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Authors
Noori, Nazanin
Kovesdy, Csaba P
Dukkipati, Ramanath
et al.

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Racial and Ethnic Differences in Mortality of Hemodialysis Patients: Role of Dietary and Nutritional Status and Inflammation

Nazanin Noori[a, b] Csaba P. Kovesdy[d] Ramanath Dukkipati[a] Usama Feroze[a, b] Miklos Z. Molnar[a] Rachelle Bross[b] Allen R. Nissenson[c, e] Joel D. Kopple[a–c] Keith C. Norris[c] Kamyar Kalantar-Zadeh[a–c]

[a]Harold Simmons Center for Chronic Disease Research and Epidemiology, and [b]Division of Nephrology and Hypertension, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, Calif., [c]David Geffen School of Medicine at UCLA and the UCLA School of Public Health, Los Angeles, Calif., [d]Salem Veterans Affairs Medical Center, Salem, Va., and [e]DaVita Inc., El Segundo, Calif., USA

Key Words

Black race · Hispanic ethnicity · African Americans · Non-Hispanic White · Nutritional status · Inflammatory markers · Dietary intake · Survival

Abstract

Background: Racial/ethnic disparities prevail among hemodialysis patients. We hypothesized that significant differences exist between Black and non-Hispanic and Hispanic White hemodialysis patients in nutritional status, dietary intake and inflammation, and that they account for racial survival disparities. ***Methods:*** In a 6-year (2001–2007) cohort of 799 hemodialysis patients, we compared diet and surrogates of nutritional-inflammatory status and their mortality-predictabilities between 279 Blacks and 520 Whites using matched and regression analyses and Cox with cubic splines. ***Results:*** In age-, gender- and diabetes-matched analyses, Blacks had higher lean body mass and serum prealbumin, creatinine and homocysteine levels than Whites. In case-mix-adjusted analyses, dietary intakes in Blacks versus Whites were higher in energy (+293 ± 119 cal/day) and fat (+18 ± 5 g/day), but lower in fiber (–2.9 ± 1.3 g/day) than Whites. In both races, higher serum albumin, prealbumin and creatinine were associated with greater survival, whereas CRP and IL-6, but not TNF-α, were associated with increased mortality. The highest (vs. lowest) quartile of IL-6 was associated with a 2.4-fold (95% CI: 1.3–3.8) and 4.1-fold (2.2–7.2) higher death risk in Blacks and Whites, respectively. ***Conclusions:*** Significant racial disparities exist in dietary, nutritional and inflammatory measures, which may contribute to hemodialysis outcome disparities. Testing race-specific dietary and/or anti-inflammatory interventions is indicated.

Introduction

Chronic kidney disease (CKD) is recognized as a global public health problem [1, 2]. CKD and, to a greater extent, end-stage renal disease (ESRD) are characterized by marked differences in the incidence, prevalence, and/or clinical outcomes across gender, age, socioeconomic status, geographic boundaries, and in particular race and ethnicity [3–6]. These different traits appear to confer either protection or increased risk for certain demographic

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Csaba P. Kovesdy, MD, FASN
Division of Nephrology, Salem VA Medical Center
1970 Roanoke Blvd.
Salem, VA 24153 (USA)
Tel. +1 540 982 2463, E-Mail csaba.kovesdy@va.gov

subpopulations, suggesting that there is much to learn beyond the traditional risk factors contributing to CKD and CKD-associated complications [7–9]. Major racial and ethnic disparities are among the important and unresolved issues in CKD patients [10–12]. Approximately one third of the 400,000 US dialysis patients are Blacks (also referred to as African Americans), even though they comprise only 14% of the US general population [13]. Hispanics compose close to one fifth of the dialysis population, but only 15% of the general population [14]. The racial and ethnic discrepancies in CKD have persisted over the past decades with 2008, incident rates in the African-American population 3.6 times greater than the rate among Whites, and the rate in the Hispanic population 1.5 times higher than that of non-Hispanics [14].

Protein-energy wasting and inflammation are among the strongest death predictors among CKD patients [15–17]. Race can confound the effects of such outcome-predictors as dialysis dose [4] and bone and mineral disorders in maintenance hemodialysis (MHD) patients [5, 18]. It is not clear whether surrogates of protein-energy wasting and inflammation, together also known as the malnutrition-inflammation complex syndrome (MICS), correlate differently with outcomes across various racial/ethnic groups based on diet, genes or other factors [13, 19]. In this study we compared dietary intakes, nutritional and body composition status, and biochemical values of MICS across racial/ethnic subgroups of MHD patients. We examined the effects of race on the association between risk factors and all-cause mortality in a group of 799 MHD patients and hypothesized that a more favorable dietary, nutritional and/or inflammatory profile accounts for survival differences across race.

Materials and Methods

Patient Population

The National Institutes of Health funded the 'Nutritional and Inflammatory Evaluation in Dialysis' (NIED) study, which was a prospective cohort study designed to examine correlates of malnutrition and inflammation in MHD patients [20–24]. The original patient cohort was derived from a pool of approximately 1,300 MHD outpatients treated in 8 DaVita dialysis clinics in the South Bay Los Angeles area (see www.NIEDStudy.org for more details). Inclusion criteria were adult outpatients who had been undergoing MHD for at least 8 weeks and who signed an Institutional Review Board-approved consent form. Patients with an anticipated life expectancy of less than 6 months (e.g. due to metastatic malignancy) were excluded. From October 1, 2001 through September 30, 2007, 893 MHD patients from the 8 clinics signed the informed consent form and were enrolled and followed in the study. Of these, after excluding Asians, Indian Americans and those of unknown racial/ethnic background, 799 patients including 279 African Americans and 520 Whites (63 non-Hispanics and 457 Hispanics) were included in this study. Dietary intakes of 128 subjects including 64 African Americans, 56 Hispanic Whites and 8 non-Hispanic Whites were assessed with a 3-day dietary record [25]. Patients were followed for up to 75 months, i.e. until December 31, 2007. The medical chart for each MHD patient was reviewed by a collaborating physician, and data pertaining to underlying kidney disease and other comorbid conditions were extracted. A modified version of the Charlson comorbidity index was used to assess the severity of comorbidities [20].

