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Associations of lipoproteins with cardiovascular and infection-related outcomes in patients receiving hemodialysis

George A. Kaysen, MD PhD[1,2], **Barbara Grimes, Ph.D**[3], **Lorien S. Dalrymple, MD, MPH**[4], **Glenn M. Chertow, MD, MPH**[5], **Julie H. Ishida, MD, MAS**[6,7], **Cynthia Delgado, MD**[6,7], **Mark Segal, PhD**[3], **Janet Chiang, MD**[8,9], **Tjien Dwyer, BS**[1], and **Kirsten L. Johansen, MD**[3,6,7]

[1]Division of Nephrology Department of Medicine University of California Davis School of Medicine

[2]Department of Biochemistry and Molecular Medicine University of California Davis School of Medicine

[3]Department of Epidemiology and Biostatistics, University of California, San Francisco, California

[4]Fresenius Medical Care North America, Waltham, MA

[5]Department of Medicine, Division of Nephrology, Stanford University School of Medicine Stanford, California

[6]Division of Nephrology and Department of Medicine University of California San Francisco

[7]Nephrology Section, San Francisco Veterans Affairs Medical Center, San Francisco, California

[8]Endocrinology Section, San Francisco Veterans Affairs Medical Center, San Francisco, California

[9]Division of Endocrinology and Department of Medicine University of California San Francisco

Abstract

Corresponding author: George A Kaysen MD, PhD, Department of Internal Medicine, Division of Nephrology, University of California, Davis, U.S.A., One Shields Avenue, 451 Health Sciences Drive, Genome and Biomedical Sciences Facility, Davis, California 95616, U.S.A., gakaysen@ucdavis.edu.

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Author Contribution: All of the authors have participated in the writing of this manuscript, the analyses provided, and in the interpretation of the findings.

George Kaysen: Proposed the idea, wrote the paper and supervised the biochemical analysis

Barbara Grimes: Performed the statistical analysis, and edited the manuscript

Lorien S. Dalrymple: Development of analysis plan, use of ICD-9-CM codes for outcomes ascertainment, and edited the manuscript.

Glenn M. Chertow: Recruitment of subjects participated in measurement of body composition, analysis of comorbidities and participated in writing and editing of the paper.

Julie Ishida: Participated in development of analysis plan, ICD-9-CM code selection, and edited the manuscript

Cynthia Delgado: Participated in patient recruitment, measurement of body composition, comorbidities, and edited the manuscript

Mark Segal: Supervised and participated in the statistical analysis

Janet Chiang: Participated in development of analysis plan, and edited the manuscript

Tjien Dwyer: Conducted all of the biochemical assays, and edited the manuscript.

Kirsten L. Johansen: Principal investigator, participated in measurement of body composition, analysis of comorbidities and participated in writing the paper.

Background—In hemodialysis patients (HD) higher lipid levels are associated with lower mortality. Lipid lowering therapy does not reduce all-cause or cardiovascular (CV) mortality. Lipoproteins play a role in the innate immune system. Our objective was to determine whether protection from infection might counterbalance adverse CV outcomes associated with lipoproteins.

Methods—We examined associations between serum apolipoprotein A1, B, C2, C3, HDL and LDL cholesterol and triglycerides (TG) levels and infectious mortality or hospitalization, CV mortality or hospitalization, and all-cause mortality in 433 prevalent HD. Cox models with time-varying apolipoprotein concentrations collected every 6 months for up to 2 years were used for analyses.

Results—Median follow-up time for all-cause mortality was 2.7 years (25^{th}–75^{th} percentile range: 2.2–3.4 years). One hundred seventy nine (41%) patients had an infection-related event. In multivariable models, higher Apo B and LDL were associated with lower risks of infection related outcomes (HR Apo B 0.92 [95% CI 0.86–0.99 per 10mg/dL, P = 0.03]; HR LDL 0.93 [95% CI 0.87–1.00 per 10 mg/dL, P = 0.05]). Sixty-three (15%) participants had a CV-related event. No significant associations were observed among lipoproteins and CV outcomes. Eighty-seven (20%) participants died. Higher Apo A1, Apo B, and Apo C3 were associated with lower risks of all-cause mortality. There was no interaction between the use of lipid lowering medication any of the outcomes.

