are independently associated with urinary albumin in type 2 diabetes mellitus. Am J Kidney Dis 2003;42:53–61
11. Fox ER, Benjamin EJ, Sarpong DF, et al. The relation of C-reactive protein to chronic kidney disease in African Americans: the Jackson Heart Study. BMC Nephrol 2010; 11:1–7
12. Kshirsagar AV, Bomback AS, Bang H, et al. Association of C-reactive protein and microalbuminuria (from the National Health and Nutrition Examination Surveys, 1999 to 2004). Am J Cardiol 2008;101:401–406
13. Sabanayagam C, Lee J, Shankar A, Lim SC, Wong TY, Tai ES. C-reactive protein and microalbuminuria in a multi-ethnic Asian population. Nephrol Dial Transplant 2010; 25:1167–1172
14. Niewczas MA, Ficociello LH, Johnson AC, et al. Serum concentrations of markers of TNFalpha and Fas-mediated pathways and renal function in nonproteinuric patients with type 1 diabetes. Clin J Am Soc Nephrol 2009;4:62–70
15. Wolkow PP, Niewczas MA, Perkins B, et al. Association of urinary inflammatory markers and renal decline in microalbuminuric type 1 diabetics. J Am Soc Nephrol 2008;19:789–797
16. Slopen N, Lewis TT, Gruenewald TL, et al. Early life adversity and inflammation in African Americans and whites in the midlife in the United States survey. Psychosom Med 2010;72:694–701
17. Bryson CL, Ross HJ, Boyko EJ, Young BA. Racial and ethnic variations in albuminuria in the US Third National Health and Nutrition Examination Survey (NHANES III) population: associations with diabetes and level of CKD. Am J Kidney Dis 2006;48:720–726
18. Jolly SE, Burrows NR, Chen SC, et al. Racial and ethnic differences in albuminuria in individuals with estimated GFR greater than 60 mL/min/1.73 m(2): results from the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis 2010;55(Suppl. 2):S15–S22
19. Festa A, D'Agostino R, Howard G, Mykkänen L, Tracy RP, Haffner SM. Inflammation and microalbuminuria in nondiabetic and type 2 diabetic subjects: The Insulin Resistance Atherosclerosis Study. Kidney Int 2000;58: 1703–1710
20. Palmas W, Ma S, Jacobs DR Jr, et al. Ethnicity and sex modify the association of serum c-reactive protein with microalbuminuria. Ethn Dis 2008;18: 324–329
21. Noori N, Kovesdy CP, Dukkipati R, et al. Racial and ethnic differences in mortality of hemodialysis patients: role of dietary and nutritional status and inflammation. Am J Nephrol 2011;33:157–167
22. Crews DC, Sozio SM, Liu Y, Coresh J, Powe NR. Inflammation and the paradox of racial differences in dialysis survival. J Am Soc Nephrol 2011;22:2279–2286
23. Chen J, Wildman RP, Hamm LL, et al.; Third National Health and Nutrition Examination Survey. Association between inflammation and insulin resistance in U.S. nondiabetic adults: results from the Third National Health and Nutrition Examination Survey. Diabetes Care 2004;27:2960–2965
24. Jalal DI, Maahs DM, Hovind P, Nakagawa T. Uric acid as a mediator of diabetic nephropathy. Semin Nephrol 2011;31:459–465
25. Sautin YY, Johnson RJ. Uric acid: the oxidant-antioxidant paradox. Nucleosides Nucleotides Nucleic Acids 2008;27:608–619
26. Navarro-González JF, Mora-Fernández C. The role of inflammatory cytokines in diabetic nephropathy. J Am Soc Nephrol 2008;19:433–442
27. Dalla Vestra M, Mussap M, Gallina P, et al. Acute-phase markers of inflammation and glomerular structure in patients with type 2 diabetes. J Am Soc Nephrol 2005;16(Suppl. 1):S78–S82
28. Banba N, Nakamura T, Matsumura M, Kuroda H, Hattori Y, Kasai K. Possible relationship of monocyte chemoattractant protein-1 with diabetic nephropathy. Kidney Int 2000;58:684–690
29. Liu F, Chen HY, Huang XR, et al. C-reactive protein promotes diabetic kidney disease in a mouse model of type 1 diabetes. Diabetologia 2011;54:2713–2723
30. Wang HR, Chen DL, Zhao M, et al. C-reactive protein induces interleukin-6 and thrombospondin-1 protein and mRNA expression through activation of nuclear factor-κB in HK-2 cells. Kidney Blood Press Res 2012;35:211–219
31. Verma S, Li SH, Badiwala MV, et al. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. Circulation 2002;105:1890–1896
32. Horii Y, Iwano M, Hirata E, et al. Role of interleukin-6 in the progression of mesangial proliferative glomerulonephritis. Kidney Int Suppl 1993;39:S71–S75
33. Kaplan M, Tendler Y, Mahamid R, Shiner M, Aviram M, Hayek T. High glucose upregulates C-reactive protein synthesis in macrophages. Clin Chem 2010;56:1036–1038
34. Devaraj S, Jialal I. C-reactive protein polarizes human macrophages to an M1 phenotype and inhibits transformation to the M2 phenotype. Arterioscler Thromb Vasc Biol 2011;31:1397–1402
35. Devaraj S, Yun J-M, Duncan-Staley C, Jialal I. C-reactive protein induces M-CSF release and macrophage proliferation. J Leukoc Biol 2009;85:262–267
36. Nguyen D, Ping F, Mu W, Hill P, Atkins RC, Chadban SJ. Macrophage accumulation in human progressive diabetic nephropathy. Nephrology (Carlton) 2006;11:226–231
37. Mourad JJ, Pannier B, Blacher J, et al. Creatinine clearance, pulse wave velocity, carotid compliance and essential hypertension. Kidney Int 2001;59:1834–1841
38. Pergola PE, Raskin P, Toto RD, et al.; BEAM Study Investigators. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. N Engl J Med 2011;365:327–336
39. Loftus P, Weaver C. Abbott Says Study of Kidney-Disease Drug Is Stopped. Wall Street Journal, 18 October 2012. Available from http://online.wsj.com/article/SB10000872396390443684104578064460504033202.html. Accessed 29 March 2013
40. Zoja C, Corna D, Nava V, et al. Analogues of bardoxolone methyl worsen diabetic nephropathy in rats with additional adverse effects. Am J Physiol Renal Physiol 2013; 304:F808–F819