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Nutritional and Inflammatory Axis of Racial Survival Disparities

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Protein energy wasting (PEW) is highly prevalent in the dialysis population (1, 2). Several studies have shown that PEW tends to occur concomitantly with inflammation and both conditions are strongly associated with higher mortality in dialysis patients (3-7). It has been proposed that the combination of PEW and inflammation in dialysis patients be designated as malnutrition-inflammation complex syndrome (MICS) (8-10) or malnutrition, inflammation, and atherosclerosis (MIA) syndrome (11).

Conditions leading to PEW and inflammation appear to overlap. Causes of MICS include inadequate nutrient intake, nutrient loss during dialysis, inflammation caused by comorbid conditions and dialysis treatment, endocrine disorders of uremia, oxidative and carbonyl stress, uremic toxins, volume overload and reduced clearance of pro-inflammatory cytokines. The presence of MICS in dialysis patients is signaled by hypoalbuminemia, hypocholesterolemia, hypohomocysteinemia, increased levels of inflammatory markers and low body mass index, and its possible consequences include erythropoietin hyporesponsiveness, increased risks of atherosclerotic cardiovascular events, poor quality of life, and increased hospitalization and mortality rates in dialysis patients (Figure 1) (8).

Race-ethnicity and survival paradoxes in CKD and ESRD

The annual mortality rate for US dialysis patients is approximately 20%; the extremely low 5-year survival rate (<35%) is lower than that for many cancer patients (12, 13). It has been recognized that ESRD is more commonly encountered in certain races/ethnicities particularly in African Americans and Hispanics (14). In 2009, incidence rates of ESRD in the United States for African Americans and Hispanics were 3.5 and 1.5 times higher than that seen in non-Hispanic whites, respectively (15). Contributing factors to these racial/ethnicity discrepancies include, but are not limited to a genetic susceptibility to select glomerular diseases, increased rates of major risk factors such as diabetes mellitus, and hypertension, disparities in socioeconomic status affecting access to care, and cultural differences such as diet and lifestyle choices (14). Even though African Americans comprise only 12% of the general population in the United States (16), approximately 37% of the
prevalent US dialysis patients are African American. Similarly, Hispanics compose 16% of the US dialysis population (15). Compared with white dialysis patients, black patients are less likely to be dialyzed adequately (17) and undergo AV fistula placement (18, 19). In the US general population, blacks have higher mortality rates than whites due to multiple factors, including but not limited to disparities in income, education, health, diet, lifestyles and co-morbidities (20, 21).

In spite of racial disparities in receipt of ESRD quality care indicators and a shorter life expectancy for blacks compared with that among whites in the general population, African American and Hispanic CKD and dialysis patients have greater survival than non-Hispanic white patients even after adjusting for such traditional risk factors as demographics, socioeconomic status, dialysis vintage, dialysis dose, co-morbid conditions and the presence of residual kidney function (22, 23). The racial/ethnic survival disparities of CKD and dialysis patients have been cited as a survival paradox for minorities including African Americans and Hispanics (24). Efforts have been made to discover the factors responsible for survival advantages of African American and Hispanic dialysis population. Better understanding the potential causes of racial/ethnic survival disparities in dialysis patients might improve outcomes in patients with chronic kidney diseases, other chronic disease states and even the general population. Possible contributing factors to racial survival disparities in dialysis patients include differences in nutritional status, dietary intake, body composition, inflammatory profiles, mineral bone disorders, psychosocial status, mental coping mechanisms, dialysis treatments and genetic polymorphisms (21, 23, 25-34) (Figure 2).

**Nutritional axis of racial survival disparities of dialysis population**

Survival disparities across various racial/ethnic groups in the dialysis population can be attributed in part to differences in nutritional status, dietary intakes and body composition. A prospective 6 year cohort study of 799 hemodialysis patients by Noori et al. (32) reported that African Americans had better nutritional status including higher body mass index, lean body mass, serum pre-albumin, creatinine and homocysteine concentrations compared with white patients. This study also observed that African Americans had significantly higher dietary energy and both unsaturated and saturated fat intake but lower dietary intake of fibers than white dialysis patients. In this study, higher serum levels of albumin, pre-albumin and creatinine correlated with greater survival in all racial/ethnic groups, though this association was not statistically significant for serum creatinine concentrations in African Americans (32).

Similarly, Streja et al. (23) studied association of race/ethnicity with 5-year survival in 124,029 US hemodialysis patients including African Americans (35%), non-Hispanic Whites (49%) and Hispanics (16%) and found that African Americans and Hispanics had greater survival rates than non-Hispanic Whites in spite of controlling for demographics, socioeconomic status, diabetes, dialysis vintage, dialysis dose and presence of residual renal function. However, after adjustment for surrogate markers of nutritional and inflammatory status, African Americans had even higher mortality rates than Whites, while Hispanics had similar survival rates compared to White patients (23), suggesting a powerful role for the influence of nutrition and inflammation on mortality.

