

Race Modifies the Association Between Adiposity and Inflammation in Patients with Chronic Kidney Disease: Findings from the Chronic Renal Insufficiency Cohort Study

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Objective: The race-specific association of inflammation with adiposity and muscle mass in subjects with chronic kidney disease (CKD) was examined.

Methods: Plasma concentration of interleukin (IL)-1 β , IL-1 receptor antagonist (IL-1RA), IL-6, IL-10, tumor necrosis factor (TNF)- α , TGF- β , high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and serum albumin was measured in 3,939 Chronic Renal Insufficiency Cohort study participants. Bioelectric impedance analysis was used to determine body fat mass (BFM) and fat-free mass (FFM).

Results: Plasma levels of hs-CRP, fibrinogen, IL-1RA, IL-6, and TNF- α increased and serum albumin decreased across the quartiles of body mass index. In multivariable analysis, BFM and FFM were positively associated with hs-CRP, fibrinogen, IL-1 β , IL-1RA, and IL-6. One standard deviation (SD) increase in BFM and FFM was associated with 0.36 (95% confidence interval [CI] = 0.33, 0.39) and 0.26 (95% CI = 0.22, 0.30) SD increase in log-transformed hs-CRP, respectively ($P < 0.001$). Race stratified analysis showed that the association between biomarkers and BFM and FFM differed by race, with Caucasians, demonstrating a stronger association with markers of inflammation than African Americans.

Conclusions: BFA and FFM are positively associated with markers of inflammation in patients with CKD. Race stratified analysis showed that Caucasians have a stronger association with markers of inflammation compared to African Americans.

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Introduction

Findings from the Chronic Renal Insufficiency Cohort (CRIC) study showed that about 86% of subjects with chronic kidney disease (CKD) have some evidence of inflammation (1). Inflammatory state is characterized by activation of an array of soluble factors such as cyto-

kine and chemokines. Elevated plasma cytokine levels in CKD could be a consequence of decreased elimination and/or increased generation. It is now well recognized that obesity is a chronic inflammatory state (2). A number of cross-sectional and longitudinal studies from diverse populations have revealed that higher body mass index (BMI)

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is a risk factor for the prevalence and progression of CKD (3). Analysis of data from the United States Renal Data System showed that among incident patients with ESRD, mean BMI increased from 25.7 to 27.5 kg/m² during the years 1995-2002 (4). However, BMI does not discriminate between muscle mass and fat mass. The inflammatory response and prognostic implications of body fat mass (BFM) and muscle mass may be different (5). Although most of the circulating cytokines are secreted from activated macrophages and lymphocytes, adipocytes and skeletal muscle are also a possible source of these cytokines (6,7). Evidence from basic science laboratory and clinical translational studies indicate that proinflammatory cytokines mediate muscle protein catabolism (8-11). The association between inflammation and body composition has not been studied in a large cohort of racially diverse CKD patients with varying level of kidney function.

We hypothesized that inflammatory biomarkers are positively associated with BFM and negatively with fat-free mass (FFM). We further hypothesized that the association between anthropometric measures and inflammation is modulated by race. Thus, in this study, we examine the association between inflammation and bioelectric impedance analysis (BIA)-derived measures of adiposity and muscle mass in CRIC study participants.

Methods

The CRIC study

The organization, design, and methods of the CRIC study have been reported previously (12). Briefly, the CRIC study is a multicenter, prospective observational cohort study of 3,939 subjects with established CKD. The exclusion criteria in CRIC were monogenetic renal disease, cirrhosis, class III or IV heart failure, HIV, cancer, autoimmune disease, or current immunosuppressive therapy, polycystic kidney disease, pregnant women, subjects with organ or bone marrow transplant, and persons who had received immunotherapy for primary renal disease or systemic vasculitis within the past 6 months or had systemic chemotherapy. The study protocol was approved by the Institutional Review Board at each participating site. Written informed consent was obtained from all study participants.

CRIC data collection

Demographic and clinical characteristics were determined at baseline. Self-reported race/ethnicity was documented. Serum creatinine was measured by the Jaffe method on a Beckman Synchron System. Serum cystatin C was measured on a Dade-Behring BNII, with a coefficient of variation of about 1.7%. We calculated the glomerular filtration rate using the estimating equation derived from the CRIC cohort (eGFR) (13). BMI was calculated as body weight in kilogram/(height in meters)².

