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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.

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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.

Body Anthropometry Test Measures

At study entry, dialysis center dietitians conducted measurements of body composition surrogates while patients underwent routine HD treatments, which included the following: BMI, subcutaneous fat (determined from biceps and triceps skinfold), visceral fat (determined from waist circumference), lean muscle mass (determined from midarm circumference [MAC] and midarm muscle circumference [MAMC]), and body fat percentage (measured by near-infrared [NIR] interactance). BMI was defined as postdialysis weight (kg) divided by height squared (m^2). Biceps and triceps skinfold thicknesses (millimeters) were measured in the nondialysis vascular access arm with a conventional skinfold caliper using standard techniques, and average values of triplicate measurements were used. Waist circumference (centimeters) was measured in a horizontal plane at the midpoint between the inferior margin of the last rib and crest of the ilium, and MAC (centimeters) was measured from the lateral tip of the acromion process of the scapula to the tip of the olecranon process with nonstretchable plastic tape. MAMC (centimeters) was estimated using the following formula: MAMC = MAC − 3.142 × triceps skinfold.[27,28] To estimate the percentage of body fat and fat-free body mass, NIR interactance body fat (percent) was measured by placing a Futrex NIR interactance sensor (portable 6100; Futrex Inc) on the non–vascular access upper arm for several seconds, after inputting the required data (date of birth, sex, weight, and height) for each patient. As has been shown in prior studies, NIR interactance body fat is highly correlated with other body fat and nutritional metrics in HD patients.[29-31]

Outcome Ascertainment

The primary outcome of interest was all-cause mortality. At-risk time began the day after serum adiponectin measurement, and patients were censored for kidney transplantation, transfer to a non-DaVita dialysis unit or peritoneal dialysis therapy, or end of the study (August 23, 2013). Each semester, information regarding mortality, censoring events, and associated dates from the preceding 6 months was collected from event forms completed by the MADRAD research assistants and reviewed by 2 MADRAD study nephrologists (C.M.R. and K.K.-Z.).

Statistical Methods

Baseline characteristics between exposure groups were compared using χ^2, analysis of variance, and Kruskal-Wallis tests as dictated by data type. We first examined the relationship of relevant clinical, laboratory, and body composition surrogates with: (1) serum adiponectin concentrations using Pearson correlation coefficients and (2) high adiponectin concentration (defined as adiponectin > 50th percentile) using logistic regression. For both Pearson correlation and logistic regression analyses, *P* values were adjusted using the false discovery rate method to account for multiplicity of comparisons by reducing the proportion of false discoveries.[32]

We then estimated the association between serum adiponectin level and all-cause mortality using Kaplan-Meier plots, log-rank testing, and Cox proportional hazard models with 3 incremental levels of covariate adjustment: (1) unadjusted analyses (model 1): no adjustment for covariates; (2) case-mix–adjusted analyses (model 2): adjusted for age, sex, race (black vs nonblack), ethnicity (Hispanic vs non-Hispanic), and dialysis vintage; and (3) Case-mix– and laboratory-adjusted analyses (model 3): adjusted for covariates in model 2, as well as diabetes, serum albumin level, total iron-binding capacity, serum creatinine, white blood cell (WBC) count, phosphate level, hemoglobin level, and normalized protein catabolic rate.

To test the hypothesis that discordant associations between adiponectin level and mortality may be observed with inconsistent adjustment for lipid levels and body anthropometry surrogates, we incrementally adjusted for lipid level and body composition components as follows: (4) lipid-adjusted analyses (model 4): adjusted for covariates in model 3, as well as serum total cholesterol, HDL cholesterol, and triglyceride levels; and (5) body anthropometry–adjusted analyses (model 5): adjusted for covariates in model 3, as well as waist circumference, biceps skinfold, MAC, and NIR interactance body fat.

The proportional hazards assumption was confirmed graphically and by Schoenfeld residual function testing. Effect modification of adiponectin-mortality associations on the basis of age (≥65 vs <65 years), sex, race (black vs nonblack), ethnicity (Hispanic vs non-Hispanic), diabetes, waist circumference (≥95 vs <95 cm), BMI (≥25 vs <25 kg/m^2), and serum albumin level (≥4 vs <4 mg/dL) was explored through the addition of 2-way interaction terms with adiponectin (separately) using likelihood ratio testing. Missing covariate data were imputed using the means or medians of observed values. Analyses were carried out using the statistical software Stata, version 12.0 (StataCorp LP), and SAS, version 9.4 (SAS Institute Inc).

