Title

Increments in serum high-density lipoprotein cholesterol over time are not associated with improved outcomes in incident hemodialysis patients.

Journal

Journal of clinical lipidology, 12(2)

ISSN

1933-2874

Authors

Chang, Tae Ik
Streja, Elani
Soohoo, Melissa
et al.

Publication Date

2018-03-01

DOI

10.1016/j.jacl.2018.01.010

Peer reviewed

Journal of Clinical Lipidology (2018) 12, 488–497

Journal of Clinical Lipidology

Increments in serum high-density lipoprotein cholesterol over time are not associated with improved outcomes in incident hemodialysis patients

Tae Ik Chang, MD, PhD, Elani Streja, MPH, PhD, Melissa Soohoo, MPH, Gang Jee Ko, MD, PhD, Connie M. Rhee, MD, MSc, Csaba P. Kovesdy, MD, Moti L. Kashyap, MD, Nosratola D. Vaziri, MD, Kamyar Kalantar-Zadeh, MD, MPH, PhD, Hamid Moradi, MD*

Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine, School of Medicine, Orange, CA, USA (Drs Chang, Streja, Soohoo, Ko, Rhee, Vaziri, Kalantar-Zadeh, and Moradi); Department of Internal Medicine, National Health Insurance Service Medical Center, Ilsan Hospital, Goyangshi, Gyeonggi–do, Republic of Korea (Dr Chang); Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea (Dr Ko); Division of Nephrology, University of Tennessee Health Science Center, Memphis TN, USA (Dr Kovesdy); Nephrology Section, Memphis Veterans Affairs Medical Center, Memphis TN, USA (Dr Kovesdy); Atherosclerosis Research Center, Gerontology Section, Geriatric, Rehabilitation Medicine and Extended Care Health Care Group, Veterans Affairs Medical Center, Long Beach, CA, USA (Dr Kashyap); and Department of Medicine, University of California, Irvine, Orange, CA, USA (Drs Kashyap, Kalantar-Zadeh, and Moradi)

KEYWORDS:
Lipid;
Dyslipidemia;
High-density lipoprotein;
Mortality;
Hemodialysis

BACKGROUND: Elevated serum high-density lipoprotein cholesterol (HDL-C) has not been associated with better cardiovascular (CV) and all-cause mortality in hemodialysis patients. However, the association between change in HDL over time and mortality has not been fully examined.

OBJECTIVE: In a nationally representative cohort of incident hemodialysis patients who had available HDL data at baseline and 6 months after dialysis initiation, we studied the association of change in HDL-C during the first 6 months of dialysis with all-cause and CV mortality.

METHODS: Associations between HDL-C change and mortality were determined in Cox proportional hazard regression models with adjustment for multiple variables.

RESULTS: In case-mix models, there was a J-shaped association between change in HDL-C and mortality, such that quartiles 1 (<–5 mg/dL) and 4 (≥7 mg/dL) were each associated with higher all-cause (hazard ratio, 1.32 [95% confidence interval, 1.21–1.45] and 1.09 [1.01–1.18]) and CV (1.28 [1.06–1.55] and 1.23 [1.04–1.45]) death risk, respectively. In fully adjusted models that included

Conflicts of interest: Kamyar Kalantar-Zadeh has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, AVEO, Chugai, DaVita, Fresenius, Gene-Tech, Haymarket Media, Hospira, Kabi, Keryx, National Institutes of Health, National Kidney Foundation, Relypsa, Resverlogix, Sanofi, Shire, Vifor, and ZS Pharma.

* Corresponding author. Nephrology Section, Medicine Health Care Group, Veterans Affairs Medical Center, 5901 East 7th Street, Long Beach, CA 90822, USA.
E-mail address: hamid.moradi@va.gov

Submitted July 26, 2017. Accepted for publication January 18, 2018.

1933-2874/Published by Elsevier Inc. on behalf of National Lipid Association.
https://doi.org/10.1016/j.jacl.2018.01.010

indices of malnutrition and inflammation, the higher death risk observed in the lowest quartile was attenuated, whereas the highest quartile continued to demonstrate significantly higher all-cause (1.11 [1.02–1.20]) and CV mortality (1.15 [1.00–1.32]). These associations persisted across various subgroups.