Bioelectric impedance analysis

All CRIC study participants underwent BIA studies at baseline with a Quantum II analyzer employing standard techniques. The bioelectrical impedance analyzer vectors the impedance signal (Z , in ohms, Ω) into resistance (R , Ω), and reactance (X_c , Ω) as a direct series measurement. Values for FFM and BFM were determined using established predictive formulae (14). Muscle mass was derived using the equation that has been validated using magnetic resonance imaging (15) and applied to patients with CKD (16).

$$FFM = (a \times Ht^2) + (b \times Wt) + (c \times A) + (d \times R) + e$$

where Ht is height in cm, Wt is weight in kg, A is age, R is impedance (Ω), and a and e are constants provided by the manufacturer.

$$\begin{aligned} BFM \text{ (kg)} &= BW - 0.55 (Ht^2/R) - 16.69 \text{ (males)} \\ &= BW - 0.55 (Ht^2/R) - 11.49 \text{ (females)} \end{aligned}$$

where BW is body weight in kg, Ht is height in cm.

Chertow et al. (17) have shown that BIA is a sensitive tool for evaluating body composition in patients with kidney disease.

Measurement of biomarkers of inflammation

High-sensitivity sandwich ELISAs (Quantikine HS, R&D Systems, Minneapolis, MN) were used to measure plasma interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF)- α levels. Standard sandwich ELISAs (Quantikine, R&D Systems) were used to quantify IL-1 receptor antagonist (IL-1RA) and transforming growth factor (TGF)- β levels. Integrated performance of IL-1 β , IL-1RA, IL-6, and TNF- α ELISAs was implemented using a robotic liquid handling platform (Biomek FXp, Beckman Coulter, Brea, CA). All cytokine assays were performed in duplicates and the mean value was used in the analysis. Several blood samples had a concentration of IL-1 β below the minimal level for detection (0.125); to these samples, we arbitrarily assigned a very low value for IL-1 β at (0.00001). High-sensitivity C-reactive protein (hs-CRP) and fibrinogen were quantified in EDTA plasma samples using specific laser-based immunonephelometric methods on the BNII (Siemens Healthcare Diagnostics, Deerfield, IL).

Calculation of inflammation score

We computed a composite score ranging from 0 to 5 based on the levels as reported by us earlier (1). When the levels of the following biomarkers were at or above the range indicated a score of "1" was assigned: (a) hs-CRP > 3 mg/l, (b) fibrinogen > 350 mg/dl, (c) IL-6 \geq 6 pg/ml, (d) TNF- α \geq 7 pg/ml, and (e) IL-1 β \geq 0.39 pg/ml. The cut-off values for individual biomarkers were chosen from the previously published literature.

Statistical analysis

Selected demographic and clinical characteristics of the study population were summarized by BMI quartiles. Continuous variables were presented as mean and standard deviation (SD), or median and interquartile range, and were compared across BMI quartiles using ANOVA or Kruskal-Wallis test, as appropriate. Categorical variables were presented as frequency and percentages and were compared across BMI quartiles using a χ^2 -test. Multivariable linear regression models were employed to estimate the association of BMI, BFM, and FFM with biomarkers of inflammation, adjusting for age, sex, clinical center, diabetes, hypertension, smoking, total cholesterol, lipid-lowering medications, aspirin and ACE-I/ARB use, metabolic equivalent of tasks (METs), and eGFR, which was estimated using an equation developed within CRIC (13). Natural logarithm transformation (ln) was applied to the biomarkers of inflammation that had skewed distribution. In the regression analyses done in each instance, adjustment was made only for one cytokine or inflammatory marker in each model tested. Both the exposures (i.e., BMI, BFM, and FFM) and outcomes of interest were standardized by dividing the SDs. An