RESULTS

Cohort Description

For 501 patients meeting the eligibility criteria, mean age of the cohort was 55.2 ± 14.9 (standard deviation) years, of whom 44% were women, 40% were African American, and 47% had diabetes. The mean, median, and range of serum adiponectin concentrations in the cohort were 26.9 ± 17.6, 22.6 (interquartile range, 13.8-36.3), and 2.83-100 μg/mL, respectively. Compared with patients in the lowest adiponectin tertile, patients in the highest tertile were more likely to be women, Hispanic, and of older dialysis vintage; were less likely to be African American; had lower platelet counts, WBC counts, triglyceride concentrations, BMI, waist circumference, biceps skinfold, triceps skinfold, NIR interactance body fat percentage, MAC, and MAMC values; and had higher HDL cholesterol concentrations (Table 1). When examining clinically and statistically significant differences in baseline characteristics in patients with versus without missing covariate data, we found that those with missing data with respect to model 3 were more likely to be younger and Hispanic, were less likely to be black, and had lower waist circumference, NIR interactance body fat, and MAMC (Table S1, available as online supplementary material).

Cross-sectional Associations With Clinical, Laboratory, and Body Anthropometry Covariates

In correlation analyses adjusted for case-mix and laboratory covariates, adiponectin level had the strongest inverse correlations with WBC count, triglyceride concentration, BMI, waist circumference, NIR interactance body fat percentage, and MAC and had the strongest positive correlation with HDL cholesterol level (Table S2; scatterplots of select bivariate correlations shown in Fig S1). After accounting for multiplicity of comparisons using the

Table 1. Baseline Characteristics According to Adiponectin Tertiles in Maintenance Hemodialysis Patients

	Tertile 1	Tertile 2	Tertile 3	*P*[a]
No. of patients	165 (32.9)	166 (33.1)	170 (33.9)	NA
Adiponectin range (μg/ml)	0-16.1	>16.1-<30.1	≥30.1-100	NA
Age (y)	52.8 ± 14.5	56.6 ± 15.6	56.0 ± 14.6	0.6
Dialysis vintage (y)	2.9 [1.2-5.3]	3.6 [1.5-7.3]	3.9 [1.9-7.1]	0.007
Female sex	57 (34.6)	80 (48.2)	81 (47.7)	0.02
Black race	75 (45.5)	60 (36.1)	65 (38.2)	0.2
Hispanic ethnicity	63 (38.2)	81 (48.8)	83 (48.8)	0.08
Diabetes	76 (46.1)	81 (48.8)	79 (46.5)	0.9
AVF/AVG	84 (50.9)	95 (57.2)	79 (46.5)	0.1
Smoking	58 (35.2)	61 (36.8)	62 (36.5)	>0.9
Laboratory tests				
Serum albumin (g/dL)	4.1 [3.9-4.3]	4.0 [3.7-4.2]	4.0 [3.7-4.2]	0.06
Creatinine (mg/dL)	9.9 [8.0-12.3]	8.9 [7.2-11.5]	9.3 [7.6-11.0]	0.05
Calcium[b] (mg/dL)	9.1 [8.7-9.7]	9.1 [8.7-9.5]	9.2 [8.8-9.6]	0.5
Phosphorus (mg/dL)	4.8 [4.2-6.1]	4.9 [4.0-5.7]	4.9 [4.1-6.1]	0.7
PTH (pg/mL)	369 [203-557]	346 [226-549]	352 [250-575]	0.8
Hemoglobin (g/dL)	10.0 [10.6-11.2]	10.8 [10.2-11.3]	10.7 [10.1-11.3]	0.4
Platelet count ($\times 10^9$/L)	229 [191-271]	226 [172-275]	198 [156-234]	<0.001
MPV (fL)	9.5 [9.0-10.3]	9.8 [9.1-10.6]	9.9 [9.1-10.8]	0.2
WBC count ($\times 10^9$/L)	7.0 [5.8-8.4]	6.6 [5.5-8.3]	5.9 [4.5-7.2]	<0.001
TIBC (μg/dL)	224 [207-251]	221 [188-253]	213 [193-242]	0.08
Ferritin (ng/mL)	676 [422-899]	693 [416-928]	684 [463-907]	0.8
nPCR (g/kg/d)	1.0 [0.8-1.2]	1.0 [0.9-1.2]	1.0 [0.8-1.2]	0.4
Glucose (mg/dL)	135 [97-199]	142 [102-196]	128 [88-189]	0.8
Hemoglobin A_{1c} (%)	6.2 [5.7-7.0]	6.2 [5.5-7.2]	6.0 [5.5-7.3]	0.8
Total cholesterol (mg/dL)	146 [126-166]	128 [112-170]	144 [130-177]	0.3
HDL cholesterol (mg/dL)	34 [30-42]	39 [30-49]	45 [38-56]	0.003
LDL cholesterol (mg/dL)	76 [59-91]	61 [47-74]	66 [53-104]	0.1
Triglycerides (mg/dL)	164 [111-265]	115 [93-171]	101 [78-141]	<0.001
Body anthropometry				
BMI (kg/m^2)	29.0 [25.5-33.7]	26.1 [23.2-30.3]	24.1 [21.9-27.7]	<0.001
Waist circumference (cm)	101 [91-115]	95 [84-106]	88.5 [81.3-100]	<0.001
Biceps SF (mm)	12.1 [8.0-22.3]	11.1 [6.7-19.7]	10.3 [5.7-17.0]	0.04
Triceps SF (mm)	20.3 [12.7-29.3]	19.2 [12.7-27.3]	16.0 [9.0-23.3]	0.007
NIR interactance body fat (%)	30.3 [23.0-39.0]	29.6 [23.3-38.0]	23.4 [18.3-34.4]	<0.001
MAC (mm)	325 [290-360]	302 [275-335]	285 [261-317]	<0.001
MAMC (mm)	261 [228-293]	235 [215-268]	236 [212-257]	<0.001