Several cohort studies observed that higher body mass index (BMI) correlated with better survival in the dialysis population (35-37). In the U.S. ESRD population, the prevalence of obesity was higher in blacks compared to non-Hispanic Whites (38). A 6 year cohort study of 109,605 hemodialysis patients by Ricks et al. (33) investigated the association of increased body mass index with mortality among different races/ethnicities. This study
showed that higher BMI was associated with lower mortality in all race groups with various
degrees of correlation. A 1 kg/m$^2$ higher BMI correlated with 2%, 2.5% and 1% lower risk
of death for non-Hispanic Whites, Blacks and Hispanics, respectively.

**Inflammatory axis and racial/ethnic survival disparities of dialysis patients**

In addition to differences in nutritional status, racial/ethnic differences in inflammation have
been postulated as potential contributors to racial/ethnic survival paradox of the dialysis
population. Crews et al. (25) investigated the association of race and inflammation with
mortality in 816 incident hemodialysis patients including 554 Caucasians and 262 African
Americans with a median follow-up of 3 years. This study (25) supported a significant lower
mortality rate in African Americans compared to that seen in Caucasians after adjusting for
demographics and traditional risk factors. Nevertheless, the survival advantage of African
American dialysis patients was only seen in the presence of the highest levels of
inflammatory markers including C-reactive protein (CRP) and interleukin-6 (IL-6), whereas
survival disparities between African Americans and Caucasians did not exist in dialysis
patients with low-level inflammation. In the setting of elevated inflammation levels the
survival advantage of African Americans over Caucasians was more pronounced in patients
aged over 60 years, men and individuals with diabetes (25).

Similarly, Noori et al. (32) reported an association of higher levels of CRP and IL-6 with
increased mortality risks in African American and white dialysis patients. Interestingly, the
highest (vs. the lowest) quartile of IL-6 correlated with 2.4 and 4.1 times higher risks of
death in African Americans and whites, respectively suggesting that African Americans
might be more resilient when confronting the deleterious effects of inflammation. Moreover,
the study by Streja et al. cited above (23) showed that African Americans tended to have
lower white blood cell counts and higher percentages of lymphocytes reflecting a lower
level of inflammation or an attenuated inflammatory response. This study also found that
African American and Hispanic dialysis patients had better survival than whites; however,
after controlling for surrogates of MICS, African Americans actually had lower survival
than whites, whereas the survival rates between Hispanics and whites were similar. The
authors concluded that more favorable nutritional and inflammatory status could be a major
cause of the survival advantage seen among minority dialysis population (23).

A potential mechanism of action explaining the association of MICS with adverse outcomes
is its effect on thrombocytosis and platelet activation, predisposing to thromboembolic
events and death. A cohort study of 40,787 hemodialysis patients by Molnar et al. (39)
reported that higher platelet count correlated with markers of MICS including lower serum
levels of albumin, creatinine, hemoglobin, the percentages of lymphocyte counts,
normalized protein nitrogen appearance and Kt/V. Higher platelet count was also associated
with higher all-cause and cardiovascular mortality; however, the association of platelet
count with all-cause and cardiovascular mortality did not exist after controlling for
surrogates of MICS. The investigators hypothesized that MICS increased the mortality risk
dialysis patients in part via elevated platelet count and activity (39). Megakaryopoiesis is
regulated by inflammatory factors including IL-6, IL-11 and leukemia inhibitor factor,
which involves megakaryocyte maturation. The elevated levels and actions of inflammatory
cytokines such as IL-6 observed among dialysis patients could result in reactive
thrombocytosis (40, 41).

African American race-ethnicity may thus be an important effect-modifier for both the
development of inflammation and for the deleterious effects caused by inflammation once it
is established. This could be caused by genetic polymorphisms or environmentally induced
epigenetic changes, which may provide permissive effects of genotype on the mortality risk

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of inflammation (25, 29, 30). Further exploration of these phenomena could aid in the better identification of populations at highest risk for adverse outcomes. A better understanding of the genetic susceptibility to the development of inflammation, and to the deleterious effects of established inflammation could also further the development of targeted interventions against inflammation and its harmful effects.

**Conclusion**

In summary, racial/ethnic differences in nutritional status and the level of inflammation including host inflammatory response among dialysis patients appear to be substantial contributors to the survival disparities of dialysis patients. Studying the basis for these associations could shed light on novel mechanisms of action of inflammation, and could spawn the development of targeted screening and intervention strategies in the most vulnerable populations exposed to the effects of inflammation.

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**References**


Figure 1.
Possible causes and consequences of MICS (8).
Figure 2.
Possible contributing factors to racial survival disparities among the dialysis population (21, 23, 25-34).