TABLE 1 Demography of the study population according to the quartiles of BMI

Variable	BMI (kg/m ²)				P-value
	<26.8 (n = 915)	≥26.8 to <30.9 (n = 920)	≥30.9 to <36.1 (n = 928)	≥36.1 (n = 921)	
Age (years)	56.7 (12.3)	59.2 (10.9)	59.2 (10.2)	57.5 (10.4)	<0.01
Male (%)	479 (52.4)	614 (66.7)	556 (59.9)	360 (39.1)	<0.01
Race/ethnicity (%)					
Caucasians	459 (50.2)	411 (44.7)	377 (40.6)	319 (34.6)	<0.01
African Americans	290 (31.7)	343 (37.3)	402 (43.3)	492 (53.4)	
Hispanics	103 (11.3)	119 (12.9)	128 (13.8)	91 (9.9)	
Other ^a	63 (6.9)	47 (5.1)	21 (2.3)	19 (2.1)	
Diabetes (%)	288 (31.5)	400 (43.5)	480 (51.7)	600 (65.2)	<0.01
Hypertension (%)	710 (77.6%)	796 (86.5%)	811 (87.4%)	851 (92.4%)	<0.01
Smokers (%)	167 (18.3)	120 (13.0)	105 (11.3)	88 (9.6)	<0.01
Educational level (%)					
College graduate	370 (40.4)	325 (35.4)	278 (30.0)	200 (21.7)	<0.01
Some college education	223 (24.4)	265 (28.8)	286 (30.8)	299 (32.5)	
Higher secondary graduation	147 (16.1)	155 (16.9)	164 (17.7)	218 (23.7)	
Less than higher secondary education	175 (19.1)	174 (18.9)	200 (21.6)	204 (22.2)	
Calorie intake (kcal/kg/day)	26.0 (11.5)	21.7 (9.5)	19.2 (8.4)	16.4 (7.6)	<0.01
Protein intake (g/kg/day)	1.0 (0.5)	0.8 (0.4)	0.8 (0.4)	0.6 (0.3)	<0.01
Total METS (kcal/kg/h)	168 (116-254)	170 (112-256)	167 (109-245)	153 (104-242)	0.03
HOMA-IR	4.1 (5.5)	5.9 (7.4)	6.9 (7.6)	9.1 (9.4)	<0.01
Hemoglobin (g/dl)	12.6 (1.8)	12.9 (1.8)	12.7 (1.7)	12.3 (1.7)	<0.01
WBC count (× 10 ³ /μl)	6.3 (2.0)	6.4 (1.9)	6.6 (2.0)	7.0 (3.0)	<0.01
Serum creatinine (mg/dl)	1.72 (0.60)	1.75 (0.57)	1.75 (0.57)	1.73 (0.56)	0.72
CRIC eGFR (ml/min/1.73 m ²)	46.8 (18.3)	46.2 (16.4)	45.4 (16.8)	41.9 (15.2)	<0.01
Cystatin C (mg/l)	1.45 (0.54)	1.46 (0.52)	1.50 (0.54)	1.62 (0.53)	<0.01
Total cholesterol (mg/dl)	187.1 (45.5)	184.3 (46.4)	183.1 (46.1)	181.9 (43.0)	0.08
Low-density lipoprotein (mg/dl)	103.9 (35.0)	103.8 (36.4)	101.5 (35.0)	102.2 (34.7)	0.37
Triglyceride (mg/dl)	130.8 (90.0)	160.3 (117.6)	170.7 (131.1)	166.7 (118.4)	<0.01
Body composition					
BFM (kg)	18.0 (5.8)	25.2 (6.5)	32.3 (7.8)	48.4 (14.5)	<0.01
FFM (kg)	49.6 (10.2)	58.8 (11.3)	63.5 (14.0)	70.2 (17.5)	<0.01
FFM/BFM	3.4 (3.9)	2.7 (2.8)	2.6 (9.8)	1.8 (2.6)	<0.01
Waist circumference (cm)	87.5 (9.3)	100.2 (8.1)	109.7 (10.2)	126.1 (13.7)	<0.01
Lipid-lowering drugs (%)	446 (49.2)	554 (60.8)	582 (62.9)	604 (66.1)	<0.01

Data presented as mean and SD or median and interquartile range.
 Abbreviations: HS, high school; METS, metabolic equivalent of tasks; HOMA-IR, homeostasis model of assessment-insulin resistance.
^aAsian/Pacific Islanders and Native Americans.