Note: Categorical variables are given as number (percentage); continuous variables, as mean ± standard deviation or median [interquartile range]. Conversion factors for units: calcium in mg/dL to mmol/L, ×0.2495; cholesterol in mg/dL to mmol/L, ×0.02586; creatinine in mg/dL to μmol/L, ×88.4; glucose in mg/dL to mmol/L, ×0.05551; fibrinogen in mg/dL to μmol/L, ×0.0294; phosphorus in mg/dL to mmol/L, ×0.3229; triglycerides in mg/dL to mmol/L, ×0.01129.

Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAC, midarm circumference; MAMC, midarm muscle circumference; MPV, mean platelet volume; NA, not applicable; NIR, near-infrared; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; SF, skinfold; TIBC, total iron-binding capacity; WBC, white blood cell.

[a]*P* value calculated by analysis of variance, χ^2, or Kruskal-Wallis test.

[b]Calcium level corrected for serum albumin level.

false discovery rate method, correlations remained statistically significant except for the triglyceride-adiponectin association. In case-mix– and laboratory-adjusted logistic regression analyses, dialysis vintage and HDL cholesterol level were directly associated with high adiponectin level, whereas WBC count, total cholesterol, triglyceride, LDL cholesterol, BMI, waist circumference, biceps skinfold, triceps skinfold, NIR interactance body fat, MAC, and MAMC values were inversely associated with high adiponectin level; these associations remained statistically significant after accounting for multiplicity of comparisons (Table S3).

Adiponectin Concentration and Mortality

Patients contributed a total of 631.1 person-years of follow-up, during which 50 death events were observed. Median at-risk time was 1.47 years. In primary analyses, the highest adiponectin tertile was associated with increased mortality risk in comparison to the lowest tertile in unadjusted Cox regression

Table 2. Association Between Adiponectin Level and All-Cause Mortality

	Model 1[a]		Model 2[b]		Model 3[c]	
	HR (95% CI)	*P*[d]	HR (95% CI)	*P*[e]	HR (95% CI)	*P*[f]
Categorical[g]						
Adiponectin tertile 2: >16.1-<30.1 μg/mL	1.81 (0.79-4.15)	0.2	1.80 (0.78-4.15)	0.2	1.71 (0.73-4.01)	0.2
Adiponectin tertile 3: ≥30.1 μg/mL	3.13 (1.46-6.72)	0.003	3.53 (1.61-7.70)	0.002	3.35 (1.50-7.47)	0.003
Continuous: per each 10.0-μg/mL increase in adiponectin	1.27 (1.13-1.42)	<0.001	1.26 (1.12-1.41)	<0.001	1.25 (1.10-1.41)	0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Unadjusted for covariates.
[b]Adjusted for age, sex, race, ethnicity, and dialysis vintage.
[c]Adjusted for age, sex, race, ethnicity, dialysis vintage, diabetes, serum albumin level, total iron-binding capacity, serum creatinine level, white blood cell count, phosphorus level, hemoglobin level, and normalized protein catabolic rate.
[d]*P* for trend for categorical = 0.002.
[e]*P* for trend for categorical = 0.001.
[f]*P* for trend for categorical = 0.002.
[g]Reference group is adiponectin tertile 1 (0-16.1 μg/mL).

