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Original Investigation

Association of Adiponectin With Body Composition and Mortality in Hemodialysis Patients

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Background: In the general population, circulating adiponectin is associated with a favorable cardiovascular risk profile (eg, lower triglycerides and body fat) and decreased mortality. Hemodialysis (HD) patients have comparatively higher adiponectin concentrations, but prior studies examining the adiponectin-mortality association in this population have not accounted for body composition or shown a consistent relationship.

Study Design: Prospective cohort study.

Settings & Participants: We examined baseline serum adiponectin concentrations in 501 HD patients across 13 dialysis centers from the prospective MADRAD (Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease) cohort (entry period, October 2011 to February 2013; follow-up through August 2013).

Predictor: Serum adiponectin concentration in tertiles (tertiles 1, 2, and 3 defined as ≤16.1, >16.1-<30.1, and ≥30.1-100.0 μg/mL, respectively). Adjustment variables included case-mix and laboratory test results (age, sex, race, ethnicity, vintage, diabetes, serum albumin, total iron-binding capacity, serum creatinine, white blood cell count, phosphate, hemoglobin, and normalized protein catabolic rate), body composition surrogates (subcutaneous, visceral, and total-body fat and lean body mass), and serum lipid levels (cholesterol, high-density lipoprotein cholesterol, and triglycerides).

Outcomes: All-cause mortality using survival (Cox) models incrementally adjusted for case-mix and laboratory test results.

Results: Among 501 HD patients, 50 deaths were observed during 631.1 person-years of follow-up. In case-mix– and laboratory-adjusted Cox analyses, the highest adiponectin tertile was associated with increased mortality versus the lowest tertile (HR, 3.35; 95% CI, 1.50-7.47). These associations were robust in analyses that additionally accounted for body composition (HR, 3.18; 95% CI, 1.61-8.24) and lipid levels (HR, 3.64; 95% CI, 1.34-7.58).

Limitations: Residual confounding cannot be excluded.

Conclusions: Higher adiponectin level is associated with a 3-fold higher death risk in HD patients independent of body composition and lipid levels. Future studies are needed to elucidate underlying mechanisms and determine therapeutic targets associated with improved outcomes in HD patients.

INDEX WORDS: Adiponectin; mortality; hemodialysis; body composition; anthropometry; body fat; body mass index (BMI); lipids; cardiovascular disease (CVD); renal replacement therapy (RRT); end-stage renal disease; MADRAD (Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease) study.

Adipose tissue has gained recognition as an important source of biologically active proteins with metabolic effects, known as adipokines.[1] Among the most abundant circulating adipokine is adiponectin, a hormone of 30 kDa produced in inverse proportion to fat mass[1,2] and which circulates in plasma as a low-, middle-, and high-molecular-weight trimer, hexamer, and multimer, respectively.[1,3]

In the general population, adiponectin has anti-inflammatory, insulin-sensitizing, and antiatherogenic properties[4] and has been associated with favorable body anthropometry characteristics (eg, decreased fat

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mass[2]) and lipid profiles (eg, lower triglyceride and higher high-density lipoprotein [HDL] cholesterol[5] levels). Epidemiologic data have shown that there is an inverse association between adiponectin levels and cardiovascular (CV) morbidity in populations with high underlying CV risk.[6-8] However, in hemodialysis (HD) patients, who bear exceedingly high CV mortality,[9] 2.5- to 3-fold higher adiponectin concentrations have been observed.[1,10,11]

Despite intensive past study, the impact of adiponectin on the CV health and survival of HD patients remains unclear. Whereas early studies suggested that higher adiponectin levels are associated with decreased CV and all-cause mortality risk in the HD population,[10,12] recent data indicate that elevated circulating adiponectin levels are associated with adverse outcomes in non−dialysis-dependent patients with chronic kidney disease and HD patients.[13-15] Heterogeneous findings across studies may be due to residual confounding relating to inconsistent covariate adjustment.[16,17] Previous studies of the adiponectin-mortality association in this population have not comprehensively considered differences in multiple individual body composition compartments (eg, visceral and subcutaneous fat mass or lean body mass) among patients with varying adiponectin levels. Furthermore, only 2 studies have accounted for serum lipid components in non−dialysis-dependent patients with chronic kidney disease and HD patients to date.[13,14]