additional subgroup analysis estimated the association of BMI, BFM, and FFM with biomarkers of inflammation by eGFR group, dividing the CRIC participants into two groups: (1) individuals with advanced CKD with an eGFR of < 30 ml/min/1.73 m² (n = 804) and individuals with an eGFR of ≥30 ml/min/1.73 m² (n = 3,123). We dichotomized the cohort because the number of subjects in each stage of CKD was too small to derive meaningful conclusions. The analysis was adjusted for age, sex, clinical center, diabetes, hypertension, smoking, total cholesterol, lipid-lowering medications, aspirin and ACE-I/ARB use, METS, and eGFR. Subgroup analyses were done in Caucasian and African Americans and formal tests of effect modification by race were done by checking the significance of the interaction terms

between race and biomarkers of inflammation. We also investigated the interaction between race and biomarkers of inflammation by eGFR level (eGFR, <30 ml/min/1.73 m²; eGFR, ≥30 ml/min/1.73 m²). Subgroup analysis was not done in Hispanics because of the relatively small sample size. All analyses were done with the SAS statistical software (V9.3, SAS Inc., Cary, NC).

Results

We studied 3,684 out of the 3,939 (93.5%) CRIC study participants, in whom BIA and inflammation biomarker results were available.

TABLE 2 Biomarkers of inflammation according to the quartiles of BMI

Variable	BMI (kg/m ²)				P-value
	<26.8 (n = 915)	≥26.8 to <30.9 (n = 920)	≥30.9 to <36.1 (n = 928)	≥36.1 (n = 921)	
Acute-phase proteins					
hs-CRP (mg/l)	1.2 (0.6-3.2)	2.0 (0.9-5.0)	2.9 (1.3-6.6)	4.7 (2.1-9.1)	<0.01
Fibrinogen (mg/l)	3,700 (3,100-4,400)	3,900 (3,300-4,600)	4,100 (3,400-4,800)	4,500 (3,800-5,200)	<0.01
Albumin (g/dl) ^a	3.99 (0.51)	3.97 (0.46)	3.96 (0.45)	3.85 (0.43)	<0.01
Cytokines					
IL-1β (pg/ml)	0.18 (0.06-1.1)	0.18 (0.06-1.1)	0.15 (0.06-1.3)	0.3 (0.06-1.4)	0.08
IL-1RA (pg/ml)	503 (291-1,177)	637 (358-1,346)	692 (419-1,471)	1,086 (575-1,909)	<0.01
IL-6 (pg/ml)	1.4 (0.9-2.4)	1.7 (1.0-3.0)	2.0 (1.2-3.1)	2.4 (1.6-3.7)	<0.01
IL-10 (>0 pg/ml) ^b	148 (16.3%)	132 (14.4%)	155 (16.8%)	148 (16.1%)	0.5
TNF-α (pg/ml)	2.1 (1.4-3.2)	2.1 (1.5-3.2)	2.2 (1.5-3.3)	2.3 (1.7-3.3)	0.006
TGF-β (pg/ml)	10.3 (6.1-17.7)	11.5 (6.4-18.4)	10.7 (6.2-17.5)	11.0 (7.1-17.8)	0.3

Data presented as median and interquartile range.

^aMean (SD).

^bn (%) where IL-10 is >0.

Baseline clinical and demographic characteristics according to the quartile of BMI are summarized in Table 1. Subjects in the highest quartile were more likely to be African American, females with hypertension, insulin resistance, and diabetes, who were physically inactive and received treatment with lipid-lowering agents. They also had the lowest hemoglobin level and highest WBC count. Individuals in the lowest BMI group were more likely to be Caucasian, smokers, with a college level education, who consumed the highest amount of protein and calories. Although serum creatinine was not significantly different across the quartiles of BMI, eGFR was lower and cystatin C level was greater in patients in the highest quartile of BMI. As expected, waist circumference, BFM, and FFM were higher in the larger BMI groups. The ratio of FFM to BFM decreased across the higher BMI categories.

Plasma levels of hs-CRP, fibrinogen, IL-1RA, IL-6, and TNF-α increased significantly across increasing quartiles of BMI (Table 2). Serum albumin, on the other hand, decreased significantly in the higher BMI group. There were 531 (14.4%) subjects with no evidence of inflammation (inflammation score, “0”) and 173 subjects (4.7%) with inflammation score of ≥4. As shown in Figure 1, subjects with a higher inflammation score tend to have larger BMI, as well as higher BFM and FFM (*P* < 0.01). Subjects with inflammation score of ≥4 had a significantly higher BMI (34.2 ± 7.9 vs. 28.5 ± 5.4 kg/m², *P* < 0.001), BFM (33.5 ± 16.2 vs. 24.8 ± 9.8 kg, *P* < 0.001), and FFM (63.0 ± 16.1 vs. 59.6 ± 15.5 kg, *P* = 0.02) compared to those with inflammation score of “0”.