Race and Ethnicity

Race and ethnicity were defined as self-described demographic categories in accordance with the United States Census Bureau as in our previous studies [4–6]. Only self-reported African-American or White MHD patients were included in this study, leading to two mutually exclusive race categories. Ethnicity was described as either Hispanic or non-Hispanic. In our study, all Hispanic MHD patients were also White.

Anthropometric and Body Composition Measures

Biceps and triceps skinfold thicknesses were measured with a conventional skinfold caliper using standard techniques as previously described [24, 26, 27]. To estimate lean body mass (LBM), fat mass and percentage of body fat, portable near-infrared interactance was measured at the same time as the anthropometry was obtained using the same upper arm [28, 29].

Laboratory Tests

All blood specimens were obtained predialysis on a mid-week day except for sera for urea which were also obtained the same day postdialysis. The single-pool Kt/V was used to represent the weekly dialysis dose [4]. Except as indicated below, all laboratory measurements were performed by DaVita Laboratories (Deland, Fla., USA) using automated methods. In this study, 3-month averaged values were used, and all laboratory measurements used established assays with well-known coefficients of variation. The measurements performed in the GCRC Laboratories of Harbor-UCLA included serum C-reactive protein (CRP) by a turbidometric immunoassay (WPCI, Osaka, Japan; unit: mg/l, normal range: <3.0 mg/l) [30, 31], interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) via immunoassay kits (R&D Systems, Minneapolis, Minn., USA; units: pg/ml; normal range: IL-6: <9.9 pg/ml, TNF-α: <4.7 pg/ml) [32, 33], and total homocysteine via high-performance liquid chromatography and serum transthyretin (prealbumin) by immunoprecipitin analysis [34].

Three-Day Food Records with Dietary Interviews

In 128 MHD patients (64 African Americans, 56 Hispanic Whites and 8 non-Hispanic Whites), a substudy was performed in the GCRC at Harbor-UCLA, wherein a 3-day diet diary with diet interviews by a trained dietitian was used to estimate daily dietary intake [25]. Dietary intake was recorded over the last hemodialysis treatment day of the week (usually Friday or Saturday) and the 2 subsequent nondialysis days. The GCRC dietitians made changes to and corrections on the food record and used the Minnesota Nutrient Data System software (version 2005; Nutrition Coordinating Center, Minneapolis, Minn., USA) to complete the nutrient analysis [25].

Statistical Methods

We divided the patients into the following 3 mutually exclusive groups according to their race/ethnicity: African Americans, non-Hispanic Whites and Hispanic Whites. ANOVA with post hoc Bonferroni was used to examine differences across 3 groups. One-to-one matched analyses were also performed, in that for each non-Hispanic White MHD patient we randomly assigned an African-American and a Hispanic patient who were matched for age (±5 years), gender and diabetes. This exhaustive match resulted in 59 fully matched subjects in each of the 3 racial/ethnic groups. Repeated measures ANOVA with post hoc Bonferroni were employed to examine the differences across 3 matched groups. In subsequent analyses we collapsed Hispanic and non-Hispanic Whites into the single racial category 'Whites' and compared data between the two races (Whites vs. African Americans) irrespective of ethnicity using t tests. Linear regression models were used to calculate dietary differences between the groups after adjusting for conventional case-mix, i.e. age, gender, diabetes mellitus and dialysis vintage.

In the 6-year cohort we also examined the association of survival with 6 biochemical markers of MICS, i.e. serum levels of prealbumin, albumin, creatinine, CRP, IL-6 and TNF-α, within the 2 main racial categories and estimated death hazard ratios (HR) using Cox proportional hazard models after adjustment for case-mix. A restricted cubic splines graph was utilized as an exploratory data analysis strategy to illustrate systematic relations between these biomarkers and mortality within each group and to examine the linearity assumptions. Descriptive and multivariate statistics were carried out with Stata statistical software (version 10.0; Stata Corp., College Station, Tex., USA).

Results

Demographic, clinical and relevant biochemical values of all the 799 MHD patients according to race/ethnic categories are shown in table 1. African Americans had higher BMI, LBM, mid-arm muscle circumference (MAMC), and biceps and triceps skinfolds in comparison to Hispanic patients. After one-to-one matching of the 3 mutually exclusive racial/ethnic groups based on age, gender and diabetes, 59 matched MHD patients remained in each racial group as shown in table 2. The matched patients averaged 58 ± 17 years of age and included 49% women and 56% diabetics in each group. Compared to non-Hispanic Whites, African Americans still exhibited higher BMI, LBM and MAMC, as well as greater predialysis serum levels of prealbumin, creatinine and homocysteine. Compared to non-Hispanic Whites, Hispanic MHD patients had lower MAMC and LBM and lymphocyte percentages, but otherwise the characteristics of both White groups of MHD patients were similar even after being matched. These results justified combining them into a single group designated as 'Whites'.

Comparisons of dietary intakes in a subgroup of 128 MHD patients according to race/ethnicity are shown in table 3. We combined the non-Hispanic and Hispanic Whites into one single 'White' group, especially since there were only 8 non-Hispanic White subjects with available dietary data. Linear regression analyses were performed to compare the dietary intakes of African Americans to Whites after adjustment for case-mix variables. In comparison with Whites, African Americans had higher intakes of energy, protein, fat, saturated fatty acid, monounsaturated fatty acid and polyunsaturated fatty acid, but less fiber (–2.9 ± 1.3 g/day). We also compared the subjective global assessment of nutrition across the groups, but the differences were not significant (data not shown).