Conclusion—Associations of lipoproteins with lower risk of serious infection accompanied by no significant association with CV events may help to explain the paradoxical association between lipids and survival and lack of benefit of lipid-lowering therapies in HD.

Keywords

Infection; lipoproteins; cardiovascular; ACTIVE/ADIPOSE; USRDS; LDL; apolipoprotein B; apolipoprotein C2

INTRODUCTION

Cardiovascular and infection-related events are the two leading causes of death among patients with end stage renal disease (ESRD) receiving hemodialysis (1,2). By United States Renal Data System (USRDS) estimates, cardiovascular mortality and cardiovascular events have stabilized, but the rates of infection-related hospitalization and death have increased (3). Total and LDL cholesterol concentrations are associated with cardiovascular mortality among persons over age 50 in the general population, but the associations among these lipoproteins and outcomes in individuals with end stage renal disease (ESRD) are less certain (4), and mortality is actually higher among ESRD patients who have *lower* serum total cholesterol concentrations compared to those with higher serum cholesterol concentrations (5,6,7). Moreover, randomized controlled trials lowering LDL cholesterol concentrations in patients receiving hemodialysis have neither enhanced survival nor reduced the incidence of major cardiovascular events (8,9,10) and have had no significant effect on all-cause or cardiovascular mortality (10), suggesting that the paradigm linking lipoproteins and mortality operative in the general population may be altered in the setting of ESRD.

Lipoproteins, and other protein constituents that compose lipoproteins are now understood to play roles in the innate immune system (11,12,13,14,15,16), providing a potential mechanism for protection against leading causes of morbidity and mortality in a population with high risk of infection. To explore this hypothesis, we examined associations among serum lipoprotein concentrations and cardiovascular and infection-related outcomes in a prevalent hemodialysis cohort. We also examined all-cause mortality to determine whether any infection-related benefit observed among patients with higher lipoprotein concentrations was offset by adverse cardiovascular effects.

Materials and Methods

The ACTIVE/ADIPOSE (A Cohort Study to Investigate the Value of Exercise in ESRD/ Analyses Designed to Investigate the Paradox of Obesity and Survival in ESRD) study enrolled 771 prevalent hemodialysis patients who had been receiving hemodialysis for at least three months from 14 centers in the San Francisco CA and Atlanta GA metropolitan areas from June 2009 through August 2011 (17). The study was approved by the Institutional Review boards at the University of California, San Francisco and at Emory University. All patients provided written informed consent for study participation and for utilization of their collected serum. In order to ascertain infection-related and cardiovascular hospitalization events, this analysis was restricted to participants who had Medicare as the primary payer and baseline laboratory values (N= 433). Fat mass was determined using multifrequency bioimpedance spectroscopy (BIS) as described previously (18). We ascertained patients' demographic information, comorbid conditions, and medication use by interview and through review of dialysis facility records and information in the Centers for Medicare and Medicaid Services (CMS) Form 2728. Blood was drawn prior to dialysis every six months for up to two years, separated by centrifugation at the local facility and then shipped on dry ice to the core laboratory at the University of California, Davis where it was thawed once, aliquoted and then frozen over liquid nitrogen until assay.

We extracted hospital claim records and causes of death from the United States Renal Data System (USRDS) using the Hospital Standard Analytic File (SAF) and Patient SAF for 433 Medicare eligible enrollees in the ACTIVE/ADIPOSE study. We considered hospitalization to be infection-related if the primary ICD-9-CM diagnosis code for an infection-related hospitalization, with an emphasis on bacterial infections (Supplemental Table 1A). For cardiovascular hospitalizations of interest, we required a cardiovascular primary diagnosis ICD-9-CM code or the presence of a cardiovascular procedure ICD-9-CM code for a in any position (Supplemental Table 1B and 1C). The cause of death field in the Patient SAF was used to determine whether deaths were related to infection or cardiovascular causes.

