Race in America
What Does It Mean for Diabetes and CKD?

Katherine R. Tuttle

Clin J Am Soc Nephrol 13: 829–830, 2018. doi: https://doi.org/10.2215/CJN.04890418

Providence Health Care, Kidney Research Institute, Nephrology Division and Institute of Translational Health Sciences, University of Washington, Spokane, Washington

Correspondence:
Dr. Katherine R. Tuttle, Providence Medical Research Center, 105 West 8th Avenue, Suite 6050 W, Spokane, WA 99204. Email: katherine.tuttle@providence.org

> Race. . .is an arranged marriage between the social and biological worlds.
>
> Cooper *et al.* (1)

What is race? Although this question may seem simple, the definition of race is a complex topic of great discourse. The US Census defines race on the basis of self-identification (white, black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander). In this case, race reflects a social definition rather than biology, anthropology, or genetics. Information on race is required for many federal programs, and it is critical for policy decisions, particularly for civil rights, equal employment opportunities, and assessment of disparities in health and environmental risks. In contrast, there are biologic definitions of race that are sociocultural-free categories (2). Five distinct ancestries are recognized in humans: (*1*) European, Near and Middle Eastern, and Central Asian; (*2*) African; (*3*) Amerindian; (*4*) East Asian; and (*5*) Pacific Islander. Importantly, these ancestral groups have <5% genetic variability between them. Thus, the vast majority of genetic variability in humans is between individuals rather than between ancestral groupings. Proposed biologic definitions for race include a reproductive community capable of exchanging gametes or >25% between-group genetic variability (3). Neither definition would distinguish ancestral groupings as races. There is certainly richness of genetic variability across the entirety of our human race. Among this variability, physical traits, such as skin color, primarily reflect adaption to environmental exposures, but these adaptive traits do not define biologic race.

Adaptive traits can have tradeoffs. Of particular relevance for kidney disease is the APOL-1 genotype (3). APOL-1 gene variants (G1 and G2) originated in sub-Saharan Africa as an adaptation to protect against sleeping sickness caused by a trypanosome transmitted by the tsetse fly vector. G1 and G2 variants increase APOL-1–activated lysis of *Trypanosome brucei*. After African populations migrated away from trypanosome-endemic areas, such as occurred with relocation by the slave trade to the United States, those same trypanosome-adaptive variants were found to have adverse genetic "side effects." The APOL-1 G1 and G2 variants, common in Americans of African ancestry, greatly increase risk for CKD and ESKD (3). Incidence and prevalence rates for ESKD are increased by three- and fivefold, respectively, in blacks compared with whites, and these findings have been attributed at least in part to APOL-1 kidney disease risk variants. Two APOL-1 variants are present in 10%–15% and one variant is present in about 50% of blacks. Many forms of CKD, including HIV-associated nephropathy, FSGS, and hypertensive nephrosclerosis, have been linked to the APOL-1 risk variants, with odds ratios ranging from seven- to 89-fold, some of the highest recorded for a common disease association (3). APOL-1–related kidney disease seems to require an external insult, termed the "two-hit hypothesis," in which the presence of APOL-1 variants requires another insult to activate risks of CKD and ESKD. However, for unclear reasons, APOL-1 risk variants do not predict CKD onset or progression to ESKD in diabetes.

How does being black associate with higher risks of CKD and ESKD in diabetes? A turn toward nongenetic attributes is in order. In the United States, race for the purpose of federally funded clinical trials follows the US Census definition by self-identification. People who self-identify as black are under-represented in pivotal clinical trials for new drug approvals by the Food and Drug Administration across therapeutic areas. Blacks constitute 7% of overall clinical trial participants, although they make up 13% of the United States population (4). In this issue of the *Clinical Journal of the American Society of Nephrology*, Gerber *et al.* (5) report a *post hoc* analysis of CKD risks in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial by black versus white race (6). The ACCORD trial participants' diabetes care was standardized by the clinical trial format so that, as much as possible, they received comparable treatment consistent with clinical practice guidelines at the time, irrespective of self-identified race (6). Blacks were adequately represented, making up 19% of participants in the ACCORD trial. They had higher-risk clinical features at baseline, including higher levels of systolic BP and hemoglobin A1c as well as more frequent macro- and microalbuminuria (5). Contrary to the original study hypothesis, the rate of eGFR decline was not greater in blacks than whites starting from a

normal eGFR. Notably, in blacks, baseline eGFR was actually higher (87±19 versus 83±17 ml/min per 1.73 m^2; $P<0.001$), and they had 27% lower risk of incident CKD defined by new-onset eGFR <60 ml/min per 1.73 m^2, eGFR decline by ≥25%, and slope of eGFR decline faster than −1.6 ml/min per 1.73 m^2 (hazard ratio, 0.73; 95% confidence interval, 0.57 to 0.92; $P<0.01$). This *post hoc* study had some relevant limitations. For example, the follow-up time may not have been long enough to fully assess key CKD outcomes. The study also did not address CKD progression by race after it occurred. Finally, the ACCORD trial participants, like clinical trial participants in general, may not reflect typical patients in terms of overall engagement and health status. Nevertheless, the ACCORD trial data show that good diabetes care can eliminate racial inequities in CKD risk.