Over the 6 years of the cohort, 317 (40%) patients, including 181 Whites and 136 African Americans, died. The survival rates among Whites and African Americans were 65 and 51%, respectively ($p = 0.008$). The death HR (and their 95% CI) across the quartiles of 6 laboratory surrogates of MICS for African Americans and Whites are shown in table 4. Higher predialysis serum albumin, prealbumin and creatinine concentrations were associated with greater survival in all patients, although this trend was not statistically significant for serum creatinine in African Americans. Among inflammatory markers, higher CRP and IL-6, but not TNF-α, were incrementally associated with increased death risk in both races. In particular, the highest quartile of IL-6 was associated with 2.4 times and 4.1 times higher death risk compared to the lowest quartile in African American and Whites, respectively (table 4). Cubic spline graphs were used to verify and compare the mortality predictability of these 6 MICS biochemical markers between the two races (fig. 1–6). Higher levels of serum albumin and prealbumin appeared protective, whereas higher CRP and IL-6 levels were associated with higher mortality in both Whites and African Americans consistent with data in table 4. TNF-α was the only marker not associated with survival in either racial groups.

Discussion

In a 6-year contemporary cohort of 799 MHD patients, we compared dietary intake and surrogates of nutritional status and inflammation and their mortality-predictabilities between African Americans and Whites ($n = 520$), who were mostly Hispanic. In age, gender and diabetes-matched analyses, African American MHD pa-

Table 1. Demographic, clinical and laboratory values in 799 MHD patients according to race and ethnicity

Variables	All patients (n = 799)	Race			p values	
		African Americans (n = 279)	Whites		unadjusted	case-mix-adjusted[a]
			Hispanics (n = 457)	non-Hispanics (n = 63)		
Age, years	54 ± 15	55 ± 15	52 ± 15	59 ± 16	<0.01	
Women, %	47	51	45	49	0.33	
Diabetes mellitus, %	53	47	57	57	0.02	
Primary insurance: % Medicare	51	57	49	41	0.04	
Marital status: % married	46	35	52	49	<0.01	
Charlson comorbidity index score	1.9 ± 1.6	1.9 ± 1.7	1.8 ± 1.6	2.1 ± 1.5	0.28	
Body composition:						
BMI	26.5 ± 6.1	27.3 ± 6.7	25.9 ± 5.5	27.0 ± 6.0	0.01	<0.01
Triceps skinfold, mm	17.5 ± 9.9	19.1 ± 11.6	16.4 ± 8.8	18.3 ± 9.8	<0.01	<0.01
Biceps skinfold, mm	9.8 ± 7.8	11.4 ± 8.9	9.0 ± 7.1	10.3 ± 6.5	<0.01	<0.01
MAMC, cm	30.8 ± 5.7	32.4 ± 5.9	29.7 ± 5.2	32.0 ± 5.7	<0.01	<0.01
NIR body fat, %	26.6 ± 10.9	26.5 ± 12.1	26.2 ± 10.5	29.3 ± 11.0	0.13	0.46
NIR lean body mass, kg	53.6 ± 22.0	59.0 ± 33.0	50.4 ± 24	50.4 ± 27	<0.01	<0.01
Hemodialysis treatment						
Dialysis vintage, months	28 ± 26	33 ± 29	26 ± 25	20 ± 22	<0.01	<0.01
Dialysis dose, Kt/V (sp)[b]	1.6 ± 0.3	1.53 ± 0.27	1.64 ± 0.31	1.55 ± 0.31	<0.01	<0.01
Erythropoietin, 10^3 U/week	14.5 ± 12.5	17.1 ± 13.5	14.9 ± 12.4	13.6 ± 16.8	0.28	0.21
Biochemical measurements[b]						
Serum albumin, mg/dl	3.90 ± 0.41	3.84 ± 0.32	3.95 ± 0.42	3.84 ± 0.41	0.11	0.33
Prealbumin, mg/dl	27.9 ± 9.6	28.9 ± 9.2	27.8 ± 9.9	24.8 ± 7.9	0.01	0.02
Total homocysteine, μmol/l	23.9 ± 11.2	26.6 ± 13.4	22.8 ± 9.7	20.2 ± 6.7	<0.01	<0.01
Creatinine, mg/dl	10.2 ± 3.3	11.3 ± 3.3	9.6 ± 3.1	8.8 ± 3.1	<0.01	<0.01
Calcium, mg/dl	9.3 ± 0.7	9.5 ± 0.7	9.2 ± 0.6	9.3 ± 0.5	0.19	<0.01
Phosphorus, mg/dl	5.8 ± 1.5	5.9 ± 1.5	5.7 ± 1.5	5.9 ± 1.7	0.83	0.88
Bicarbonate, mEq/l	22.2 ± 2.9	22.8 ± 2.9	22.0 ± 2.9	21.6 ± 2.6	<0.01	<0.01
TIBC, mg/dl	207 ± 40	203 ± 39	207 ± 40	223 ± 44	<0.01	<0.01
Iron, mg/dl	65 ± 26	59 ± 23	69 ± 27	65 ± 31	<0.01	<0.01
CRP, mg/l	5.9 ± 7.1	6.5 ± 7.9	5.3 ± 6.4	7.8 ± 7.9	<0.01	<0.01
IL-6, pg/ml	18.8 ± 52.2	11.7 ± 12.4	12.0 ± 14.8	13.7 ± 15.1	0.62	0.60
TNF-α, pg/ml	8.7 ± 12.1	10.0 ± 16.8	7.8 ± 8.2	9.5 ± 10.2	0.05	0.04
Blood hemoglobin, g/dl[b]	12.0 ± 1.0	12.0 ± 1.0	12.1 ± 1.0	11.9 ± 1.0	0.12	0.30
Lymphocyte, %	22.8 ± 8.0	24.1 ± 8.3	22.7 ± 7.5	17.3 ± 7.1	<0.01	<0.01

p values are based on ANOVA. NIR = Near-infrared; TIBC = total iron-binding capacity. [a] Case-mix = Age, gender, diabetes and vintage. [b] Serum and blood values were obtained immediately predialysis except for serum urea which was obtained pre-and postdialysis.