Laboratory measures

All apolipoproteins, lipoproteins, and C reactive protein (CRP), were measured in duplicate in serum with a Polychem Nephelometer (Walpole, MA 02081). Albumin was measured by Bromocresol Green (Polymedco Walpole, MA 02081). Both LDL and HDL were measured directly. Supplemental Table 2 shows the assay ranges and intra- and inter-assay coefficients of variation.

Statistical Analysis

We used Cox regression analysis to examine the univariate associations between time updated values of each of the individual apolipoproteins (Apo A1, Apo B, Apo C2, Apo C3), as well as their associated lipoproteins (high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides (TG)) and infection-related mortality or hospitalization, cardiovascular mortality or hospitalization, and all-cause mortality in separate models. Up to 5 time updated values of each apolipoprotein/lipoprotein per participant were included in each analysis. Participants were followed from the date of enrollment through September 30, 2013. Censoring criteria included end of study and receipt of a kidney transplant for all outcomes and death from other causes for the two cause-specific mortality outcomes.

We then added a pre-specified set of covariates to each Cox model and calculated adjusted hazard ratios for each apolipoprotein and for each lipoprotein. Covariates included age, sex, race, presence of diabetes and heart failure at baseline, time updated presence of a tunneled catheter for dialysis vascular access and time updated values of Quételet's (body mass) index (BMI), CRP and serum albumin concentrations. The time varying covariates were updated at the time of each laboratory measurement. In each Cox model, we tested for linearity of the continuous variables by adding squared versions of each variable to the model. If the estimate for the squared term was significant, we retained the squared term in the model. In addition, because models with linear and quadratic terms may be difficult to interpret, we examined models in which the lipoprotein predictor was divided into quartiles in order to better examine and describe the shape of the associations.

We did not include use of lipid lowering agents in our primary analyses because we hypothesized that the concentrations of lipids themselves were related to outcomes regardless of how those levels were achieved. However, in sensitivity analysis, we tested whether use of lipid lowering medications was associated with outcomes and whether there was an interaction between lipid lowering medication use and lipid levels in the association with outcomes of interest. In a second sensitivity analysis, we adjusted for percentage of body fat based on BIS rather than BMI among the 364 participants for whom we had body composition data. We used SAS 9.4 (Cary, NC, USA) for all analyses.

Results

Patient characteristics

Median or mean values for each parameter are presented in Table 1. The mean age was 56.6 years, 41.1% were women, 15.9% were white, and 53.6% had diabetes. During follow-up, 63 (15%) participants had a cardiovascular-related event, 179 (41%) had an infection-related event and 87 (20%) died. The median follow-up time for all-cause mortality was 2.7 years (25th, 75th percentile range 2.2 – 3.4 years). Patients prescribed lipid lowering medication had significantly lower LDL cholesterol (64.9 ± 28.7 vs 73.6 ± 28.6 mg/dL, $P<0.001$) and HDL cholesterol levels (46.7 ± 14.9 vs 51.3 ± 17.0 mg/dl, $P = 0.001$), but apo B concentrations did not differ significantly (71.8 ± 32.5 vs 70.6 ± 26.9 mg/dL, $P = 0.54$)

Associations of lipoproteins with infection-related and cardiovascular outcomes

In unadjusted analyses, higher serum concentrations of Apo B and LDL were associated with lower risks of infection-related outcomes, while Apo A1, Apo C2, Apo C3, and both HDL and triglycerides were not (Table 2). After adjustment, Apo B and LDL remained significantly associated with lower risk of infection-related outcomes.

In contrast to infection-related outcomes, none of the lipoproteins or accompanying apolipoproteins was significantly associated with cardiovascular death or hospitalizations (Table 3).

