Chronic dialysis therapy legislated in the United States through the ESRD program was started in the early 1970s as an early prototype of universal health care coverage for a chronic disease. Since then, several unique features of dialysis patients have stood out without any clear explanation, including racial and ethnic disparities, cardiovascular disease, and extremely high mortality. \(^1\) Racial and ethnic discrepancies in ESRD patients have their roots in the earlier stages of chronic kidney disease (CKD), among others, because of access to care\(^2\) and the higher likelihood of hypertension and diabetes in African Americans.\(^1,3\) Across virtually all age groups, one-third of dialysis patients in the United States are African American as compared with 14% of the general population.\(^4,5\) Other minorities, including Hispanics, have higher ESRD rates.\(^6\) The incident rates of ESRD for African Americans and Hispanics are 3.5 and 1.5 times greater than non-Hispanic whites, respectively.\(^4\) Another unique feature is that although dialysis therapy is expected to be lifesaving, some 20% of dialysis patients die each year, resulting in a low 5-year survival (<35%), worse than many fatal cancers. Over half of the CKD deaths are attributable to cardiovascular or infectious deaths. The etiology of the poor ESRD survival is unknown. A 4-decade focus on treating conventional cardiovascular risk factors in dialysis patients, including hyperlipidemia and hypertension, has changed the mortality only marginally, evidenced by slight improvement over the last few years, which is possibly linked to increased use of cardiovascular and renoprotective agents.\(^7\)

Strangely enough, there is a unique connection between the two aforementioned distinctive features of the ESRD patients in that, for reasons that have remained unexplained, dialysis patients from minority groups have greater longevity than non-Hispanic whites. The ESRD racial survival disparities of dialysis patients can even be referred to as a survival paradox for African Americans, in whom the lower dialysis mortality contrasts sharply with the general population in which African Americans have a shorter life expectancy than whites.\(^4\)

Although a recent study found that the survival advantage of African-American dialysis patients exists mainly among those older than 50 years of age,\(^5\) the study’s reference group comprised all white patients including Hispanic whites, who are also known to have greater survival than non-Hispanic whites.\(^8\) Indeed, the greater survival of African Americans and Hispanics persists despite adjustments for demographics, residency, dialysis modality or technique, and causes of death, among others.\(^6\)

Examining these unusual disparities and paradoxes may be the key to discovering factors that can improve longevity in all CKD patients and probably in other populations with chronic disease and will be a major step to improving outcomes for all patients. In line with ongoing efforts to discover the roots of the racial survival disparities in CKD, several candidate factors have been suggested\(^4,7\): racial/ethnic differences in nutritional and inflammatory profile and diet; differences in mineral-bone disorders, including higher parathyroid hormone levels in African-American patients leading to higher likelihood of receiving active vitamin D agents; differences in psychosocial status and coping mechanisms, including perception of quality of life; differences in dialysis treatment and techniques; and genetic or other inherent differences related to CKD and cardiovascular disease progression.

Emerging data indicate that the nutritional-inflammatory axis is an important and biologically plausible mechanism in engendering survival differentials across race.\(^9\) At least two-thirds of all dialysis patients show evidence of muscle and fat wasting and increased levels of inflammatory markers, in-
cluding circulating proinflammatory cytokines. The concurrence of protein-energy wasting (malnutrition), chronic inflammation, and oxidative stress in CKD patients who also have a high prevalence of cardiovascular disease and thromboembolic events has resulted in new terminologies such as malnutrition-inflammatory atherosclerosis or the malnutrition-inflammation complex (or cachexia) syndrome (MICS).6

In dialysis patients, evidence suggests that measures of MICS such as low levels of serum albumin, low body mass index (BMI), or high inflammatory markers (such as C-reactive protein (CRP) or IL-6) are by far stronger predictors of death and cardiovascular events than traditional risk factors.9 Other surrogates of protein-energy wasting such as anorexia and low dietary protein intake are also associated with inflammation and death.10 Malnutrition and inflammation may be involved in thrombocytosis and platelet activation, endothelial dysfunction, and adhesion molecule modulation, leading to increased risk of thromboembolic and cardiovascular events.11

Theoretically, an intervention that can correct MICS among dialysis patients may save as many as 20,000 lives each year.12 The effect of most surrogate markers of MICS, such as inflammatory cytokines or sarcopenia, has not been well studied across racial and ethnic groups of CKD patients. It is not clear how different the predictability of mortality of the surrogates is across age or different races, or how inflammation, body composition, nutrient intake, or other factors can modulate inflammation or contribute to racial/ethnic survival disparities in CKD. Examining these important questions may lead to discovering new mechanisms and interventions to improve longevity in millions of individuals with chronic wasting syndromes.13

