Americentrism in estimation of glomerular filtration rate equations

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Social determinants of racial health disparities in kidney disease have an important role as environmental components, especially for Black populations, who are disproportionately disadvantaged, as Black Americans have a much higher risk for progression to kidney failure. The debate concerning the posited phenomenon of structural racism embedded in the original versions of the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimating equations for glomerular filtration rate (GFR), based on serum creatinine concentration, has culminated in the development of new equations that avoid the use of a race-based coefficient.[1] These modifications were designed to minimize the biases that were generated when the equations were applied to individuals and groups of self-identified Black Americans geographically located in the United States. Little discussion was apparently given to the impact of these modifications on individuals and groups of subjects of Black African ancestry residing elsewhere in the world. In this brief essay, it is our intent to broaden this debate to a more global scope, to address what might be perceived as *Americentrism*, a term signifying a tendency to view the world in an overly American-focused perspective.

It is a given that serum creatinine concentration is still used as the main variable for estimating GFR in daily practice throughout the world. Creatinine is the catabolic product of creatine and phosphocreatine, predominantly of skeletal muscular origin. This fact explains (in part) the difference of serum creatinine levels observed between men and women and children and adults. The immutable variable *sex* is thus logically present in creatinine-based estimated glomerular filtration are (eGFR) equations, because body surface area–indexed measured GFR is not different between men and women (of the same age) or children aged >2 years and adults aged <40 years. To have a single estimating equation with acceptable performance characteristics, the age and sex differences in creatinine generation need to be taken into account.[1,2] These observations imply that an important distinction should be made between men and women and the young or elderly,[3] which might be considered problematic in the transgender or geriatric community.

In America, a vigorous debate raged concerning the application of a unique coefficient for Black American individuals in creatinine-based eGFR equations. The difficulties and consequences of such a required race coefficient for estimating GFR in terms of structural racial discrimination have been widely and appropriately discussed. But a reasonable question that might be asked is what was the justification of such a race-based coefficient in the first place? Measured GFR indexed by body surface area seems not to be different between healthy Black and White Americans of the same age, even if unfortunately, data in Black Americans are limited, but serum creatinine concentration at the population level seems to be higher in Black Americans compared with White Americans (more so in men than in women). From the National Health and Nutrition Examination Survey trial, the mean serum creatinine in the US population within an age range of 20–39 years (including people without hypertension or diabetes) was 1.14 mg/dl for White men versus 1.24 mg/dl for Black men, and 0.93 mg/dl for White women versus 0.96 mg/dl for Black women[4] (see also Figure 1). These differences in creatinine concentrations could explain why race, like for sex, was considered as an explaining variable in both the MDRD and CKD-EPI eGFR equations. These equations were developed (and verified) mostly from American cohorts.[1] However, the way the racial coefficient was applied was problematic from a strict medical point of view. Self-identified "White people" were set as the reference population, whereas self-identified "Black people" were the ones requiring a supplemental coefficient, because of the design of the regression analysis, where "race" was a "dummy" variable. *First*, good

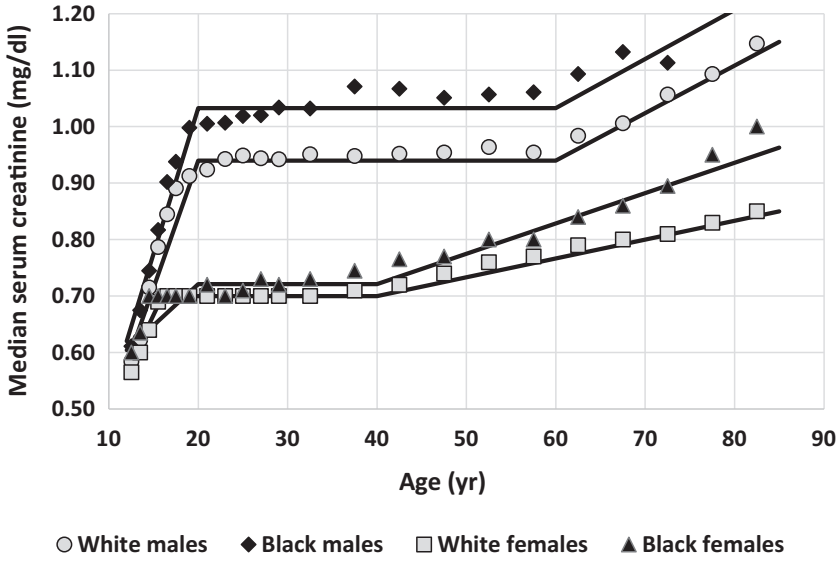

Figure 1 | Serum creatinine, according to age and sex, in a Black and White American population. Median serum creatinine (of 1-year [12–18 years], 2-year [18–30 years], and 5-year [>30 years] age groups) are plotted against age for White and Black American males and females (from National Health and Nutrition Examination Survey trial). The medians are then modeled with 3 linear splines. The middle spline is horizontal and corresponds to $Q = 0.94$ mg/dl for White American males, $Q = 1.03$ mg/dl for Black American males, $Q = 0.70$ mg/dl for White American females, and $Q = 0.72$ mg/dl for Black American females.