tients exhibited higher measures of muscle and lean mass, including larger BMI, LBM and MAMC, and higher levels of predialysis serum prealbumin, creatinine and homocysteine than Whites. In case-mix-adjusted analyses, African Americans had higher dietary intakes of energy and fat, but lower intake of dietary fiber than Whites. In survival analyses within each racial group, higher serum albumin, prealbumin and creatinine were associated with greater survival, although the trends were not statistically significant for serum creatinine in African Americans. Higher CRP and IL-6, but not TNF-α, were associated with increased death risk. In particular, the highest (vs. lowest) quartile of IL-6 was associated with 2.4-fold and 4.1-fold increased death risk in African Americans and Whites, respectively, which may indicate that the impact of inflammation on dialysis patient mortality may be somewhat mitigated in African Americans. These findings imply racial disparities in dietary, nutritional

Table 2. Matched groups of MHD patients and their demographic, clinical and laboratory values

Variables	AA (n = 59)	HW (n = 59)	NHW (n = 59)	p value AA vs. NHW	p value HW vs. NHW
Age, years (matched ± 5 years)	58 ± 16	58 ± 17	59 ± 17	0.98	0.84
Women, % (matched)	49	49	49	0.99	0.99
Diabetes mellitus, % (matched)	56	56	56	0.99	0.99
Primary insurance, % Medicare	57	49	38	0.11	0.38
Marital status, % married	41	48	47	0.58	0.98
Charlson comorbidity index score	2.4 ± 1.8	1.7 ± 1.4	2.0 ± 1.6	0.12	0.10
Body composition					
BMI	29.1 ± 7.6	25.8 ± 4.6	27.0 ± 6.4	0.04	0.28
Triceps skinfold, mm	19.3 ± 12.6	16.6 ± 9.5	18.2 ± 9.9	0.33	0.37
Biceps skinfold, mm	12.1 ± 9.2	10.4 ± 10.7	10.4 ± 6.7	0.12	0.99
MAMC, cm	33.4 ± 5.8	29.7 ± 5.8	31.9 ± 5.8	0.04	0.04
NIR measured body fat, %	26.9 ± 12.4	27.1 ± 10.0	28.8 ± 10.8	0.57	0.14
NIR lean body mass, kg	59.8 ± 11.0	48.8 ± 9.1	53.1 ± 12.0	<0.01	0.01
Hemodialysis treatment					
Dialysis vintage, months	30 ± 27	21 ± 20	18 ± 18	<0.01	0.19
Dialysis dose, Kt/V single pool	1.48 ± 0.27	1.70 ± 0.36	1.56 ± 0.32	0.27	0.03
Erythropoietin dose, 10^3 U/week	19,380 ± 2,357	15,476 ± 2,288	14,598 ± 1,929	0.12	0.82
Biochemical measurements					
Serum albumin, mg/dl	3.8 ± 0.4	3.8 ± 0.4	3.8 ± 0.4	0.79	0.61
Prealbumin, mg/dl	29.0 ± 9.5	25.1 ± 8.4	24.7 ± 8.1	<0.01	0.90
Total homocysteine, μmol/l	28.0 ± 12.3	23.0 ± 14.5	20.8 ± 6.5	<0.01	0.32
Creatinine, mg/dl	11.1 ± 2.9	9.0 ± 2.7	8.9 ± 3.2	<0.01	0.62
Calcium, mg/dl	9.5 ± 0.6	9.3 ± 0.7	9.2 ± 0.5	0.06	0.56
Phosphorus, mg/dl	5.9 ± 1.5	5.6 ± 1.3	6.0 ± 1.7	0.96	0.94
Bicarbonate, mg/dl	22.4 ± 3.5	22.3 ± 0.3	21.6 ± 2.4	0.22	0.20
TIBC, mg/dl	207 ± 40	210 ± 45	225 ± 45	0.06	0.09
Iron, mg/dl	62 ± 27	68 ± 27	66 ± 32	0.58	0.87
CRP, mg/l	6.7 ± 6.4	5.6 ± 5.9	7.8 ± 8.3	0.47	0.21
IL-6, pg/ml	10.3 ± 9.7	11.6 ± 9.6	13.4 ± 15.1	0.52	0.83
TNF-α, pg/ml	7.5 ± 7.7	7.4 ± 4.9	9.6 ± 9.6	0.20	0.14
Blood hemoglobin, g/dl	12.2 ± 3.1	12.3 ± 3.2	11.9 ± 2.1	0.31	0.11
Lymphocyte, %	21.1 ± 5.7	17.7 ± 7.2	21.6 ± 7.7	0.01	<0.01

For each non-Hispanic White MHD patient, an age- (±5 years), gender- and diabetes-matched MHD patient from among African-American and Hispanic White MHD patients was selected randomly. p values are based on post hoc Bonferroni. Serum and blood values were obtained immediately predialysis except for serum urea which was obtained pre- and postdialysis. AA = African American; NHW = non-Hispanic White; HW = Hispanic White; NIR = near-infrared; TIBC = total iron-binding capacity.

and inflammatory measures in MHD patients, which may bear on the disparities in clinical outcomes. Hence, our findings may have major clinical and public health implications on the clinical and dietary management of advanced CKD patients.

