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Pontoglio M: Defective planar cell polarity in polycystic kidney disease. *Nat Genet* 38: 21–23, 2006
16. Nishio S, Tian X, Gallagher AR, Yu Z, Patel V, Igarashi P, Somlo S: Loss of oriented cell division does not initiate cyst formation. *J Am Soc Nephrol* 21: 295–302, 2010
17. Karner C, Wharton KA Jr, Carroll TJ: Planar cell polarity and vertebrate organogenesis. *Semin Cell Dev Biol* 17: 194–203, 2006
18. Karner CM, Chirumamilla R, Aoki S, Igarashi P, Wallingford JB, Carroll TJ: Wnt9b signaling regulates planar cell polarity and kidney tubule morphogenesis. *Nat Genet* 41: 793–799, 2009
19 McNeill H: Planar cell polarity and the kidney. *J Am Soc Nephrol* 20: 2104–2111, 2009
20. McNeill H: Planar cell polarity: Keeping hairs straight is not so simple. *Cold Spring Harb Perspect Biol* 2:a003376, 2010

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Is the Malnutrition-Inflammation Complex the Secret behind Greater Survival of African-American Dialysis Patients?

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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]: 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.[6] At least two-thirds of all dialysis patients show evidence of muscle and fat wasting and increased levels of inflammatory markers, in-

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cluding circulating proinflammatory cytokines.[9] 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-inflammation 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 mechanisms. 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 ($+293 \pm 119$ cal/d) and fat ($+18 \pm 5$ 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 μ/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 studies[9,14] 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.[19] 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.

DISCLOSURES

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REFERENCES

1. Norris K, Nissenson AR: Race, gender, and socioeconomic disparities in CKD in the United States. *J Am Soc Nephrol* 19: 1261–1270, 2008
2. Prakash S, Rodriguez RA, Austin PC, Saskin R, Fernandez A, Moist LM, O'Hare AM: Racial composition of residential areas associates with access to pre-ESRD nephrology care. *J Am Soc Nephrol* 21: 1192–1199, 2010
3. Alves TP, Wang X, Wright JT Jr, Appel LJ, Greene T, Norris K, Lewis J: Rate of ESRD exceeds mortality among African Americans with hypertensive nephrosclerosis. *J Am Soc Nephrol* 21: 1361–1369, 2010
4. Kalantar-Zadeh K, Golan E, Shohat T, Streja E, Norris KC, Kopple JD: Survival disparities within American and Israeli dialysis populations: Learning from similarities and distinctions across race and ethnicity. *Semin Dial* 23: 586–594, 2010
5. Kucirka LM, Grams ME, Lessler J, Hall EC, James N, Massie AB, Montgomery RA, Segev DL: Association of race and age with survival among patients undergoing dialysis. *JAMA* 306: 620–626, 2011
6. Streja E, Kovesdy CP, Molnar MZ, Norris KC, Greenland S, Nissenson AR, Kopple JD, Kalantar-Zadeh K: Role of nutritional status and inflammation in higher survival of African American and Hispanic hemodialysis patients. *Am J Kidney Dis* 57: 883–893, 2011
7. U.S. Renal Data System: *USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, Bethesda, MD, National Institute of Health, National Institute of Diabetes and Digestive and Kidney Disease, 2011
8. Kalantar-Zadeh K, Kopple JD, Norris, KC: Racial survival paradox of dialysis patients: Robust and resilient [Invited Editorial]. *Am J Kid Dis* 2011, in press
9. Noori N, Kovesdy CP, Dukkipati R, Feroze U, Molnar MZ, Bross R, Nissenson AR, Kopple JD, Norris KC, Kalantar-Zadeh K: Racial and ethnic differences in mortality of hemodialysis patients: Role of dietary and nutritional status and inflammation. *Am J Nephrol* 33: 157–167, 2011
10. Kalantar-Zadeh K, Cano NJ, Budde K, Chazot C, Kovesdy CP, Mak RH, Mehrotra R, Raj DS, Sehgal AR, Stenvinkel P, Ikizler TA: Diets and enteral supplements for improving outcomes in chronic kidney disease. *Nat Rev Nephrol* 7: 369–384, 2011
11. Molnar MZ, Streja E, Kovesdy CP, Budoff MJ, Nissenson AR, Krishnan M, Anker SD, Norris KC, Fonarow GC, Kalantar-Zadeh K: High platelet count as a link between renal cachexia and cardiovascular mortality in end-stage renal disease patients. *Am J Clin Nutr* 94: 945–954, 2011
12. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, McAllister CJ, Alcorn H Jr, Kopple JD, Greenland S: Revisiting mortality predictability of serum albumin in the dialysis population: Time dependency, longitudinal changes and population-attributable fraction. *Nephrol Dial Transplant* 20: 1880–1888, 2005
13. Friedman AN, Fadem SZ: Reassessment of albumin as a nutritional marker in kidney disease. *J Am Soc Nephrol* 21: 223–230, 2010
14. Crews DC, Sozio SM, Liu Y, Coresh J, Powe, NR: Inflammation and the paradox of racial differences in dialysis survival. *J Am Soc Nephrol* 22: 2279–2286 2011
15. Ricks J, Molnar MZ, Kovesdy CP, Kopple JD, Norris KC, Mehrotra R, Nissenson AR, Arah OA, Greenland S, Kalantar-Zadeh K: Racial and ethnic differences in the association of body mass index and survival in maintenance hemodialysis patients. *Am J Kidney Dis* 58: 574–582, 2011
16. Miller JE, Kovesdy CP, Nissenson AR, Mehrotra R, Streja E, Van Wyck D, Greenland S, Kalantar-Zadeh K: Association of hemodialysis treatment time and dose with mortality and the role of race and sex. *Am J Kidney Dis* 55: 100–112, 2010
17. Feroze U, Noori N, Kovesdy CP, Molnar MZ, Martin DJ, Reina-Patton A, Benner D, Bross R, Norris KC, Kopple JD, Kalantar-Zadeh K: Quality-of-life and mortality in hemodialysis patients: Roles of race and nutritional status. *Clin J Am Soc Nephrol* 6: 1100–1111, 2011
18. Kalantar-Zadeh K, Miller JE, Kovesdy CP, Mehrotra R, Lukowsky LR, Streja E, Ricks J, Jing J, Nissenson AR, Greenland S, Norris KC: Impact of race on hyperparathyroidism, mineral disarrays, administered vitamin D mimetic, and survival in hemodialysis patients. *J Bone Miner Res* 25: 2448–2458, 2010
19. Kovesdy CP, Kalantar-Zadeh K: Do genes allow inflammation to kill or not to kill? *J Am Soc Nephrol* 20: 1429–1431, 2009

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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-