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Original Investigation

Race, Serum Potassium, and Associations With ESRD and Mortality

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Background: Recent studies suggest that potassium levels may differ by race. The basis for these differences and whether associations between potassium levels and adverse outcomes differ by race are unknown.

Study Design: Observational study.

Setting & Participants: Associations between race and potassium level and the interaction of race and potassium level with outcomes were investigated in the Racial and Cardiovascular Risk Anomalies in Chronic Kidney Disease (RCAV) Study, a cohort of US veterans (N = 2,662,462). Associations between African ancestry and potassium level were investigated in African Americans in the Atherosclerosis Risk in Communities (ARIC) Study (N = 3,450).

Predictors: Race (African American vs non–African American and percent African ancestry) for cross-sectional analysis; serum potassium level for longitudinal analysis.

Outcomes: Potassium level for cross-sectional analysis; mortality and end-stage renal disease for longitudinal analysis.

Results: The RCAV cohort was 18% African American (N = 470,985). Potassium levels on average were 0.162 mmol/L lower in African Americans compared with non–African Americans, with differences persisting after adjustment for demographics, comorbid conditions, and potassium-altering medication use. In the ARIC Study, higher African ancestry was related to lower potassium levels (−0.027 mmol/L per each 10% African ancestry). In both race groups, higher and lower potassium levels were associated with mortality. Compared to potassium level of 4.2 mmol/L, mortality risk associated with lower potassium levels was lower in African Americans versus non–African Americans, whereas mortality risk associated with higher levels was slightly greater. Risk relationships between potassium and end-stage renal disease were weaker, with no difference by race.

Limitations: No data for potassium intake.

Conclusions: African Americans had slightly lower serum potassium levels than non–African Americans. Consistent associations between potassium levels and percent African ancestry may suggest a genetic component to these differences. Higher and lower serum potassium levels were associated with mortality in both racial groups.

INDEX WORDS: Race; serum potassium; African American; African ancestry; genetic risk factor; hypokalemia; hyperkalemia; racial differences; mortality; end-stage renal disease (ESRD); kidney disease.

Potassium is one of the major intracellular cations and is essential for several important body functions in humans, such as maintaining normal neuromuscular functioning, preserving fluid volumes in cells, and regulating blood pH. Potassium levels outside the range of normal have been associated with increased risk for all-cause and cardiovascular mortality, as well as cardiac arrhythmias and end-stage renal disease (ESRD).[1-6]

Recent studies suggest that, on average, African Americans have lower serum potassium levels

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than European Americans.[1,6] Some have posited that the difference may be explained by lower dietary potassium intake in African Americans compared to European American individuals,[7-9] but racial differences in other potassium-influencing factors, such as medication use and comorbid conditions, might also play a role. Alternatively, some have proposed biological differences by ethnicity.[1,10] In this context, a recent study investigating markers of mineral metabolism reported that genetic African ancestry in African Americans correlated with fractional excretion of phosphorus.[11] One small study of persons with chronic kidney disease (CKD) found that risk relationships between potassium levels and adverse outcomes differed by race, potentially supporting a biological basis; however, sample size was limited.[1]

In response to these uncertainties, we investigated the association of race with serum potassium concentration in 2 cohorts, the Racial and Cardiovascular Risk Anomalies in CKD (RCAV) Study, a cohort of US veterans accessing health care, and the population-based Atherosclerosis Risk in Communities (ARIC) Study. We evaluated potential explanatory factors in the cross-sectional association between serum potassium level and race in the RCAV cohort and, to assess the evidence for a genetic component, the association between percent African ancestry and serum potassium level among African Americans in the ARIC Study. Finally, we investigated whether the longitudinal relationship between potassium level and mortality and between potassium level and ESRD differed by race in the RCAV cohort.