It has long been recognized that CKD, and particularly ESRD, is more common in certain racial and ethnic groups [13, 35]. The racial and ethnic disparities of CKD have been extensively reported in the United States, with the African-American population having the highest reported incidence and prevalence of treated ESRD worldwide [14, 36]. Compared with non-Hispanic Whites, African Americans are more likely to have hypoalbuminemia and severe anemia, and are less likely to receive erythropoietin therapy before dialysis [12, 37]. Despite advances in renal replacement therapy, including dialysis techniques, overall long-term survival in ESRD is dreadfully low [12, 14, 38]. There exists, however, a racial survival paradox [13, 39]. Despite evidence that non-White ESRD patients are more likely to have such poor survival indicators as hypoalbuminemia and anemia or limited pre-ESRD care, their survival chance on dialysis are par-

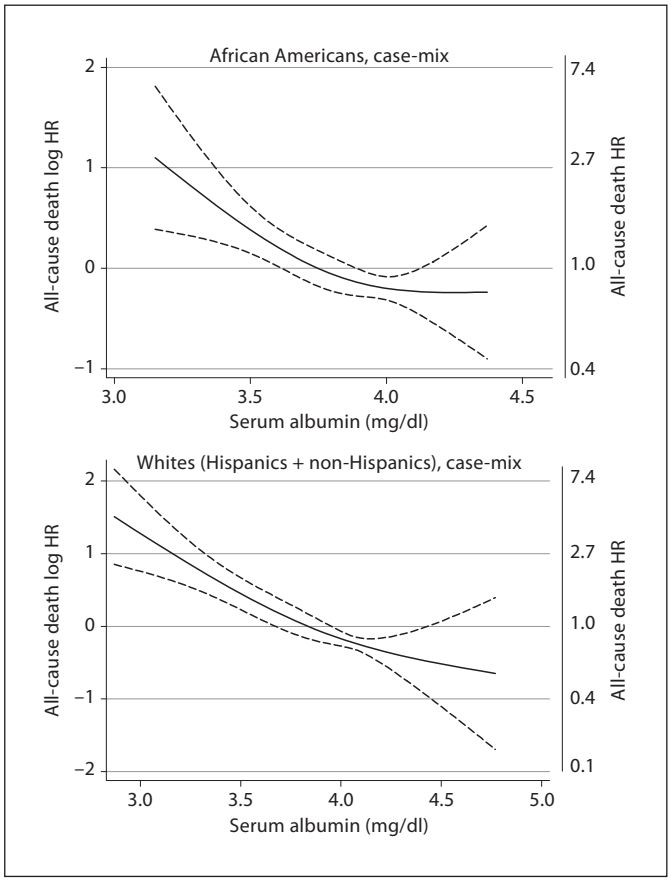

Fig. 1. Cubic spline models of the Cox proportional regression analyses reflecting adjusted mortality-predictability (with 95% CI) according to predialysis serum albumin in African-American (upper panel) vs. White (Hispanic and non-Hispanic, lower panel) MHD patients over 6 years. Spline models are with 2 degrees of freedom. Case-mix includes age, gender, diabetes mellitus, Charlson comorbidity index score and dialysis vintage.

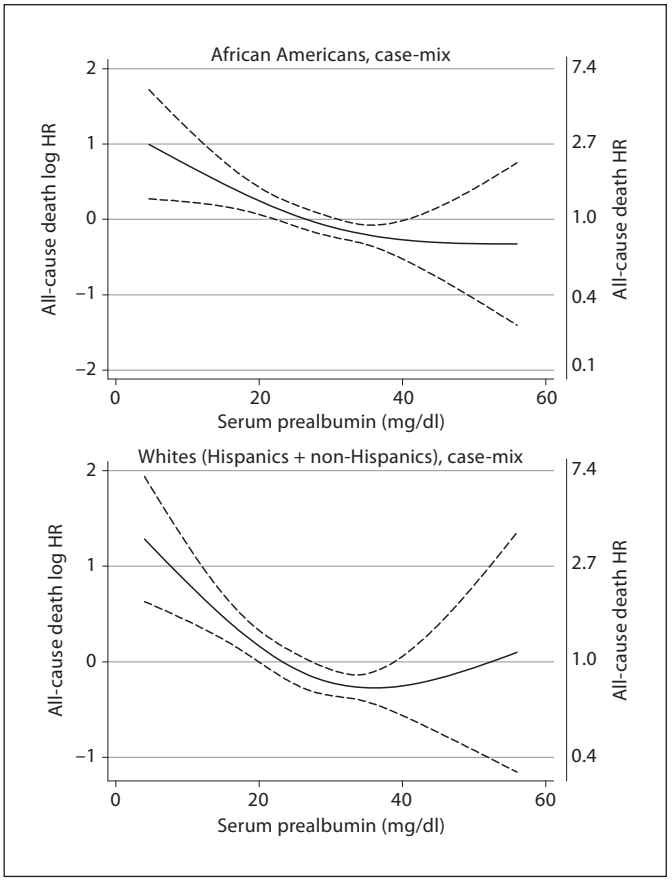

Fig. 2. Cubic spline models of the Cox proportional regression analyses reflecting adjusted mortality-predictability (with 95% CI) according to predialysis serum prealbumin in African-American vs. White (Hispanic and non-Hispanic) MHD patients over 6 years. Spline models are with 2 degrees of freedom. Case-mix includes age, gender, diabetes mellitus, Charlson comorbidity index score and dialysis vintage.

Table 3. Differences of the reported daily nutrient intake in 64 African-American MHD patients compared to 64 White[a] MHD patients

Dietary nutrient intakes	Whites (baseline data)	African Americans					
		model 1	p	model 2	p	model 3	p
Energy, kcal/day	1,497 ± 486	+279 ± 115	0.02	+311 ± 115	<0.01	+293 ± 119	0.01
Carbohydrates, g/day	193 ± 64	+18 ± 16	0.23	+23 ± 15	0.13	+20 ± 15	0.20
Protein, g/day	62 ± 24	+7 ± 5	0.16	+8 ± 5	0.09	+8 ± 5	0.11
Fat, g/day	54 ± 24	+18 ± 5	<0.01	+19 ± 5	<0.01	+18 ± 5	<0.01
Saturated fat, g/day	16.8 ± 8.3	+6.0 ± 1.9	<0.01	+6.4 ± 1.9	<0.01	+6.0 ± 2.0	<0.01
MUFA, g/day	20.8 ± 9.8	+7.2 ± 2.0	<0.01	+7.6 ± 2.0	<0.01	+7.4 ± 2.1	<0.01
PUFA, g/day	11.4 ± 5.7	+3.4 ± 11.4	<0.01	+3.5 ± 1.2	<0.01	+3.5 ± 1.3	<0.01
Fibers, g/day	14.7 ± 7.0	−2.9 ± 1.2	0.02	−2.8 ± 1.2	0.03	−2.9 ± 1.3	0.02

Comparisons were made with age adjustment (model 1) and after multivariate adjustment for case-mix including age, gender and diabetes (model 2) and further adjustment for Charlson comorbidity index score and dialysis vintage (model 3). MUFA = Monounsaturated fatty acid; PUFA = polyunsaturated fatty acid. [a] Combined 56 Hispanics and 8 non-Hispanics.