In multivariable linear regression, after adjusting for age, sex, clinical center, diabetes, hypertension, smoking, total cholesterol, lipid-lowering medications, ACE-I/ARB, METS, aspirin use, and eGFR, BMI was positively associated with IL-1β, IL-1RA, IL-6, hs-CRP, and fibrinogen, but negatively with serum albumin (Table 3). Similar association between the biomarkers of inflammation with BFM and FFM was noted, except that the association between serum albumin and BFM was not significant. One SD increase in BFM and FFM was associated with a 0.36 (95% confidence interval [CI] = 0.33, 0.39) and a 0.26 (95% CI = 0.22, 0.30) unit increase in ln hs-CRP, respectively (*P* < 0.001 for both). FFM was weakly, but negatively associated with TNF-α and serum albumin. We examined whether the association between body composition and inflammation differs in patients with eGFR < 30 ml/min/1.73 m² and ≥30 ml/min/1.73 m² (Table 4). Positive association between BFM, FFM, and IL-1β, FFM and IL-10, as well as negative association between TNF-α and FFM noted in those with higher eGFR did not retain significance in subjects with lower eGFR.

While examining the association between body composition and inflammation, significant interaction with race was evident. Interaction between race and BFM was noted for IL-6 (*P* = 0.03), IL-1RA (*P* = 0.004), and the inflammation score (*P* = 0.003) in the full cohort (Figure 2). On subgroup analysis, such interaction was evident only in

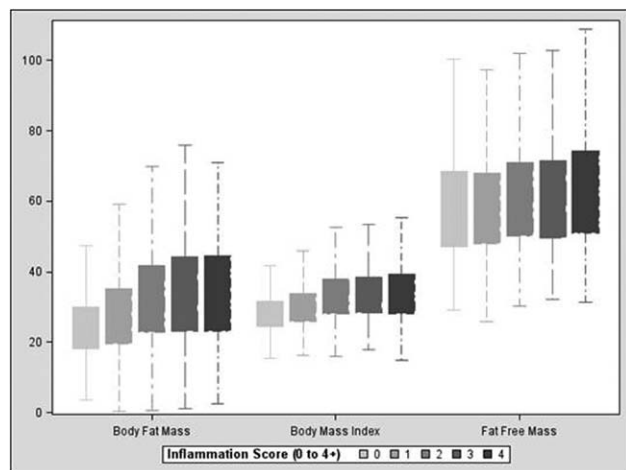


Figure 1 Association between inflammation score and BMI, BFM, and FFM in CRIC study participants. All anthropometric measures were higher in CRIC study participants with higher inflammation score (*P* < 0.01).

TABLE 3 Multivariable-adjusted association between body composition and biomarkers of inflammation

Outcome variable	Predictor variable					
	BMI		BFM		FFM	
	Est/1 SD(95% CI)	P-value	Est/1 SD (95% CI)	P-value	Est/1 SD (95% CI)	P-value
<i>Acute-phase proteins</i>						
ln(hs-CRP + 1)/1 SD	0.34 (0.31, 0.37)	<0.001	0.36 (0.33, 0.39)	<0.001	0.26 (0.22, 0.30)	<0.001
Fibrinogen/1 SD	0.20 (0.17, 0.23)	<0.001	0.18 (0.15, 0.21)	<0.001	0.17 (0.14, 0.21)	<0.001
Serum albumin/1 SD	-0.07 (-0.10, -0.04)	<0.001	0.02 (-0.01, 0.06)	0.2	-0.15 (-0.19, -0.11)	<0.001
<i>Cytokines</i>						
ln (IL-1β + 1)/1 SD	0.05 (0.02, 0.08)	0.002	0.04 (0.01, 0.07)	0.02	0.05 (0.01, 0.09)	0.02
ln (IL-1RA + 1)/1 SD	0.20 (0.17, 0.24)	<0.001	0.22 (0.19, 0.25)	<0.001	0.16 (0.12, 0.20)	<0.001
ln (IL-6 + 1)/1 SD	0.15 (0.12, 0.18)	<0.001	0.14 (0.11, 0.18)	<0.001	0.13 (0.09, 0.17)	<0.001
ln (IL-10 + 1)/1 SD	-0.00 (-0.04, 0.03)	0.8	-0.01 (-0.05, 0.02)	0.5	0.03 (-0.01, 0.07)	0.2
ln (TGF-β + 1)/1 SD	0.00 (-0.03, 0.04)	0.8	0.01 (-0.02, 0.05)	0.4	-0.03 (-0.07, 0.01)	0.1
ln (TNF-α + 1)/1 SD	-0.01 (-0.04, 0.02)	0.6	-0.01 (-0.04, 0.02)	0.6	-0.04 (-0.08, -0.01)	0.03