analyses in model 1: unadjusted hazard ratio (HR), 3.13; 95% confidence interval (CI), 1.46-6.72; $P = 0.003$ (Table 2; Kaplan Meier curves and log-rank test shown in Fig 1). The magnitude of these estimates became stronger with multivariable adjustment in models 2 and 3, respectively: adjusted HRs of 3.53 (95% CI, 1.61-7.70; $P = 0.002$) and 3.35 (95% CI, 1.50-7.47; $P = 0.003$), respectively (Table 2). Compared with the lowest adiponectin tertile, the middle tertile was associated with numerically greater risk but this did not reach statistical significance in models 1, 2, and 3. In analyses incrementally adjusted for serum lipid levels (model 4) and body composition surrogates (model 5), the association between higher adiponectin level and increased mortality remained robust: adjusted HRs of 3.64 (95% CI, 1.61-8.24; $P = 0.002$) and 3.18 (95% CI, 1.34-7.58; $P = 0.009$), respectively (Table 3). We did not detect effect modification of the adiponectin-mortality association on the basis of age, sex, race, ethnicity, dialysis vintage, presence of diabetes, waist circumference, BMI, or serum albumin level: *P* for interaction = 0.8, 0.5, 0.5, 0.6, >0.9, 0.4, 0.4, >0.9, and 0.6, respectively.

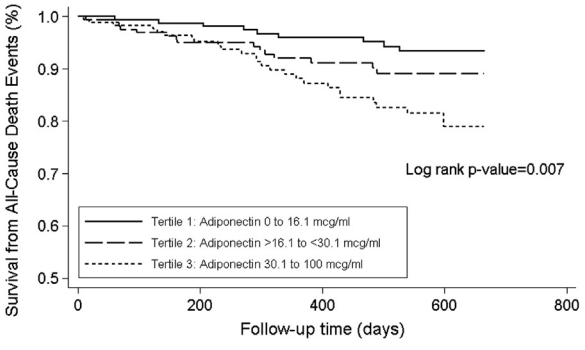

Figure 1. Kaplan-Meier survival analysis for adiponectin tertiles in maintenance hemodialysis patients.

In secondary analyses, we observed that a 10-μg/mL increase in adiponectin concentration was associated with ~25% increased mortality risk across models 1 through 5 (Tables 2 and 3). In analyses examining the association between continuous adiponectin and all-cause mortality using a cubic spline function adjusted for covariates in model 3, we observed that there was a monotonic increase in death risk across the entire range of adiponectin concentrations (Fig 2).

DISCUSSION

In a prospective cohort of maintenance HD patients from the MADRAD study, we observed that HDL cholesterol level was directly associated with high adiponectin concentration, whereas visceral, subcutaneous, and total-body fat; lean body mass; total cholesterol level; triglyceride level; and LDL cholesterol level showed inverse associations. We also found that higher circulating adiponectin concentrations are associated paradoxically with increased mortality risk. These findings were robust across clinically relevant subgroups, as well as analyses that comprehensively adjusted for multiple individual body composition surrogates and serum lipid components.

Adiponectin has known complex associations with multiple biological pathways, including those that favorably affect atherogenic risk.[1,33] In addition to improving the insulin sensitivity of hepatic and skeletal muscle[34,35]; suppressing and increasing expression of proinflammatory and anti-inflammatory cytokines, respectively[36,37]; maintaining endothelial homeostasis (ie, augmentation of nitric oxide production and inhibition of neointimal formation)[38-41]; and attenuating platelet aggregation and thrombus

Table 3. Association Between Adiponectin Level and All-Cause Mortality Incrementally Adjusted for Serum Lipid and Body Anthropometry Covariates

	Model 4[a]		Model 5[b]	
	HR (95% CI)	*P*[c]	HR (95% CI)	*P*[d]
Categorical[e]				
Adiponectin tertile 2: >16.1-<30.1 μg/mL	1.78 (0.75-4.21)	0.2	1.46 (0.61-3.50)	0.4
Adiponectin tertile 3: ≥30.1 μg/mL	3.64 (1.61-8.24)	0.002	3.18 (1.34-7.58)	0.009
Continuous: per each 10.0-μg/mL increase in adiponectin	1.27 (1.11-1.45)	<0.001	1.23 (1.08-1.41)	0.003

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Adjusted for covariates in model 3 (see Table 2) and serum total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels.