Associations of lipoproteins with all-cause mortality

In univariate models, higher serum concentrations of Apo A1, Apo B, Apo C2, Apo C3, LDL, and triglycerides were associated with lower risks of all-cause mortality (Table 4). The associations of all-cause mortality with Apo A1 and Apo C3 were non-linear. For both of these lipoproteins, the hazard of death was lower among participants with higher lipoprotein concentrations, but the association was relatively flat at higher concentrations, which was evident when we examined quartiles of the predictors (Supplemental Table 3) and which led to statistically significant quadratic terms in our models (Table 4). Higher concentrations of Apo A1, Apo B, and Apo C3 remained significantly associated with lower all-cause mortality after multivariable adjustment with baseline covariates including age, sex, race/ethnicity, diabetes mellitus, and heart failure and time updated covariates including BMI, presence of a tunneled dialysis catheter albumin and log-transformed CRP.

Sensitivity analyses

Use of lipid lowering medication was not associated with infectious or cardiovascular outcomes or with overall mortality. In addition, there was no interaction between the use of lipid lowering medication and the effect of lipoproteins on outcomes. Inclusion of use of lipid lowering agents in the models did not materially change the results (data not shown).

Estimates of fat mass were available for a subset of 364 patients. The relationships between apo B and LDL cholesterol and outcomes remained essentially unchanged when percent fat was used in the analysis in place of BMI (Supplemental Table 4–6).

Discussion

The two leading causes of death and hospitalization in patients on maintenance hemodialysis are related to cardiovascular disease and infection (1,2), and we hypothesized that higher lipoprotein concentrations might provide protection from infection, which might offset potential adverse cardiovascular effects. We found that higher concentrations of some lipoproteins, specifically LDL and its associated apolipoprotein, Apo B, were associated with lower risk of infection-related outcomes. In contrast to data from the general population (5,6), we found no significant association between lipoprotein concentrations and hospitalization or mortality related to cardiovascular events. Generally, higher lipoprotein concentrations were associated with lower all-cause mortality.

Lipoproteins play an important role in the innate immune response, potentially providing protection from infection (14,16,19). High density lipoprotein (HDL) adsorbs endotoxin (lipopolysaccharide (LPS)), binding it to lipoprotein binding protein (LBP) (20). The LPS is then returned it to the liver for degradation (16) or transferred to low density lipoprotein (LDL) (21,22) for detoxification by the liver (23). HDL has a protective effect against polymicrobial sepsis in mice (24), perhaps via these mechanisms. Staphylococcal toxins are also bound and inactivated by a variety of lipoproteins (25). We have previously published the proteomic differences in HDL from patients resistant to infection (none within 800 days) and infection prone (infection within less than 60 days). In that analysis, there was a significant difference in structure of infection favoring proteins (serum amyloid A) and infection resisting proteins (α1 anti trypsin, one glycated fetuin A (26). HDL cholesterol concentrations did not differ between these groups. LDL and chylomicrons bind bacterial toxins, including LPS, lipoteichoic acid (27,28,29), and alpha toxin (30) and downregulate the expression of toll-like receptors 2 and 4 (31). While chylomicrons and very low density (VLDL) remnant particles were not measured directly, they are associated apolipoprotein Apo B, which was, like LDL, protective against infection.

Our finding that high lipoprotein concentrations were not associated with risk of cardiovascular-related hospitalizations and death is consistent with data from randomized clinical trials of lipid-lowering interventions. Specifically, three large clinical trials of lipid-lowering agents in patients on dialysis yielded no demonstrable effects on all-cause or cardiovascular mortality or composite cardiovascular endpoints (8,9,10). The association of higher lipoprotein concentrations with lower all-cause mortality is consistent with prior studies showing that low serum cholesterol concentrations are associated with higher mortality (5,6). Taken together, the lack of association with cardiovascular events, combined with the lower risk of infection-related events among patients with higher lipoprotein concentrations, suggest a potential mechanism for the paradoxical association of higher lipoprotein concentrations with lower all-cause mortality.

This study has several strengths. The sample size was relatively large and the sample was diverse according to age, sex, race/ethnicity and underlying comorbidity, although the white population was limited. We obtained repeated lipoprotein values at times that were predetermined thus avoiding confounding from laboratory measurements by indication and allowing us to conduct analysis using time-varying serum concentrations. By using measurements obtained prior to infection-related events we were able to reduce the likelihood that serious infection (e.g., requiring hospitalization) affected lipid concentrations, since several apolipoproteins and lipoproteins are themselves acute phase proteins and change in response to inflammation (32,33). Laboratory measurements for lipids as well as the apolipoproteins were direct immunologic measurements. In addition to lipoproteins, we adjusted for serum albumin and CRP, which are known to be strongly associated with infection-related and cardiovascular outcomes.