reasons exist to suggest that the "race" coefficient used in the seminal MDRD and CKD-EPI equations was inaccurate in Black healthy subjects, because very few healthy Black people were used in the development database.[4] *Second*, the coefficient was also probably questionable, in terms of performance, in Black women.[4] This point has been largely understudied, but the societal impact of inaccurate GFR estimation in Black women deserves more extensive investigation. In the Multi-Ethnic Study of Atherosclerosis, the CKD-EPI equation was particularly poor in Black American women (with a bias leading to overestimation of 16.4 ml/min per 1.73 m^2 and an accuracy within 30% of only 65.7%).[5] This large overestimation by an equation with race in Black American women is also well illustrated in the recent publication of the "new" CKD-EPI equation (see Supplementary Figure S10 j andk in Inker *et al.*[1]). *Third*, both MDRD and CKD-EPI equations were adjusted, correcting for race *at the GFR level*, which artificially emphasizes the questionable impact, as measured GFR is not influenced by race, but serum creatinine is influenced by population-dependent factors (e.g., age, sex, and race; see Figure 1).[4]

The European Kidney Function Consortium (EKFC), with a Euro-centric focus, has recently proposed an eGFR equation where the variable "creatinine" is normalized by "normal median creatinine," named the *Q* value, as established in dedicated populations (with separated *Q* values for the most important variables influencing serum creatinine; i.e., sex).[2] The word "population" is important, and this is not a hypocritical semantic. The difference in serum creatinine concentration between White and Black individuals has nothing to do with the color of skin from a biological perspective. Hsu *et al.* convincingly showed that the difference in serum creatinine concentration between Black and White Americans was due to neither a difference in creatinine tubular secretion nor muscular mass.[3] It is remarkable that after one century of use, we still do not know why the serum creatinine level is higher in Black American men than in White ones for the same measured GFR level. The EKFC eGFR equations using uniquely American *Q* values have never been tested adequately in American Black and White cohorts—a deficiency that needs to be remedied. *Fourth*, the MDRD and CKD-EPI eGFR equations have been published in highly respected journals read everywhere in the world.[1] In the seminal MDRD and CKD-EPI equations, the race coefficient was established for "Black people". Beyond the facts that race is a social construct (without any biological justification) and that skin color does not influence GFR or serum creatinine in a biological

sense, this assertion omits the inescapable fact that most Black individuals live outside America, mostly in Africa. For a variety of reasons, research on measured and estimated GFR is difficult in African countries. Although limited, the current literature argues for the inadequacy of the race coefficient in MDRD and CKD-EPI equations in Africa. The *Q* values for serum creatinine in Central Africa and West Africa seem to be quite similar to the *Q* values in Europe. The absence of any added value of racial coefficients has also been suggested in data from Brazil. In European Black people, the American Black coefficient was demonstrated to be much too high.[4]

The debate on the race coefficient in America has led to the publication of a new creatinine-based equation without the race variable.[1] Because there is a difference in the relationship between creatinine and GFR in Black and White Americans, the new equation was designed to be *equally* biased by race, but in opposite direction. The bias, of the new CKD-EPI equation (overestimation of 3.9 ml/min per 1.73 m^2) is larger than the previous one with race (overestimation of 0.5 ml/min per 1.73 m^2) in non-Black Americans. The absolute bias of the new equation (3.6 ml/min per 1.73 m^2) in the Black American cohort was similar than with the previous CKD-EPI version (3.7 ml/min per 1.73 m^2), with the first equation overestimating, and the new one underestimating, measured GFR.[1] A point little discussed is that the new CKD-EPI–creatinine eGFR equation obviously corrects, at least in part, the large bias that was observed with the previous equations in Black women, which is certainly a positive step. In the social networking response to the modified "racially neutral" equations, it seems that these new equations are greatly accepted by most of American nephrologists. Most consider that the slightly poorer performance of the new eGFR equation in White people is a reasonable price to pay to avoid the highly questionable race variable. The new equation has been directly endorsed by the American Society of Nephrology (ASN) and the National Kidney Foundation (NKF). This might be the end of what has been a galvanizing story that attracted much attention. However, until now, the performance of the new "racially neutral" eGFR equations has not been tested beyond America, as the vast majority of the cohorts included in the CKD-EPI consortium are US-based cohorts. Arguments can be posited in favor of using the previous CKD-EPI creatinine equation in Europe, Africa, Brazil, and elsewhere without any race correction. Should these countries, and others, use a new equation, developed in America to remedy a specific issue of structural racism relating to the Black American population, for a problem that may not be relevant in their own country? Especially if the performance characteristics of the new equation are poorer than the current equation when used without any race variable?

To finish this essay on Americentrism in eGFR equations with a more harmonious touch, we fully agree with the NKF and ASN recommendations that cystatin C might be a solution to estimate GFR without race (and maybe also without sex), but a much better global standardization of the assays for cystatin C is still required. Moreover, measuring cystatin C is still challenging in different parts of the world, like in Africa, notably (but not only) for financial reasons. A major stumbling block that will be difficult to overcome is the intrinsic imprecision of all eGFR equations, regardless of the biomarker on which they are based. This should stimulate efforts to develop and universally harmonize a single, simple, inexpensive, and reliable method for directly measuring GFR, which would make arguments about racial adjustments moot, all over the world. We also fully agree with the ASN and NKF that further research on measurement and estimation of GFR should be encouraged and funded. We add that such studies are urgently needed beyond America.

DISCLOSURE

All the authors declared no competing interests.

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