METHODS

Data Source and Study Population

The RCAV cohort used data from the national Veterans Affairs (VA) Corporate Data Warehouse LabChem data files, which have been previously described.[12,13] The original cohort consisted of all patients with estimated glomerular filtration rates (eGFRs) $>$ 60 mL/min/1.73 m^2 (calculated using the CKD-EPI [CKD Epidemiology Collaboration] creatinine equation[14]) measured October 1, 2004, to September 30, 2006 (N = 3,582,478).[15] In the current study, we subset this population to the 2,894,950 US veterans with measured serum potassium and creatinine in the outpatient setting after 2007, with the aim of studying a more contemporary population with a greater prevalence of reduced eGFR.[14] Index date was defined as the first concomitant creatinine and potassium measurement on or after January 1, 2007. We excluded 232,488 participants with missing vital status and demographic characteristics, leaving a final population size of 2,662,462.

Measurement of Exposure and Baseline Covariates

The primary exposure in the RCAV Study was race (African American vs non–African American), which was determined by self-report and obtained from the VA Corporate Data Warehouse along with other demographic variables. Blood pressure was measured in outpatient encounters; baseline systolic and diastolic blood pressures were assessed as the mean level in the year prior to the index date. Index date serum creatinine level and demographic characteristics were used to calculate eGFR using the CKD-EPI creatinine equation.[14,16,17] Body mass index (BMI) was defined as body weight (in kg) divided by the square of body height (in m). Urine albumin-creatinine ratio (ACR) was assessed from outpatient laboratory assessments during the same year prior to the index date for sensitivity analysis. Comorbid conditions—including hypertension; diabetes; history of coronary artery disease, cardiovascular disease, or peripheral artery disease; and history of congestive heart failure—were defined using a qualifying inpatient or outpatient *International Classification of Diseases, Ninth Revision, Clinical Modification* code present prior to the index date, as previously described.[7] Information for medication use, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), loop or thiazide diuretics, potassium-sparing diuretics, β-blockers, and other antihypertensive medications, were extracted from VA Pharmacy dispensation records.[18]

Outcomes

The outcome variable for cross-sectional analysis was serum potassium level obtained from the national VA Corporate Data Warehouse LabChem data files. Using the index value, serum potassium level was defined as a continuous variable and as a categorical variable (hypokalemia, defined as serum potassium $<$ 3.5 mmol/L; hyperkalemia, defined as serum potassium $\geq$ 5 or $\geq$5.5 mmol/L), in order to be consistent with the existing literature.[2,4,6] The outcomes of survival analyses were mortality and ESRD (defined as participants on dialysis therapy or with a kidney transplant) and were obtained from VA Vital Status File and the US Renal Data System. Due to a lag in the availability of linked data, the end date of follow-up for mortality and ESRD was September 15, 2011.[15]

Statistical Analysis

Cross-sectional Associations Between Race and Potassium in RCAV

We used χ^2 and *t* tests to assess differences in categorical and continuous variables by African American race. Kernel density plots were used to plot the distribution of index potassium levels in the population. We used linear regression and logistic regression to investigate the association between race and potassium levels as a continuous variable and categorical variables (hypokalemia and hyperkalemia), respectively. An unadjusted model included race as a single covariate. Progressively adjusted models were used in order to evaluate potential explanatory factors in the race-potassium association. The demographic-adjusted model included age and sex. The covariate-adjusted model additionally accounted for eGFR; systolic blood pressure; BMI; diabetes mellitus; history of coronary artery disease, cardiovascular disease, or peripheral artery disease; and history of congestive heart failure. The fully adjusted model additionally adjusted for the use of ACE inhibitor or ARB medications, loop or thiazide diuretics, potassium-sparing diuretics, β-blockers, and any other antihypertensive medications. Interaction terms of race and loop/thiazide diuretics with serum potassium level, as well as race and ACE inhibitors or ARBs with serum potassium level, were tested in each of the models.

Cross-sectional Associations Between Percent African Ancestry and Potassium in ARIC

The ARIC Study is a prospective epidemiologic study conducted in 4 US communities in which 15,792 middle-aged participants were recruited at the baseline visit (1987-1989).[19] Associations between race and serum potassium levels were confirmed using kernel density plots in the 15,539 participants with nonmissing serum potassium levels at the baseline visit. To assess whether racial differences in serum potassium levels might