Ethnicity and Unprovoked Hypokalemia in the ARIC Study

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Among the many memorable facets of the immediate Past-President of the United States are his plans to “build a bridge to the 21st century.” The article by Andrew et al, “Ethnicity and Unprovoked Hypokalemia in the Atherosclerosis Risk in Communities (ARIC) Study,”1 represents a fundamental population-based observation that bridges diverse research findings from clinical epidemiology to cellular and molecular biology in the 20th and 21st centuries. The authors conservatively recognize the implications of their report in stating that “the detection of a higher prevalence of unprovoked hypokalemia in the African American population would point to areas of research that may lead to better understanding of differences in disease prevalence.”

The editorial commentator has greater liberties in speculating on the broad significance and implications of the observations than do the authors of the original article. Let’s take a look at their bridge building report based on a retrospective analysis of the ARIC cohort findings from 1990 to 1993. We will explore and speculate on the diverse associations and implications of their findings for ethnic differences in cardiovascular pathophysiology and outcomes.

A Perspective on the Principal Observation

The authors document that unprovoked hypokalemia, defined as a serum K⁺ <3.5 mEq/L among individuals not receiving K⁺-sparing or -depleting diuretics, is approximately five times more frequent in African Americans at 2.6% (N = 2416) than European Americans at 0.5% (N = 9226). The ethnic differences in spontaneous hypokalemia are probably understated, as K⁺ supplements (3.3% v 1.4%, P < .001) and angiotensin converting enzyme inhibitors (5.0% v 3.5%, P < .01) were more commonly taken by African than by European Americans. Of possibly greater significance to ethnic disparities in health, serum K⁺ levels in the lowest half of African Americans are shifted to the left of values in the lowest half of white patients for both men and women. Thus, the implications of the findings probably extend far beyond the 2.6% of African Americans with spontaneous hypokalemia in the ARIC cohort.

Dietary K⁺, Plasma Renin Activity,Salt Sensitivity, and Hypertension

Dietary K⁺ is lower in African American than in white populations,2,3 and may contribute to ethnic differences in serum K⁺. In normotensive African American men, increasing dietary K⁺ from 30 to 70 and 120 mmol/day produces a dose-dependent reduction in salt sensitivity and ethnic differences in the pressor response to a high-salt diet.4 Moreover, the antihypertensive effects of K⁺ supplements are generally larger in black than in white persons.5 Of note, plasma renin activities are reportedly lower or modulate less with changes of Na⁺ intake among salt-sensitive than salt-resistant subjects.6 Increasing dietary K⁺ in African Americans raises plasma renin activity and ablates the ethnic difference between African and European Americans.7 Thus, the comparatively K⁺ deficient diets of many African Americans may contribute to lower plasma renin activity, greater salt sensitivity, and a higher prevalence of hypertension compared with those in white persons. Epithelial Na⁺ channel (ENaC) activity is greater in African than European Americans and could also contribute to lower serum K⁺ and higher BPs, despite lower aldosterone levels.8 The adverse effects of higher ENaC conductivity would be exacerbated by lower dietary K⁺ intake in African relative to European Americans.

Potassium and Pathophysiology

The mechanisms by which K⁺ modulates BP are not fully elucidated, but a substantial body of literature provides clues. Among these are the previously noted effects on the renin-angiotensin system as well as renal sodium ho-
meostasis, endothelial function, autonomic and pressor reactivity, and oxidative stress–sensitive processes.\textsuperscript{9–12} Oxidative stress, in particular, is a topic of current interest with links to hypertension, diabetes, vascular remodeling, and clinical events.\textsuperscript{13} The impact of dietary K\textsuperscript{+} on biomarkers of oxidative stress emerges as an especially intriguing topic for further investigation.

**Ethnic Disparities in Stroke**

The observation that spontaneous hypokalemia is more common among African than European Americans has important implications for the striking ethnic disparity in stroke mortality. Death from stroke is approximately twofold greater in African American than in white populations, especially in southeastern United States.\textsuperscript{6,14} The variance in stroke mortality with estimates of dietary K\textsuperscript{+} consumption is impressive, with approximately threefold greater death rates among those in the lowest compared with the mid and upper tertiles.\textsuperscript{15}

**More Speculative Implications of Lower Serum K\textsuperscript{+} in African Americans and Women**

The epidemic of diabetes, especially in African Americans, appears to be primarily obesity related. The relatively lower K\textsuperscript{+} intakes and serum concentrations in African than European Americans may play a role, inasmuch as K\textsuperscript{+} is important in insulin secretion and action.\textsuperscript{16} The report by Andrew et al clearly demonstrates that hypokalemia is more prevalent in women than in men. The sex differences in serum K\textsuperscript{+} may contribute to the higher incidence of symptomatic arrhythmias and sudden death in women than in men, especially in the absence of coronary heart disease, although other explanations have been proposed.\textsuperscript{17}

In summary, the demonstration in the ARIC Study that spontaneous hypokalemia is more common among African than European Americans converges with evidence from multiple sources indicating that variations in nutritional intake and biologic regulators of K\textsuperscript{+} may contribute to ethnicity-related disparities in cardiovascular risk and health outcomes. Moreover, the findings strengthen the rationale for further research on nutritional and biologic differences in K\textsuperscript{+} homeostasis to better define and address ethnic disparities in cardiovascular health.

**References**