Accounting for differences in body composition and lipoprotein fractions in the examination of adiponectin and HD patient outcomes bears particular relevance. For example, although body mass index (BMI) has been deemed to be a potent and paradoxical predictor of mortality in HD patients (ie, higher BMI is associated with decreased mortality),[18] some studies suggest that individual body composition components (eg, waist circumference and triceps skinfold as surrogates of visceral and subcutaneous fat) have a similar or even stronger association with survival than BMI.[19-21] Recent data suggest that the association between adiponectin and mortality may be dependent on BMI or waist circumference.[16,17] To our knowledge, no studies of adiponectin and mortality have comprehensively accounted for differences in other body composition components, such as subcutaneous fat and lean body mass. Furthermore, some,[22-25] but not all,[26] studies have shown that total serum cholesterol and its individual components, such as low-density lipoprotein (LDL) and HDL, have paradoxical associations with mortality in HD patients (ie, lower total and LDL cholesterol and higher HDL cholesterol levels associated with increased death risk). Thus, to better inform the field, we sought to examine the association between serum adiponectin level and mortality in a large prospective cohort of maintenance HD patients undergoing rigorous protocoled measurement of clinical, laboratory, and individual body anthropometry and serum lipid characteristics.

METHODS

Study Population

The study population was comprised of a cohort of maintenance HD patients enrolled in the initial phase of the Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease (MADRAD) study (study registration: ClinicalTrials.gov; study number NCT01415570), a prospective cohort study examining the differential association between dietary factors and nutritional status across racial and ethnic HD subgroups. In this substudy, patients were recruited from 13 DaVita Healthcare Partners Inc dialysis facilities in the South Bay−Los Angeles area from October 2011 through February 2013. Patients were included provided that they were aged 18 to 85 years, received thrice-weekly in-center HD treatment for at least 4 consecutive weeks, signed a local institutional review board−approved consent form, and had serum adiponectin measurement at study entry. Patients were excluded if they were actively receiving peritoneal dialysis, had life expectancy less than 6 months (eg, stage IV cancer), or were unable to provide consent without a proxy (eg, dementia). The study was approved by the institutional review committees of the Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, CA, and the University of California Irvine Medical Center, Orange, CA.

Exposure Ascertainment

Baseline adiponectin levels were measured from frozen serum samples that were obtained predialysis during weekday HD treatments at the time of study entry and that chronologically coincided with routine blood tests conducted at DaVita facilities. Serum adiponectin was measured using immunoassay kits based on solid-phase sandwich enzyme-linked immunosorbent assay (EMD Millipore Corp) in the General Clinical Research Center Laboratories of Harbor-UCLA Medical Center with a lower limit of detection of 0.0002 μg/mL for adiponectin. Coefficients of variation for intra- and interassay precision were 0.9% and 2.4%, respectively.

In primary analyses, we examined the association between serum adiponectin concentrations, categorized into tertiles, and all-cause mortality. In secondary analyses, adiponectin level was considered as a continuous variable and scaled to a 10-μg/mL change. To flexibly model the association between continuous adiponectin concentrations and mortality, we also conducted analyses in which adiponectin was examined as a restricted cubic spline with knots corresponding to the 25th (13.8 μg/mL), 50th (22.6 μg/mL), and 75th (36.3 μg/mL) percentiles of observed values.

Sociodemographic, Comorbidity, and Laboratory Test Measures

At study entry, baseline information for sociodemographics, comorbid conditions, and dialysis treatment characteristics (eg, vascular access type) were collected. Dialysis vintage was defined as the time between the date of study entry and the date of HD therapy initiation. Routine dialysis laboratory measurements were performed by DaVita Healthcare Inc laboratories (Deland, FL) on a monthly or quarterly basis using automated methods. In this study, baseline values from routine laboratory tests, including serum lipids (total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol) were used.