In this issue of JASN, a study by Crews et al.14 advances our understanding of the racial survival paradox in dialysis patients and the role of the inflammatory and nutritional axis as one of the intervention-amenable and biologically plausible mechanims. The investigators here examined a cohort of 554 white and 262 African-American dialysis patients for up to 9.5 years and confirmed 30% lower 5-year mortality in the latter group after adjusting for demographics and several other covariates. A risk differential was noted across tertiles of inflammatory markers in that an even higher survival advantage of African-American race was reported among those with a worse inflammatory profile, whereas no survival differential existed in the lowest CRP or IL-6 tertiles.14

The study has a few limitations, including a lack of repeat measures of inflammation and missing data on dietary assessment and body composition methods. Moreover, there may be overadjustment that can introduce new sources of bias given an extended multivariate adjustment for such heterogeneous factors as dialysis modality, smoking, BMI, diabetes, BP, cholesterol, cardiovascular disease, congestive heart failure, comorbid disease, hemoglobin, albumin, CRP, and IL-6, in addition to demographic variables. Notwithstanding all of these limitations, the results of the study contribute to advancing the field.14

The findings by Crews et al.14 are similar to several recently published studies examining patterns and predictors of racial survival paradoxes. Streja et al.6 found that in over 124,000 hemodialysis patients across the United States, African Americans and Hispanics had lower unadjusted and case-mix-adjusted mortality over 5 years than non-Hispanic whites, but after controlling for surrogates of nutritional status and inflammation, Hispanics had mortality similar to non-Hispanic whites whereas African Americans had even higher mortality. These findings suggest that the racial/ethnic differences in survival are due, at least in part, to a more favorable nutritional/inflammatory profile in certain groups. Ricks et al.,15 examining the consistency of the obesity paradox across racial and ethnic groups of a large and nationally representative cohort of hemodialysis patients, also found that whereas the survival advantage of high BMI was consistent across all racial/ethnic groups, African-American patients had the strongest and most consistent association of higher BMI with greater survival. In a contemporary 6-year cohort of 799 hemodialysis patients in Southern California, Noori et al.9 reported that 279 African Americans had higher lean body mass and serum prealbumin, creatinine, and homocysteine levels, and their dietary intakes were higher in energy (+293 ± 119 cal/d) and fat (+18 ± 5 g/d) but lower in fiber (−2.9 ± 1.3 g/d) than whites. Whereas in the latter study CRP and IL-6, but not TNF-α, were associated with increased mortality in both races, the highest versus lowest quartile of IL-6 was less strongly (2.4 times) associated with increased mortality in African Americans than in whites (4.1 times),9 a finding similar to the study by Crews et al.14

Racial differences in survival pattern have also been reported for conditions other than nutrition and inflammation. Miller et al.16 found that dose of hemodialysis treatment and time had different associations with survival in different sex or race groups. Feroze et al.17 recently reported that hemodialysis patients with higher percentage body fat or lower serum albumin or creatinine concentration perceived a poorer health-related quality of life, and that poor mental health in all and poor physical health in non-African-American patients correlated with mortality. A recent study related to metabolic bone disease found that the most prominent survival advantage of African-American dialysis patients was among those who received the highest dose of paricalcitol (>10 μg/wk), whereas the low dose group (>0 but <10 μg/wk) exhibited weaker survival, and no survival difference (or even a tendency toward higher mortality of African Americans) was noted among those who did not receive any vitamin D receptor activation therapy.18 In the latter study, the driving force for active vitamin D prescription and dose selection was the higher parathyroid hormone levels in African Americans.18

In summary, there are now at least two recent studies9,14 suggesting that in African Americans, the mortality predict-
ability of IL-6 is significantly less than whites, implying that the effect of key inflammatory biomarkers on mortality is mitigated in African Americans. That African Americans may be more resilient against the death effect of inflammation appears similar to the permissive effect of genotype on the lethality of inflammation in other studies. Racial disparities in nutritional and inflammatory measures in dialysis patients may have a bearing on disparities in clinical outcomes and, in particular, on survival. Additional studies including randomized controlled trials of race and genotype-tailored dietary and/or pharmacologic interventions could provide much needed information on these associations.

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REFERENCES


See related article, “Inflammation and the Paradox of Racial Differences in Dialysis Survival,” on pages 2279–2286.

Chronotherapy in Hypertension: A Pill at Night Makes Things Right?

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BP, as well as many other important physiologic variables, is synchronized in a predictable manner with the circadian activity-rest cycle. Many cardiovascular, renal, and gastrointestinal functions also undergo a day–night pattern, influencing BP as well as absorption, metabolism, and elimination of antihypertensive medications. Particularly relevant is the circadian pat-