Self-identified race is a strong predictor of health outcomes in CKD (7). Blacks in the United States are disadvantaged across social determinants of health: socioeconomic status, psychosocial factors, health care access, neighborhood, and environment. Because CKD screening is associated with better health care and outcomes, a recent study addressed barriers and facilitators for CKD screening among focus groups composed of blacks in Nashville, Tennessee (8). Among other factors, they identified lack of knowledge, mistrust, and financial burden as major barriers. To the contrary, key facilitators included CKD education, culturally sensitive communication, and better access by convenient screening. The accompanying editorial amplified these themes with a call for ongoing authentic engagement with partnership and respect to attenuate mistrust and activate black communities to take a stand for their health (9). The structure of the ACCORD clinical trial leveled the playing field and showed that standardized clinical approaches produced CKD outcomes in blacks with diabetes that were just as good as, if not better than, outcomes in whites. American Indians and Alaskan Natives are other groups that have been disadvantaged, and historically, they have some of the highest rates of ESKD attributed to diabetes. Remarkably, standardized care by population health management of diabetes and CKD in American Indians and Alaskan Natives reduced incidence of ESKD by 54% between 1996 and 2013 to a rate equivalent to that in whites (10). Thus, racial disparities in CKD onset and progression in diabetes can be mitigated by access and quality of health care.

"Time's up!" Optimal care for diabetes and CKD can and must be achieved by strategic focus: for example, by increasing opportunity for clinical trial participation and through broad-based population health management. These approaches could also be adapted for other underserved groups, such as people who live in rural America. The time is now to lead the way forward to better kidney health for all without distinction.

Acknowledgments

Sincere thanks are extended to Keith Norris, Sterling McPherson, Radica Alicic, Susanne Nicholas, and Andrew Boulet for providing their expert guidance, review, and commentary on this editorial.

K.R.T. receives research support from the following agencies and organizations: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)/National Institutes of Health (NIH) grant U01 DK085689, National Center for Advancing Translational Science/NIH grant UL1 TR00043, NIDDK/NIH grant UM1 DK100846-02, NIDDK/NIH grant UC4 DK101108-01, NIDDK/NIH grant U54 DK083912, NIDDK/NIH grant U01 DK085689, NIDDK/NIH grant R34 DK094016, and Providence Saint Joseph Health.

Disclosures

None.

References

1. Cooper RS, Kaufman JS, Ward R: Race and genomics. *N Engl J Med* 348: 1166–1170, 2003
2. Templeton AR: Biological races in humans. *Stud Hist Philos Biol Biomed Sci* 44: 262–271, 2013
3. Kruzel-Davila E, Wasser WG, Skorecki K: APOL-1 nephropathy: A population genetics and evolutionary medicine detective story. *Semin Nephrol* 37: 490–507, 2017
4. Downing NS, Shah ND, Neiman JH, Aminawung JA, Krumholz HM, Ross JS: Participation of the elderly, women, and minorities in pivotal trials supporting 2011-2013 U.S. Food and Drug Administration approvals. *Trials* 17: 199, 2016
5. Gerber C, Cai X, Lee J, Craven T, Scialla J, Souma N, et al.: Incidence and progression of chronic kidney disease in individuals with type 2 diabetes. *Clin J Am Soc Nephrol* 13: 884–892, 2018
6. Gerstein HC, Miller ME, Byington RP, Goff DC Jr., Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr., Probstfield JL, Simons-Morton DG, Friedewald WT; Action to Control Cardiovascular Risk in Diabetes Study Group: Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358: 2545–2559, 2008
7. Norton JM, Moxey-Mims MM, Eggers PW, Narva AS, Star RA, Kimmel PL, Rodgers GP: Social determinants of racial disparities in CKD. *J Am Soc Nephrol* 27: 2576–2595, 2016
8. Umeukeje EM, Wild MG, Maripuri S, Davidson T, Rutherford M, Abdel-Kader K, Lewis J, Wilkins CH, Cavanaugh K: Black Americans' perspectives of barriers and facilitators of community screening for kidney disease. *Clin J Am Soc Nephrol* 13: 551–559, 2018
9. Norris KC, Nicholas SB: Community-based CKD screening in Black Americans. *Clin J Am Soc Nephrol* 13: 521–523, 2018
10. Bullock A, Burrows NR, Narva AS, Sheff K, Hora I, Lekiachvili A, Cain H, Espey D: Vital signs: Decrease in incidence of diabetes-related end-stage renal disease among American Indians/Alaska Natives - United States, 1996-2013. *MMWR Morb Mortal Wkly Rep* 66: 26–32, 2017

Published online ahead of print. Publication date available at www.cjasn.org.

See related article, "Incidence and Progression of Chronic Kidney Disease in Black and White Individuals with Type 2 Diabetes," on pages 884–892.