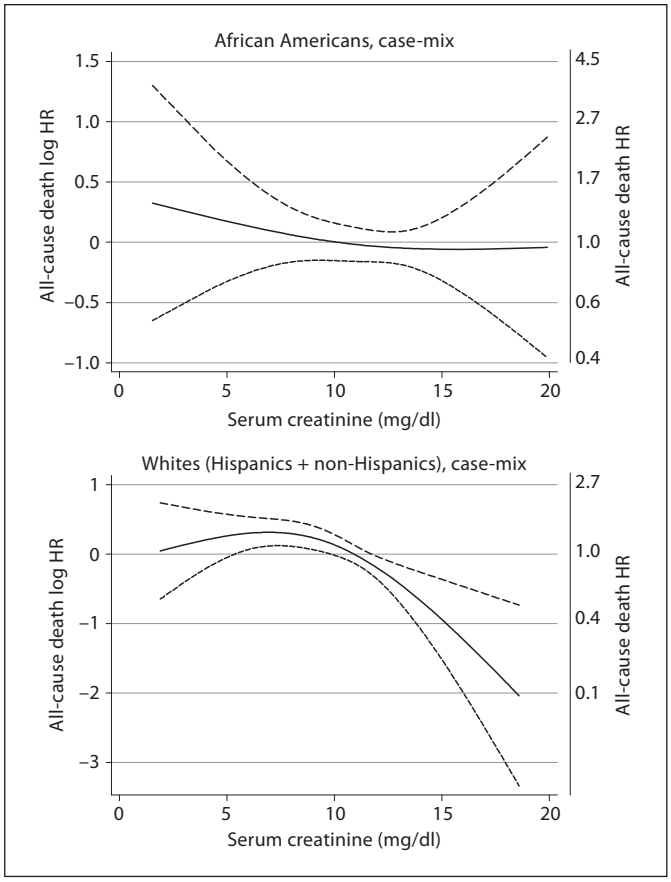

Fig. 3. Cubic spline models of the Cox proportional regression analyses reflecting adjusted mortality-predictability (with 95% CI) according to predialysis serum creatinine in African-American vs. White (Hispanic and non-Hispanic) MHD patients over 6 years. Spline models are with 2 degrees of freedom. Case-mix includes age, gender, diabetes mellitus, Charlson comorbidity index score and dialysis vintage.

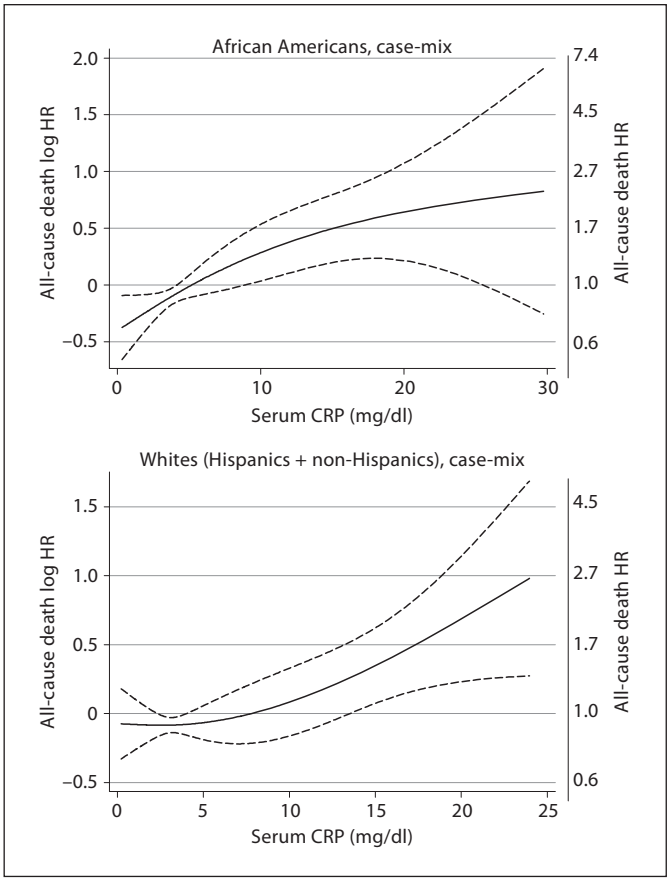

Fig. 4. Cubic spline models of the Cox proportional regression analyses reflecting adjusted mortality-predictability (with 95% CI) according to predialysis serum CRP in African-American vs. White (Hispanic and non-Hispanic) MHD patients over 6 years. Spline models are with 2 degrees of freedom. Case-mix includes age, gender, diabetes mellitus, Charlson comorbidity index score and dialysis vintage.

adoxically better as compared with non-Hispanic Whites [9]. The annual death rate for non-Hispanic White dialysis patients is significantly higher than that of African Americans. Similarly, for the healthier dialysis patients on the transplant wait list, the annual mortality rate is also higher for non-Hispanics compared with African Americans [40, 41].

