Race, Biomarkers, and Cardiovascular Disease in Patients With Chronic Kidney Disease

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Chronic kidney disease (CKD) is not only a powerful risk factor for both cardiovascular disease (CVD) and premature mortality, but more people with CKD die before they reach end-stage kidney disease and the need for renal replacement therapy with dialysis or transplantation. The disproportionately high rates of CKD and CVD among most minoritized racial and ethnic groups compared with their White peers have been well described in the United States and globally. Interestingly, although Black Americans in the general population experience a higher mortality rate compared with White American peers, Black Americans with end-stage kidney disease treated with dialysis have a lower mortality rate than White Americans with end-stage kidney disease treated with dialysis even after adjusting for many covariates and comorbidities. The reason for this appears to be selective survivorship (individuals who live to reach dialysis), which may be owing to differences in preclinical disease among the survivors as well as other possibilities including the patient’s inflammatory state.

See Article by Barrows et al.

Among the many societal factors that underlie these disparities in CKD and CVD are the observations of health-affirming opportunities and resources, commonly termed structural racism. These include, but are not limited to, longstanding and persistent community-level disinvestment in systems that support education, employment, health insurance, safety, physical activity, food security, environmental justice, and more that lead to poor health, as well as distrust of federal and state systems including the medical system. In addition, a greater burden of personal and societal levied psychological insults (eg, discrimination, marginalization, invalidation) leading to anxiety, stress, states of hypervigilance and more becoming manifest as group differences in neurohormonal activation, expression of inflammatory mediators, and immune function and/or epigenetic modifications (Figure). Together, these and other insults may contribute to the more rapid development and/or progression of CVD and CKD as well as their major risk factors, such as hypertension and diabetes, adding to the increased disease burden levied upon most minoritized racial and ethnic groups.

Racial and ethnic differences in health conditions, health outcomes, and/or response to treatment tell us there are many important elements affecting socially assigned groups differently, and it is our task as researchers to now try to understand which factors are most relevant for different disease states. It should also be noted that in addition to those societal factors described here, in some instances there may be relevant group-level differences in the prevalence of gene

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polymorphisms. These polymorphisms are often a result of geo-evolutionary influences or founder effects that may affect a subset of people that happen to be assigned to a given racial or ethnic group. However, these epidemiologic observations should not be confused with innate group differences, as exclusive of phenotype there is more genetic heterogeneity within racial and ethnic groups than across groups. They should be viewed as novel findings that allow us to better understand the relation of a polymorphism to a health condition.

Thus, it is important to examine the constellation of demographic factors, community-level factors, medical comorbidities, common laboratory values, and medications, as well as to assess possible novel biologic markers if these are available, as they might be targets for fairly immediate and direct therapeutic interventions.

To this end Barrows et al. in this issue of the Journal of the American Heart Association (JAHA) examined 2 novel biologic markers, plasma interleukin 6 (IL-6) and transmembrane serine protease 6 (TMPRSS6) genotype, and their interaction with race as determinants of CVD and mortality in over 3000 participants in the CRIC (Chronic Renal Insufficiency Cohort) Study. Inflammatory mediators have previously been shown to have strong associations with clinical outcomes in patients with CVD and CKD, but our understanding of TMPRSS6 genotype and CVD and CKD is much more limited. Prior genome-wide studies have demonstrated a strong association between the TMPRSS6 allele A736V (rs855791) and significantly lower levels of serum iron, transferrin saturation, hemoglobin, and mean corpuscular volume, which are also altered in patients with advancing CKD. Barrows and colleagues posited that given there was a previously reported differential prevalence of the TMPRSS6 gene allele rs855791 across racial and ethnic groups, if it could modify the cellular responsiveness to IL-6, it could have a significant impact on the relation of IL-6 and clinical outcomes in Black and White CRIC participants.

Barrows and colleagues found that after adjusting for multiple covariates, higher levels of IL-6 were strongly associated with the primary composite outcome (incident myocardial infarction, stroke, heart failure and peripheral arterial disease, and all-cause mortality), with a 40% higher risk of the primary outcome across each quintile of IL-6. However, the association was noted to be more robust in White than in Black study participants. Despite group differences in the prevalence of TMPRSS6 genotypes (~20% in Black Americans and ~40% in non-Black Americans), the authors found no association between TMPRSS6 genotype and the primary outcomes after adjusting for covariates, nor did TMPRSS6 genotype affect the relation between race or IL-6 levels and primary outcomes.
In addition, they performed good-fitting path models to better refine the associations and found the relation of race with mortality and CVD events to be strongly mediated through several common clinical and laboratory variables including estimated glomerular filtration rate, urinary albumin to creatinine ratio, diabetes, and IL-6.\textsuperscript{14} This finding reinforced our understanding of these factors as important targets in the clinical care of patients with CKD and at risk for CVD.

The finding of a higher risk of cardiovascular outcomes and premature death with increasing serum levels of IL-6, being greater in White than in Black CKD study participants has been noted previously.\textsuperscript{7,8} This finding confirms existing clinical and epidemiological reports that have not only shown racial and ethnic differences in the relation of the level of inflammatory biomarkers and estimated glomerular filtration rate,\textsuperscript{9} but clinical sequelae of CKD as well. Crews et al. followed a cohort of nearly 1000 patients with end-stage kidney disease treated with hemodialysis over 3 years and found that across increasing tertiles of inflammation (C-reactive protein and/or IL-6) the adjusted relative hazards for mortality increase was much greater for White patients than for Black patients.\textsuperscript{7} Streja and co-workers reported similar findings from a cohort of over 124,000 adult patients undergoing hemodialysis where they controlled for a composite of nutrition and inflammation (malnutrition-inflammation complex) but did not directly measure C-reactive protein or IL-6. However, after controlling for the malnutrition-inflammation complex syndrome they also found an increase in the relative hazard for mortality for White compared with both Black and Hispanic patients.\textsuperscript{8}

**WHAT ARE THE IMPLICATIONS FOR CLINICIANS?**

It is important for practicing physicians to recognize that a patient with CKD is at high risk for premature cardiovascular and death. In addition to the more common risk factors we use to assess risk in patients with CKD such as presence of adverse social determinants of health, disease states such as diabetes, baseline or rate of kidney estimated glomerular filtration rate decline, and urinary albumin to creatinine ratio, the assessment of IL-6 appears to be an emerging tool to further define the risk of early adverse clinical events and the need to ensure patients with CKD are receiving optimal evidence-based care. By contrast, there was no evidence of genetic-based group differences, at least for polymorphisms of the TMPRSS6 gene. Although higher serum levels of IL-6 were found to be associated with a greater risk for adverse clinical outcomes in White patients compared with Black patients with CKD, the high degree of heterogeneity within and across racial groups and other elements of race, such as being a group-level social variable with no direct relation to health, makes it futile to ascribe the difference in racial group-level risk equally to individual group members with a modifier. Prospective studies are clearly warranted to assess which interventions are most efficacious in individual patients with CKD and elevated serum IL-6 levels. As our understanding of and treatment for CKD and the role of emerging biomarkers such as IL-6 and others evolve, we must remain diligent to address long-established risk factors and ensure all patients have access to pharmacologic and nonpharmacologic evidence-based therapies as important steps to advance health equity and improve the care of all patients.

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