[b]Adjusted for covariates in model 3 (see Table 2) and waist circumference, biceps skinfold, near-infrared interactance body fat percentage, and midarm circumference.

[c]*P* for trend for categorical < 0.001.

[d]*P* for trend for categorical < 0.001.

[e]Reference group is adiponectin tertile 1 (0-16.1 μg/mL).

formation,[1] adiponectin is also associated with a favorable serum lipid profile.[5,42,43] Similar to patterns observed in prior studies of the general population and dialysis patients,[5,42] we found that adiponectin levels were associated inversely with triglyceride, LDL cholesterol, and total cholesterol levels and positively with HDL cholesterol level.

Adiponectin has also been linked with potent predictors of mortality in HD patients, namely unfavorable body anthropometry characteristics such as decreased lean body mass, subcutaneous fat, and visceral fat.[18-21] Loss of body fat and lean body mass have been shown to induce adiponectin secretion in both the general and dialysis populations,[33,44] and experimental data in animals have shown that adiponectin stimulates energy expenditure and induces weight loss by direct action in the brain.[45] Consistent with these data, we found that adiponectin level was inversely associated with visceral fat, total body fat, and lean body mass.[33,46-50]

There has been inconsistent adjustment for atherogenic risk factors (eg, serum lipid levels) and body composition characteristics across prior studies of the adiponectin-mortality association in HD patients, which have shown mixed findings.[10,11,13,15] In a seminal study of 227 HD patients by Zoccali et al,[11] a 1-μg/mL higher adiponectin concentration was associated with a 3% lower CV event risk, although an association with mortality was not observed. Subsequently, Rao et al[10] observed that higher baseline and time-dependent adiponectin concentrations were associated with decreased mortality among 182 HD patients from the HEMO (Hemodialysis) Study and 2 Boston dialysis centers, and these findings have been corroborated in other studies of HD patients. In contrast, Menon et al[14] observed higher adiponectin levels to be associated with increased all-cause and cardiovascular mortality in a secondary analysis of 585 patients with chronic kidney disease stages 3 to 4 from the Modification of Diet in Renal Disease (MDRD) Study. In a cohort of 85 Japanese HD patients, Ohashi et al[15] showed that a 1-μg/mL higher adiponectin concentration was associated with a 10% increase in all-cause mortality risk, although these estimates were attenuated to the null when patients with serum albumin levels < 3.5 mg/dL (ie, surrogate of malnutrition) were excluded. In the largest study of adiponectin and mortality in dialysis patients to date, Dreschler et al[13] found that higher adiponectin concentrations were associated with increased risk of

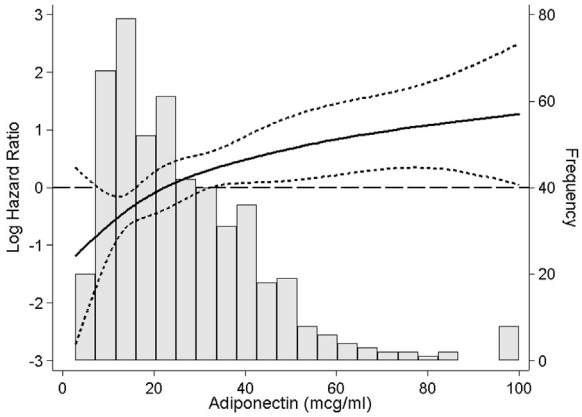

Figure 2. Association between gradations of adiponectin and all-cause mortality in maintenance hemodialysis patients. Figures present log hazard ratios (short-dashed lines indicate 95% confidence intervals) for adiponectin analyzed as a spline with knots at 14 (25th percentile) and 36 μg/mL (75th percentile). A histogram of observed adiponectin values and a log hazard reference ratio of 0 (long-dashed line) is overlaid. Analyses adjusted for age, sex, race, ethnicity, dialysis vintage, diabetes, serum albumin level, total iron-binding capacity, serum creatinine level, white blood cell count, phosphorus level, hemoglobin level, and normalized protein catabolic rate.

sudden cardiac death among 1,255 HD patients with diabetes type 2 from 4D (Die Deutsche Diabetes Dialyse Studie), although estimates were no longer significant after adjustment for BMI, serum lipid levels (triglycerides and HDL cholesterol), and other covariates. Two recent studies by Tsigalou et al[16] and Zoccali et al[17] show that the adiponectin-mortality association is dependent on underlying BMI and waist circumference, but none of the mentioned studies have concurrently adjusted for individual body composition components (eg, lean body mass and visceral, subcutaneous, and total-body fat).