In our study we found that after matching for age, gender and diabetes, African Americans still had both larger LBM and muscle mass than Whites, but fat mass was not different. Even though higher fat mass is reportedly associated with greater survival in MHD patients [27, 29], recent data indicate that larger MAMC, a surrogate of total body muscle mass, is associated with greatest survival [26]. We also found that 3 key biomarkers of greater survival had higher concentrations in African Americans compared to Whites, i.e. prealbumin [34], creatinine [39, 42] and homocysteine [43]. We also found there were very few differences in nutritional, inflammatory or survival status between Hispanic and non-Hispanic Whites in matched analyses, which allowed us to combine these two groups into a single 'White' group.

The regression analyses of the dietary data in the subgroup of 128 MHD patients showed that compared with Whites, African Americans had higher intakes of energy and both saturated and unsaturated fat. Indeed they also had a 13% higher intake of protein, but while this difference is probably clinically significant, it was not statistically significant ($p = 0.11$), which may be due to the small sample size. Higher unsaturated fat intake has recently

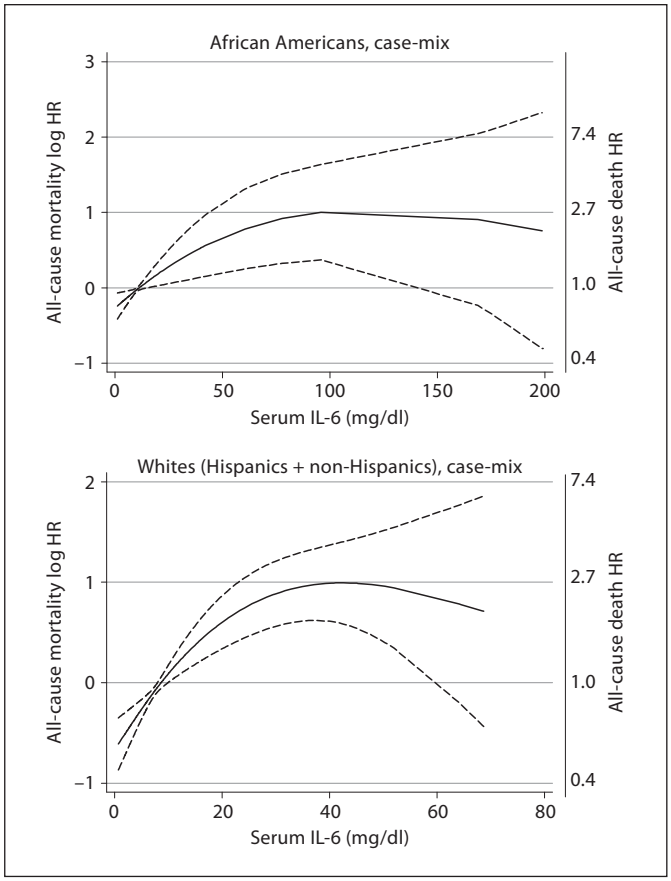

Fig. 5. Cubic spline models of the Cox proportional regression analyses reflecting adjusted mortality-predictability (with 95% CI) according to predialysis serum IL-6 in African-American vs. White (Hispanic and non-Hispanic) MHD patients over 6 years. Spline models are with 2 degrees of freedom. Case-mix includes age, gender, diabetes mellitus, Charlson comorbidity index score and dialysis vintage.

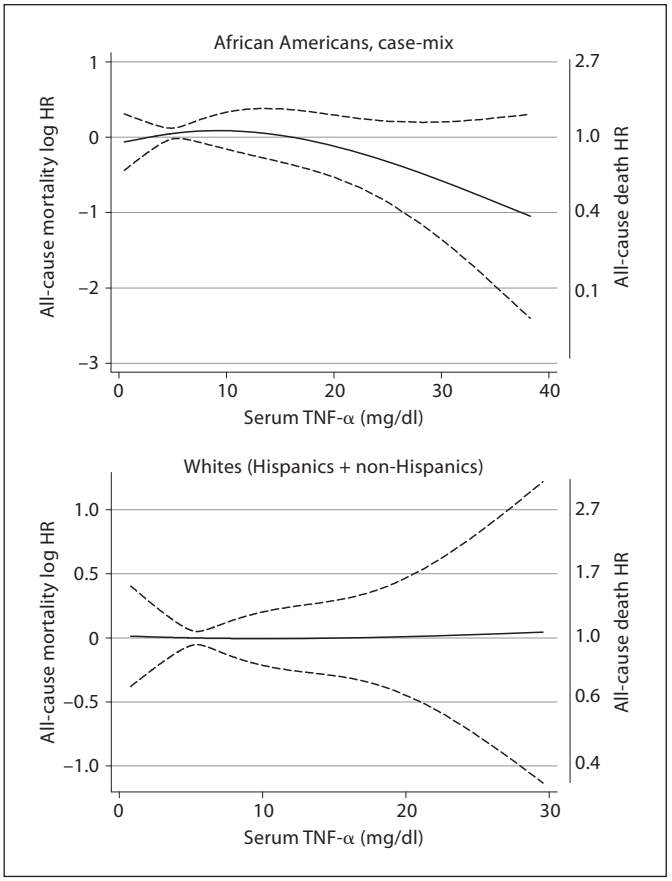

Fig. 6. Cubic spline models of the Cox proportional regression analyses reflecting adjusted mortality-predictability (with 95% CI) according to predialysis serum TNF-α in African-American vs. White (Hispanic and non-Hispanic) MHD patients over 6 years. Spline models are with 2 degrees of freedom. Case-mix includes age, gender, diabetes mellitus, Charlson comorbidity index score and dialysis vintage.

been shown to improve nutritional status and reduce systemic inflammation, probably by lowering serum CRP concentrations in MHD patients [44]. Mechanistically, the increased cellular influx of oxidized lipoproteins, heightened fatty acid synthesis pathway and downregulation of fatty acid oxidation system in CKD may be attenuated by a high-calorie diet, which may downregulate mediators of lipid influx (LOX-1), lipid efflux (LXR-α/β and ABCA1) and fatty acid biosynthesis (ChREBP and ACC), and upregulate factors involved in fatty acid oxidation (PPAR-α, CPT1 and L-FABP) [45]. Whereas it is highly speculative to relate the greater survival of African-American dialysis patients to higher fat intake, our findings in humans are consistent with animal models of improved CKD outcomes with high-calorie, high-fat diets and can be considered as an impetus for additional research to examine these hypotheses.

