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Original Investigation

Associations of Body Mass Index and Body Fat With Markers of Inflammation and Nutrition Among Patients Receiving Hemodialysis

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Background: Understanding the extent to which visceral and subcutaneous body fat are associated with markers of nutrition and inflammation in patients on dialysis therapy could shed light on the obesity paradox and the biology of subcutaneous fat.

Study Design: Cross-sectional.

Setting & Participants: 609 adults receiving hemodialysis who participated in the ACTIVE/ADIPOSE Study.

Predictors: Body mass index (BMI), waist circumference, and bioelectrical impedance spectroscopy–derived estimates of percent body fat.

Outcomes: C-Reactive protein (CRP), interleukin 6 (IL-6), prealbumin, albumin, leptin, and adiponectin concentrations.

Measurements: We performed linear regression analyses to examine the extent to which proxies of visceral and subcutaneous fat were associated with inflammation, nutrition, and adiposity-related hormones.

Results: BMI was directly associated with markers of inflammation (standardized estimate for ln[CRP in mg/L]: 0.30 [95% CI, 0.22-0.38] per 10 kg/m^2; for ln[IL-6 in pg/mL]: 0.10 [95% CI, 0.02-0.18] per 10 kg/m^2), but was not associated with markers of nutrition. BMI was also inversely associated with adiponectin and directly associated with leptin. With waist circumference and percent body fat (as a proxy of visceral and subcutaneous fat, respectively) modeled together, waist circumference was associated with markers of inflammation (standardized estimate for ln[CRP in mg/L]: 0.21 [95% CI, 0.09-0.34] per 10 cm; for ln[IL-6 in pg/mL]: 0.18 [95% CI, 0.07-0.29] per 10 cm), whereas percent body fat was not associated with CRP (standardized estimate for ln[CRP in mg/L]: 0.03 [95% CI, −0.10 to 0.15] per 1%) and was inversely associated with IL-6 (standardized estimate for ln[IL-6 in pg/mL]: −0.15 [95% CI, −0.27 to −0.02] per 1%). In addition, waist circumference was inversely associated with prealbumin and albumin (standardized estimates of −0.12 [95% CI, −0.23 to −0.02] mg/dL per 10 cm and −0.17 [95% CI, −0.28 to −0.06] g/dL per 10 cm, respectively), and percent body fat was directly associated with prealbumin and albumin (0.20 [95% CI, 0.07-0.32] mg/dL and 0.15 [95% CI, 0.02-0.28] g/dL per 1%, respectively). Higher waist circumference was associated indirectly with adiponectin and directly with leptin concentrations.

Limitations: Although the observed associations implicate visceral fat as the cause of inflammation, it cannot be determined in this cross-sectional study.

Conclusions: Proxies of visceral and subcutaneous fat appear to have opposing associations with biomarkers of inflammation and nutrition. Subcutaneous fat may be an indicator of nutritional status, and visceral fat, an indicator of inflammation.

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INDEX WORDS: End-stage renal disease (ESRD); obesity; inflammation; nutrition; visceral fat; subcutaneous fat; body composition; body fat; waist circumference; body mass index (BMI); obesity paradox; adiposity; hemodialysis; interleukin 6 (IL-6); C-reactive protein (CRP).

High body mass index (BMI), even in the range considered morbidly obese (>35 kg/m^2), is associated with better survival among patients with end-stage renal disease (ESRD) than BMI in the normal range.[1-3] This finding is contrary to the higher mortality seen among obese individuals in the general population.[4] There are several possible explanations for the survival advantage of obesity in the dialysis

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population. Adiposity may serve as an energy reserve against the catabolic effects of the acute superimposed illnesses and acute and chronic inflammation that accompany ESRD and its treatment.[5] It is also possible that associations between obesity and inflammation observed in the general population are not present or are attenuated in the setting of ESRD, perhaps under the influence of stronger inflammatory stimuli or uremic perturbation of adiponectin and leptin production. However, available evidence suggests that obese patients with ESRD have higher levels of inflammation than those who are not obese.[6]

Although BMI is often used as a general indicator of adiposity, it does not distinguish between muscle and adipose tissue and does not distinguish subcutaneous and visceral adipose tissue, the latter now recognized to be more metabolically active and more strongly associated with the adverse sequelae of obesity.[7-11] Recent studies have shown that larger waist circumference, a commonly used indicator of visceral fat, is associated with higher mortality and higher levels of inflammation in the ESRD population.[12-14] Obese dialysis patients have both a large waist circumference and high percentage of body fat.[15] If visceral and subcutaneous fat deposits have opposite metabolic and inflammatory characteristics, they may exert opposing influences on survival and other outcomes. However, the biology of subcutaneous fat has received little attention.