Adjusted for age, sex, clinical center, diabetes, hypertension, smoking, total cholesterol, lipid-lowering medications, aspirin and ACE-I/ARB use, METS, and estimated GFR.

subjects with only in those with eGFR ≥ 30 ml/min/1.73 m² (n = 3,123) and confined to the inflammation score (P = 0.015) and IL-1RA (P = 0.023; data not shown). Interaction was significant for IL-1RA (P = 0.045) for FFM in the full cohort (Figure 3). On further analysis, such interaction was confined to those with eGFR < 30 ml/min/1.73 m² (n = 804) for fibrinogen, TGF-β, and IL-1β (P-values of 0.04, 0.006, and 0.039, respectively; data not shown). These associations were stronger in Caucasians compared to African Americans.

Discussion

In this study, we examined the association between body composition determined by BIA and biomarkers of inflammation in a large, cohort of subjects with a broad range of kidney function. In general, a robust positive association between BFM and several proinflammatory biomarkers was evident. However, contrary to our hypothesis, a positive association between FFM and some inflammatory markers was noted. Race stratified analysis showed that the association between inflammatory biomarkers and body composition differs by race, with Caucasians demonstrating a stronger association with markers of inflammation as compared to African Americans.

BMI is a simple index to classify adults as overweight or obese (18). We found that about 84.2% of the CRIC study participants were either overweight or obese, with 55.6% being obese. Not unexpectedly, we noted higher representation of African American females in the larger BMI category (Table 1). Obesity among African Americans has been variously attributed to genetics, weight misperception, and lower socioeconomic status. Several cross-sectional and longitudinal studies have shown that higher BMI is associated with prevalent CKD and a risk factor for the progression of CKD (3,19). Accordingly, we found that eGFR was lower and cystatin C higher across increasing quartiles of BMI (P < 0.01). Cystatin C is claimed to be a more sensitive marker for kidney function than serum creatinine (20), and it has also greater association with inflammation (1). Reanalysis of the data using the traditional defini-

tion of obesity by BMI (21) did not change any of the observations except that those with BMI < 18.5 and ≥ 35 had higher level of TNF-α compared to others. However, there were only 23 subjects in the BMI < 18.5 category.

We found that the plasma level of proinflammatory cytokines (IL-6 and TNF-α) and positive acute-phase proteins (hs-CRP and fibrinogen) increased across the quartiles of BMI (Table 2). Although the IL-1β level was not different, the plasma level of IL-1RA was significantly higher in subjects with larger BMI. Circulating cytokine receptors may provide additional information in chronic inflammatory conditions because they generally have a longer half-life than the cytokines themselves, and therefore exhibit more constant levels over time (22).

There is mounting evidence to suggest that BMI may not be an ideal measure of obesity as it does not discriminate between fat mass and muscle mass (21). BIA determines electrical impedance of body tissues from which BFM and FFM can be reliably estimated in subjects with and without kidney disease (14,17,23). Contribution of adipose tissue and skeletal muscle mass to the prevailing inflammatory state and clinical outcomes may be different (24). In response to inflammatory signals, adipocytes induce the expression of several mediators of inflammation (25). Adipocytokines, through autocrine, paracrine, and endocrine mechanisms, mediate changes in body composition (5). To clearly chart the association between inflammation and body composition, it is important to integrate information derived from multiple biomarkers as a measure of prevailing inflammatory state (1). We computed an inflammation score using multiple proinflammatory markers and found that the BMI, BFM, and FFM increased progressively and significantly with a higher intensity of inflammation (Figure 1).