There are also several important limitations. Because our study was observational, there is likely to be residual confounding. There may be underlying processes affecting lipoprotein concentrations rather than the lipoprotein concentrations themselves – such as inflammation – affecting the levels of Apo A1 and HDL, both negative acute phase proteins (32), and

nutritional status that may be ultimately responsible for the findings. Furthermore, structural differences within lipoprotein classes may play a role in their biological activity that cannot be ascertained by measurements that do not include further structural details of other proteins incorporated into HDL (34). We restricted the study sample to patients receiving hemodialysis who were Medicare beneficiaries in order to capture all hospitalization events; as such, these findings may not be generalizable to younger patients on hemodialysis or with alternative types of insurance coverage or no health insurance or patients receiving peritoneal dialysis. Additionally, LDL cholesterol levels were somewhat lower than reported in an incident USRDS population of similar age (35). LDL was also measured directly in this study.

In summary, we evaluated the associations of lipoprotein concentrations with infection-related and cardiovascular outcomes and all-cause mortality among a cohort of patients on hemodialysis from two major metropolitan areas in the United States. Even after adjusting for demographic characteristics, body composition, comorbidities, and markers of inflammation, we found that higher serum concentrations of lipoproteins were associated with lower risks of infection-related events and all-cause mortality. That higher lipoprotein levels were not associated with cardiovascular events and may confer protection from infection, may explain the association with lower all-cause mortality. Recognizing the complex biological roles of lipoproteins within the innate immune system, the observation that higher levels of lipoproteins are associated with lower all-cause mortality and have no significant relationship to cardiovascular outcomes may help to explain why randomized trials of lipid lowering agents failed to show a benefit on mortality or cardiovascular events in patients on dialysis, despite their well-established benefits in other populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

LDL and apo B are inversely associated with infectious events in dialysis patients

Higher Apo A1, Apo B, and Apo C3 are associated with lower all-cause mortality

Lipoproteins are not associated with cardiovascular outcomes

Table 1

Characteristics of the study cohort*

Variable	N=433
Age, years	56.6 ± 13.7
Dialysis Vintage (years)	4.37 ± 3.57
Non White	364 (84.1%)
Female	178 (41.1%)
Lipid Lowering Medication	158 (37%)
CAD history	139 (32.1%)
CHF history	145 (33.5%)
Albumin, g/dL	4.0 ± 0.36
Heart failure, N (%)	145 (33.5%)
Diabetes mellitus, N (%)	232 (53.6%)
Catheter, N (%)	90 (20.8%)
BMI, kg/m^2	28.4 ± 6.91
CRP mg/L Median (Q1–Q3)	4.23 (1.67–10.83)
Apo A1, mg/dL	113 ± 33.9
Apo B, mg/dL	70.9 ± 29.0
Apo C2, mg/dL	3.97 ± 2.65
Apo C3, mg/dL	12.5 ± 5.5
HDL, mg/dL	49.6 ± 16.3
LDL, mg/dL	70.3 ± 28.9
TG, mg/dL	130 ± 81.4

*Abbreviations: BMI, body mass index; CRP, C-reactive protein; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; Apo C2, apolipoprotein C2; Apo C3, apolipoprotein C3; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides.

Mean ± Standard deviation reported for continuous variables unless otherwise noted.