The purpose of this study was to determine the extent to which visceral and subcutaneous body fat are associated with serum concentrations of markers of inflammation and nutrition in patients on dialysis therapy. We used proxies for the comparison of visceral and subcutaneous fat using waist circumference and estimates of body fat derived from whole-body bioimpedance spectroscopy. We hypothesized that waist circumference would be associated with markers of inflammation, but that body fat adjusted for waist circumference would not. We further hypothesized that subcutaneous fat would be associated with indicators of better nutritional status.

METHODS

Study Design and Participants

We analyzed data from a cohort of 771 prevalent adult patients receiving hemodialysis from 14 centers around San Francisco and Atlanta enrolled in the US Renal Data System ACTIVE/ADIPOSE (A Cohort Study to Investigate the Value of Exercise/Analyses Designed to Investigate the Paradox of Obesity and Survival in ESRD) from 2009 to 2011.[16] Participants were older than 18 years, able to give consent in English or Spanish, and on dialysis therapy for at least 3 months. Patients provided informed consent for study participation, and the study was approved by the University of California at San Francisco Committee on Human Research and the Emory Institutional Review Board.

Body Composition

Study coordinators measured height using a stadiometer and recorded postdialysis weight from the previous 3 dialysis sessions in kilograms. Waist circumference was measured to the nearest tenth of a centimeter with participants in a standing position, and the average of 2 measurements was recorded. BMI was calculated as the average postdialysis weight divided by height in meters squared. We performed whole-body bioimpedance spectroscopy immediately before a midweek dialysis session for assessment of body composition, as previously described in detail.[17] Bioimpedance spectroscopy–derived body composition estimates have been validated against other body composition measures, including magnetic resonance imaging and dual-energy x-ray absorptiometry (DXA) among patients receiving dialysis.[18-22] Fat mass was estimated by subtracting total-body water (estimated using resistance extrapolated to infinite frequency) divided by 0.73 from body weight. Percent body fat was calculated using fat mass divided by total-body weight. Participants with complete data for body composition measures and biomarkers were included in this analysis (n = 609).

Markers of Inflammation, Nutrition, and Adiposity-Related Hormones

Study coordinators collected blood for examination of markers of inflammation, nutrition, and adiposity at participants' dialysis facilities at the time of study testing. Specimens were then centrifuged and frozen for mailing to the central laboratory located at the University of California, Davis. Samples were stored over liquid nitrogen at −80°C until the time of analysis. C-Reactive protein (CRP; interassay coefficient of variation [CV], 3.2%), prealbumin (interassay CV, 1.4%), and serum albumin (intra-assay CV, 2.6; interassay CV, 3.2%) were measured in duplicate with a Polychem Nephelometer. Interleukin 6 (IL-6) was measured with a Millipore enzyme-linked immunosorbent assay, and adiponectin and leptin were measured using radioimmune enzyme-linked immunosorbent multiplex assays (leptin CV, 6.4%; adiponectin CV, 6.08%; Millipore). Measurements were performed in duplicate, and we used the mean of the 2 measurements in analyses.

Statistical Methods

We compared characteristics of individuals with body composition and biomarker data with individuals not included in analyses because of missing data using analysis of variance for continuous variables and χ^2 for categorical variables. Among patients with data for body composition and biomarkers, we used linear regression with BMI, waist circumference, and body fat percentage as independent variables and concentrations of biomarkers related to inflammation, nutrition, and adiposity as dependent variables. We used waist circumference as an indicator of visceral fat.[23-26] Percent body fat served as an indicator of subcutaneous fat after adjusting for waist circumference. Models that did not satisfy assumptions of linearity were further evaluated in a stepwise manner beginning with examination of residual plots and, when required, examination of polynomial forms of independent variables.

Markers of inflammation and adiposity-related hormones (CRP, IL-6, adiponectin, and leptin) were natural log transformed (ln) for analysis, whereas albumin and prealbumin were included in the models without transformation. All models were adjusted for age, sex, race, and diabetes mellitus. For the purpose of direct comparison across the different measures of body composition, standardized estimates were included in regression modeling.

We performed model diagnostics, including checking for interactions (markers of body composition × sex and markers of body composition × race) and completing stratified analysis, when appropriate. We tested for trend in linearity for the association of