In multivariable linear regression after adjusting for confounding variables, a positive association between several markers of inflammation and body composition was evident (Table 3). The association between inflammatory biomarkers and BFM and FFM was

TABLE 4 Multivariable-adjusted association between body composition and biomarkers of inflammation by eGFR

Outcome variable	Predictor variable					
	BFM			FFM		
	eGFR < 30 ml/min/ 1.73 m ² (n = 804)	P-value	eGFR ≥ 30 ml/min/ 1.73 m ² (n = 3,123)	eGFR < 30 ml/min/ 1.73 m ² (n = 804)	eGFR ≥ 30 ml/min/ 1.73 m ² (n = 3,123)	P-value
	Est/1 SD(95% CI)	P-value	Est/1 SD (95% CI)	Est/1 SD (95% CI)	Est/1 SD (95% CI)	P-value
<i>Acute-phase proteins</i>						
ln (hs-CRP + 1)/1 SD	0.34 (0.27, 0.42)	<0.001	0.36 (0.33, 0.40)	0.28 (0.18, 0.38)	0.26 (0.22, 0.31)	<0.001
Fibrinogen/1 SD	0.17 (0.10, 0.25)	<0.001	0.19 (0.16, 0.22)	0.27 (0.18, 0.37)	0.15 (0.11, 0.19)	<0.001
Serum albumin/1 SD	0.09 (0.01, 0.16)	0.03	0.00 (-0.03, 0.04)	-0.18 (-0.27, -0.08)	-0.15 (-0.19, -0.10)	<0.001
<i>Cytokines</i>						
ln (IL-1β + 1)/1 SD	0.02 (-0.05, 0.09)	0.6	0.05 (0.01, 0.08)	0.06 (-0.02, 0.15)	0.04 (-0.00, 0.09)	0.06
ln (IL-1RA + 1)/1 SD	0.21 (0.14, 0.28)	<0.001	0.22 (0.18, 0.26)	0.18 (0.09, 0.26)	0.16 (0.12, 0.21)	<0.001
ln (IL-6 + 1)/1 SD	0.11 (0.03, 0.19)	0.006	0.16 (0.12, 0.19)	0.14 (0.04, 0.24)	0.13 (0.09, 0.18)	<0.001
ln (IL-10 + 1)/1 SD	-0.05 (-0.13, 0.03)	0.2	0.00 (-0.04, 0.04)	-0.06 (-0.16, 0.04)	0.05 (0.01, 0.10)	0.03
ln (TGF-β + 1)/1 SD	0.02 (-0.05, 0.09)	0.6	0.01 (-0.02, 0.05)	0.04 (-0.04, 0.13)	-0.04 (-0.09, 0.00)	0.05
ln (TNF-α + 1)/1 SD	0.01 (-0.05, 0.08)	0.7	-0.02 (-0.05, 0.02)	0.01 (-0.08, 0.09)	-0.06 (-0.10, -0.01)	0.01

Adjusted for age, sex, clinical center, diabetes, hypertension, smoking, total cholesterol, lipid-lowering medications, aspirin and ACE-I/ARB use, METS, and estimated GFR.

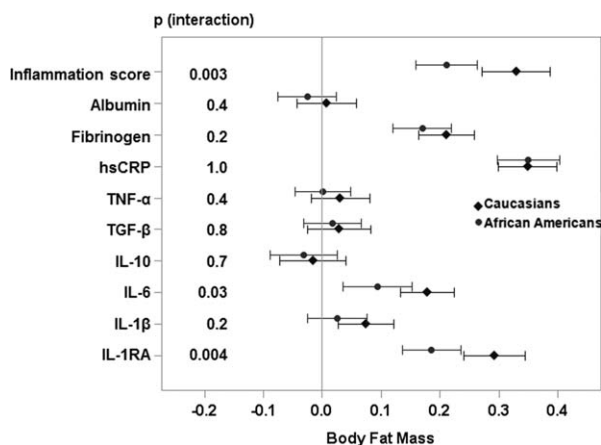


Figure 2 Multivariable-adjusted association between BFM and biomarkers of inflammation in Caucasians and African Americans. A significant interaction between race and BFM was noted for IL-6, IL-1RA, and the inflammation score.