To our knowledge, ours is the first study of the adiponectin-mortality association in HD patients to rigorously measure and account for a comprehensive cadre of individual body composition components using reliable metrics (eg, MAC, MAMC, waist circumference, biceps and triceps skinfold, and NIR interactance body fat). In analyses that incrementally adjusted for these factors, there was a robust association between higher adiponectin concentration and decreased survival. We additionally conducted sensitivity analyses in which we adjusted for serum lipid levels, and we observed a persistent association between higher adiponectin concentration and death risk in contrast to the mentioned Dreschler et al[13] study.

Our findings suggest that past studies' discordant findings may not be due to variable consideration of body composition characteristics and atherogenic risk factors. Further studies are needed to determine the mechanisms underlying this robust yet paradoxical association between adiponectin level and death and other mechanisms by which high adiponectin level may be linked with heightened mortality, including: (1) volume overload (ie, volume overload stimulates natriuretic peptide release, which in turn increases adiponectin production[51]), (2) reduced WBC count and impaired immune function resulting from inhibition of bone marrow myelopoiesis,[15] (3) loss of residual kidney function (ie, decreased kidney function leads to impaired adiponectin clearance),[1] or (4) counter-regulation of inflammation, vascular disease, and atherosclerosis, which are highly prevalent in HD patients.[13] Furthermore, additional factors accounting for the discrepant associations across the mentioned studies, including varying durations of follow-up and heterogeneous study population characteristics, should be explored. We did not detect effect modification of the adiponectin-mortality association by various clinically relevant characteristics, including age, sex, race, ethnicity, underlying diabetes, waist circumference, BMI, or serum albumin level. Although our study population was of moderately large size, our analyses may have been underpowered to detect a statistically significant interaction. Future studies are needed to confirm findings and account for volume status using sophisticated and validated metrics (ie, bioelectrical impedance), novel and traditional inflammatory markers, and residual kidney function in order to elucidate the complex association between adiponectin and mortality risk.

The strengths of our study include its: (1) examination of a study population with case-mix characteristics similar to that of the HD population in the United States; (2) rigorous protocoled measurement of sociodemographic, comorbidity, body anthropometry, and laboratory data; and (3) uniform laboratory measurements of adiponectin conducted in 1 centralized laboratory. However, several limitations bear mention. First, adiponectin concentrations were based on single measurements obtained at study entry, and change in adiponectin levels over time was not considered. Second, we had limited ability to examine markers of insulin resistance and inflammation and cannot exclude the possibility of residual confounding on this basis. Third, our adiponectin measurements did not differentiate between adiponectin moieties (eg, high- vs low-molecular-weight isoforms), which are associated with differential biological activity.[50,52,53] Fourth, the body anthropometry surrogates selected as Cox regression model covariates were moderately correlated (unadjusted Pearson correlation $R = 0.41$-0.52). Whereas these surrogates represent distinct body composition components and are associated with both adiponectin concentration and mortality based on published evidence, residual confounding by body composition cannot be excluded. Fifth, our analyses did not take into consideration specific causes of death (eg, CV). Last, as with all observational studies, we cannot exclude the possibility of residual confounding.

In summary, our study supports an association between serum adiponectin level and mortality in HD patients independent of body composition. Further studies are needed to confirm findings, explore mechanistic pathways underlying the adiponectin-mortality association, and determine the therapeutic impact of lowering adiponectin concentrations in HD patients.

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Contributions: Research idea and study design: CMR, KK-Z; data acquisition: CMR, KK-Z; data analysis/interpretation: CMR, DVN, HM, SMB, RD, JJ, TN, CPK, GAB, KK-Z; statistical analysis: CMR; supervision or mentorship: KK-Z. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. CMR takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

SUPPLEMENTARY MATERIAL

Table S1: Baseline characteristics in HD patients with vs without missing data.

Table S2: Unadjusted and multivariable-adjusted Pearson correlation coefficients of adiponectin and other relevant covariates.

Table S3: Association of demographic, clinical, and lab measures with high adiponectin using logistic regression.

Figure S1: Bivariate correlations of adiponectin with selected lab test and body composition surrogates.

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