We found that, as previously observed for the general dialysis population, higher predialysis serum albumin, prealbumin and creatinine levels were associated with greater survival in both races (table 4 and fig. 1–3). This association, however, was not significant for serum creatinine in African Americans (fig. 3). This different observation may be due to higher serum creatinine levels in African Americans as a result of their higher muscle mass or the trend toward a 13% higher protein intake, which was probably largely due to increased meat intake in the African Americans, as also shown in this current study

Table 4. Comparing death HR across the quartiles of the selected biochemical markers of nutritional status and inflammation in 279 African-American and 520 White (including 475 Hispanic) MHD patients in the 6-year cohort (2001–2007)

Predialysis serum	Q1	Q2	Q3	Q4	p trend
African Americans (n = 279)					
Albumin	1	0.44 (0.27–0.72)*	0.51 (0.32–0.83)*	0.52 (0.31–0.85)*	0.01
Prealbumin	1	0.82 (0.51–1.30)	0.57 (0.34–0.94)*	0.53 (0.31–0.91)*	<0.01
Creatinine	1	0.79 (0.48–1.29)	0.90 (0.55–1.48)	0.77 (0.41–1.42)	0.50
CRP	1	1.71 (0.98–2.97)	1.84 (1.05–3.21)*	2.42 (1.39–4.19)*	<0.01
IL-6	1	1.04 (0.57–1.89)	1.53 (0.87–2.71)	2.20 (1.28–3.79)*	<0.01
TNF-α	1	1.16 (0.69–1.94)	0.97 (0.57–1.65)	0.80 (0.46–1.40)	0.30
All Whites (Hispanics and non-Hispanics; n = 520)					
Albumin	1	0.48 (0.33–0.69)*	0.32 (0.20–0.51)*	0.34 (0.19–0.58)*	<0.01
Prealbumin	1	0.56 (0.37–0.84)*	0.53 (0.35–0.81)*	0.55 (0.33–0.90)*	<0.01
Creatinine	1	0.79 (0.54–1.15)	0.64 (0.42–0.99)*	0.43 (0.24–0.77)*	<0.01
CRP	1	1.59 (0.95–2.67)	2.03 (1.23–3.35)*	1.87 (1.14–3.05)*	<0.01
IL-6	1	1.88 (0.97–3.66)	2.29 (1.20–4.37)*	4.13 (2.22–7.67)*	<0.01
TNF-α	1	1.21 (0.76–1.93)	1.37 (0.86–2.17)	1.37 (0.86–2.18)	0.15

All values are adjusted for case-mix which includes age, gender, diabetes mellitus, Charlson comorbidity index score and dialysis vintage. * $p < 0.05$.

(table 2), and might result in the dilution of the creatinine-survival gradient in African Americans. Prior studies have shown that elevated levels of circulating proinflammatory cytokines, including IL-6, predict higher mortality in MHD patients [46–48]. However, we are not aware of any study which examined these relationships across different races. In the present study, we found that higher serum CRP and IL-6 were incrementally associated with increased death risk in both races, but that TNF-α was not (fig. 6), a finding also shown in previous studies [49, 50]. Interestingly, even though the highest (vs. lowest) quartile of IL-6 was associated with a 2.4 times higher death risk in African Americans, this mortality association was even greater among Whites (4.1-fold; table 4 and fig. 5). Hence, African Americans may indeed be more resilient against the death-effect of inflammation, a question which should be further examined in future studies.

One of the study's limitations is the selection bias during enrollment, in that more malnourished or sicker patients were less likely to enroll. However, selection bias in this direction would lead to bias toward the null; therefore, without this bias, our results may have been even stronger. Another limitation is the prevalent nature of our cohort and the slightly longer dialysis vintage in African Americans than Whites; however, there are mixed data as to whether patients with longer vintage are more or less malnourished or inflamed than others [51, 52]. A third limitation is the lack of information regarding type of dialysis modality, dialysis access, dialysis membrane and several other known confounders, such as healthy lifestyles and socioeconomic status, as well as unknown confounders. Fourth is the low sample size in our non-Hispanic White group and our combining both Hispanic and non-Hispanic White patients into a single 'White' category. However, given many highly acculturated Hispanics of the second and third generation in Southern California [53], including among our MHD patients, we prefer to avoid strong inferences about ethnicity, whereas the racial distinction of White versus African American in our cohort was rather robust.

There are several strengths to this study, including the relatively long follow-up period (72 months), the comprehensive laboratory evaluations, the concomitant assessments of body composition, and the detailed evaluation of the clinical and comorbid states of the patients by study physicians at baseline. Our cohort has been extensively characterized for markers of inflammation and nutritional status, energy intake, the multiple types of fat ingested and direct measurements of total body fat. Finally, participants were selected randomly without prior knowledge of their inflammatory status.

Conclusions

African-American MHD patients have higher measures of muscle and lean mass, higher serum levels of prealbumin and creatinine and higher dietary intakes of energy and fat, but lower intake of dietary fiber than Whites. Higher serum albumin and prealbumin and lower CRP and IL-6 are associated with greater survival in both races. In African Americans the mortality-predictability of IL-6 was almost half of its predictability among Whites, implying that the impact of inflammation on mortality is mitigated in African Americans. The racial disparities in dietary, nutritional and inflammatory measures in MHD patients observed in this study may have a bearing on disparities in clinical outcomes and in particular on survival. Additional studies, including prospective dietary intervention trials, could provide much needed information on these associations with survival.

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