Table 2

Association between lipoproteins and infection-related hospitalization or mortality

	Univariate models		Multivariable models	
Variable	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Apo A1, per 10 mg/dL	0.97 (0.92, 1.01)	0.17	0.97 (0.92, 1.03)	0.33
Apo B, per 10 mg/dL	0.93 (0.87, 0.99)	0.03	0.92 (0.86, 0.99)	0.03
Apo C2, per mg/dL	0.94 (0.88, 1.01)	0.08	0.95 (0.89, 1.03)	0.20
Apo C3, per mg/dL	0.98 (0.95, 1.01)	0.20	0.99 (0.95, 1.02)	0.43
HDL, per 10 mg/dL	1.0 (0.91, 1.11)	0.94	1.0 (0.89, 1.13)	0.95
LDL, per 10 mg/dL	0.93 (0.87, 1.0)	0.039	0.93 (0.87, 1.00)	0.05
Log TG, per mg/dL	0.95 (0.73, 1.20)	0.66	1.05 (0.79, 1.38)	0.75

* Each multivariable model includes the lipoprotein of interest and is adjusted for age, sex, race, body mass index, diabetes, heart failure, dialysis catheter, serum albumin and log CRP.

Apolipoprotein A1 (Apo A 1), apolipoprotein B (Apo B), apolipoprotein C2 (Apo C2), Apolipoprotein C2 (Apo C3), high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TG).

Table 3

Association between lipoproteins and cardiovascular hospitalization or mortality

	Univariate models		Multivariable models	
Variable	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Apo A1, per 10 mg/dL	0.93 (0.84, 1.02)	0.11	0.96 (0.87, 1.06)	0.39
Apo B, per 10 mg/dL	0.90 (0.79, 1.04)	0.15	0.92 (0.80, 1.06)	0.27
Apo C2, per mg/dL	0.94 (0.84, 1.06)	0.31	0.95 (0.85, 1.06)	0.35
Apo C3, per mg/dL	0.98 (0.93, 1.04)	0.59	0.99 (0.93, 1.05)	0.68
HDL, per 10 mg/dL	0.94 (0.80, 1.12)	0.51	0.96 (0.80, 1.16)	0.68
LDL, per 10 mg/dL	0.90 (0.77, 1.05)	0.19	0.93 (0.80, 1.07)	0.31
Log TG, per mg/dL	0.89 (0.44, 1.47)	0.66	0.95 (0.61, 1.48)	0.83

* Each multivariable model includes the lipoprotein of interest and is adjusted for age, sex, race, body mass index, diabetes, heart failure, dialysis catheter, serum albumin and log CRP.

Apolipoprotein A1 (Apo A 1), apolipoprotein B (Apo B), apolipoprotein C2 (Apo C2), Apolipoprotein C2 (Apo C3), high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TG).

Table 4

Association between lipoproteins and all-cause mortality

	Univariate models		Multivariable models	
Variable	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Apo A1, per 10 mg/dL	0.64 (0.47, 0.86)	0.004	0.65 (0.46, 0.90)	0.01
Apo A1 squared, per 10 mg^2/dL^2	1.01 (1.00, 1.03)	0.007	1.01 (1.00, 1.03)	0.02
Apo B, per 10 mg/dL	0.83 (0.74, 0.93)	0.001	0.87 (0.77, 0.98)	0.03
Apo C2, per mg/dL	0.89 (0.81, 0.98)	0.02	0.93 (0.84, 1.03)	0.15
Apo C3, per mg/dL	0.86 (0.79, 0.93)	<0.001	0.91 (0.83, 0.99)	0.03
Apo C3 squared, per 10 mg^2/dL^2	1.03 (1.01, 1.05)	<0.001	1.02 (1.00, 1.04)	0.05
HDL, per 10 mg/dL	1.04 (0.90, 1.19)	0.62	1.02 (0.86, 1.21)	0.83
LDL, per 10 mg/dL	0.84 (0.75, 0.95)	0.004	0.90 (0.80, 1.01)	0.07
Log TG, mg/dL	0.65 (0.45, 0.95)	0.025	0.83 (0.55, 1.26)	0.38

*Each multivariable model includes the lipoprotein of interest and is adjusted for age, sex, race, BMI, DM, heart failure, dialysis catheter, serum albumin and log CRP; a squared term was included for models including Apo A1 or Apo C3 because associations were nonlinear.

Apolipoprotein A1 (Apo A 1), apolipoprotein B (Apo B), apolipoprotein C2 (Apo C2), Apolipoprotein C2 (Apo C3), high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TG).