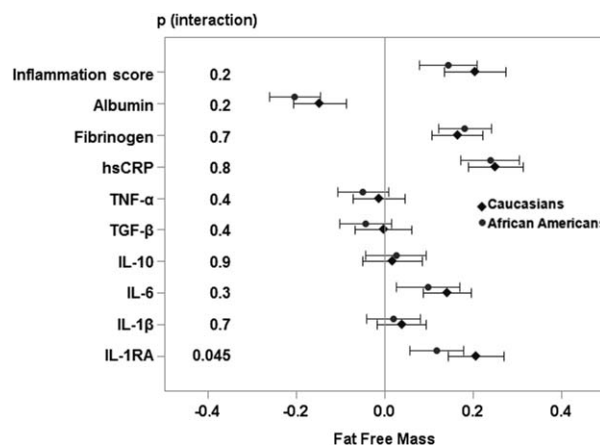


Figure 3 Multivariable-adjusted association between FFM and biomarkers of inflammation in Caucasians and African Americans. A significant interaction between race and FFM was evident for IL-1RA.

influenced by the level of eGFR (Table 4). These findings should be interpreted with caution as the number of patients with eGFR < 30 ml/min/1.73 m² was small. The relative contribution of adipocytokines released from adipocytes and myokines from skeletal muscle to the systemic inflammation is not known (10,24). Preliminary evidence indicates that skeletal muscle and adipose tissue contribute to about 12% and 10-35% of the circulating IL-6, respectively (11). Using arteriovenous balance studies and immunohistochemistry techniques, we showed that skeletal muscle is an important source of cytokines in patients with ESRD (7,10). When secreted from the muscle, IL-6 acts as a hormone, signaling and affecting the liver and adipose tissue. Besides its well-recognized role in mediating muscle protein catabolism, cytokines are also essential for successful muscle regeneration (10,26). In this study, we noted that one SD increase in BFM and FFM was associated with 0.14 SD (95% CI = [0.11, 0.18]) and 0.13 SD (95% CI = [0.09, 0.17]) SD increase in ln(IL-6), respectively (Table 3). Surprisingly, we noted a weak but negative association between serum albumin and FFM. Raj et al. (10,27) studied protein kinetics in patients with kidney disease using a three-compartmental model and showed that IL-6 mediates muscle protein breakdown, and the amino acid released from muscle is utilized for acute-phase protein synthesis in the liver. However, the differential role for adipocytokines and myokines on albumin kinetics needs further investigation using techniques that determine muscle mass more precisely.

In a large prospective cohort study that examined the association between BMI and death rates among US adults, mortality rates increased with higher BMI, but less so for African Americans (28). In our study, we observed that the association between adiposity and inflammation is modified by race. The associations were more robust in Caucasians than in African Americans (Figure 2). African Americans have less visceral fat compared to Caucasians with similar waist to hip ratio and BMI (29,30). This may explain the lower degree of inflammation present in African Americans as visceral fat is known to have higher expression of proinflammatory cytokines such as TNF- α and IL-6 (31). The amount of FFM also differs between ethnicities. African Americans have more FFM compared to Caucasians, which may also contribute to the racial differences observed between

these ethnicities (32). The attenuated inflammatory signals from fat mass may explain in part the improved survival reported in obese members of the racial minority groups with kidney disease.

Our study has number of strengths, which includes a large cohort of patients with representation of different races, broad range of kidney function, study of a number of biomarkers, and determination of body composition using BIA. However, our findings should be considered within the context of several limitations: (a) this is a cross-sectional study and hence temporal associations and causality cannot be inferred; (b) cytokine profile and acute-phase response exhibit inter- and intraindividual variability over time (33); (c) the determination of body composition by BIA could be influenced by changes in hydration (34); and (d) BIA does not distinguish between visceral and subcutaneous adiposity. It has been shown that visceral fat is a stronger predictor of inflammation than fat deposits in other sites (35).

Conclusions

To summarize, we examined the association of adiposity and muscle mass with biomarkers of inflammation in CRIC study participants and noted a strong positive association between several markers of inflammation and BFM. The association between FFM and inflammatory biomarkers was also positive in general, but less pronounced. Race stratified analysis showed that the association between adiposity and inflammation was stronger in Caucasians compared to African Americans. Additional studies aimed toward understanding the genetic and molecular mechanisms for the racial differences in inflammatory response to adiposity are warranted. **O**

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