CONCLUSIONS: Although malnutrition and inflammation may explain the increased risk for mortality in patients with decreasing serum HDL-C concentrations over time, these indices do not mitigate the elevated risk in patients with rising serum HDL-C. We found that increasing serum HDL-C over time is paradoxically associated with worse outcomes in incident hemodialysis patients.
Published by Elsevier Inc. on behalf of National Lipid Association.

Introduction

Chronic kidney disease (CKD) is associated with major alterations in lipid and lipoprotein metabolism. In turn, it is believed that the dyslipidemia of CKD can lead to progression of renal injury and development of CKD-associated complications such as cardiovascular (CV) disease. The nature of lipid abnormalities in CKD is influenced by several unique factors including the presence and severity of proteinuria, dietary restrictions, pharmacologic therapy, preexisting genetic disorders of lipid metabolism, and type of renal replacement therapy a patient is receiving.[1] Patients with end-stage renal disease (ESRD) on maintenance hemodialysis (MHD) typically have normal or low levels of serum total cholesterol and low-density lipoprotein cholesterol (LDL-C), whereas serum high-density lipoprotein cholesterol (HDL-C) levels are commonly reduced, and serum triglycerides and very low–density lipoprotein levels are modestly elevated.[2] While hyperlipidemia is not a hallmark of ESRD, the dyslipidemia observed in patients on MHD is typically marked by an accumulation of highly atherogenic and proinflammatory lipoproteins.[3]

In the general population, increased levels of serum HDL-C are generally thought to protect against CV disease via multiple different mechanisms including reverse cholesterol transport, antiinflammatory, antioxidant, and antithrombotic activities.[3] Therefore, it is not surprising that increasing levels of serum HDL-C have been shown to be associated with better CV outcomes in observational studies.[4-7] However, the findings of recent clinical trials and genetic studies have shed light on the complex nature of the HDL particle and the many factors that determine its functional abilities that ultimately impact its associations with outcomes. For instance, several randomized clinical trials that aimed to improve CV outcomes by increasing serum HDL-C concentrations using pharmacologic agents such as niacin and cholesterol ester transfer protein inhibitors failed to show a survival benefit.[8,9] Furthermore, Mendelian randomization analyses have indicated that some genetic mechanisms, which increase serum HDL-C levels, do not prove to be effective in reducing the risk of myocardial infarction.[10] These findings have brought into question the notion that elevated serum HDL-C levels are always protective against CV disease.

In fact, these seemingly paradoxical associations between serum HDL-C level and outcomes have also been observed in patients on MHD, in whom elevated levels of serum HDL-C were found to be associated with worse survival.[11] These unexpected findings might be explained by the fact that there are structural and functional changes in the HDL lipoprotein from patients on dialysis, which can alter its performance and lead to HDL dysfunction.[12–14] For example, ESRD is associated with reduced levels of serum apolipoprotein A1 (ApoA1), HDL-C and HDL phospholipids, and elevated levels of HDL-triglycerides. Furthermore, maturation of cholesterol ester–poor HDL3 to cholesterol ester–rich HDL2 is impaired, and HDL antioxidant, antiinflammatory, and reverse cholesterol transport properties are defective in the patients with ESRD.[15,16] In addition, we have found that HDL from a subset of patients on MHD was in fact proinflammatory, a finding that has been replicated by other investigators as well.[17–20] These laboratory findings help explain why we have found that elevated serum levels of baseline HDL-C can be associated with worse CV and all-cause mortality in patients on MHD.[11] However, it is possible that baseline serum HDL-C levels may not be an adequate indicator of overall HDL levels, and that change in HDL over time may provide a more accurate account of the association of this lipoprotein with outcomes in patients on MHD. Therefore, in this study, we aimed to further address the role of serum HDL levels in ESRD-associated death risk and evaluated the association of change in serum HDL-C concentrations over time with all-cause and CV mortality. We hypothesized that increasing serum HDL levels over time may not be associated with improved survival given the findings of our previous study.[11]

Methods

Study population and data source

The study cohort comprised all patients with ESRD who were initiated on hemodialysis between January 2007 and December 2011 within one of the outpatient facilities of a large dialysis organization and were followed up over a period of 5 years. Patients were included provided that they were 18 years or older, were treated with only in-center

hemodialysis for at least 60 days, and had serum HDL-C measured during the first 91-day period of hemodialysis (baseline quarter). To examine the change in HDL during the first 6 months following dialysis, we additionally excluded those patients with missing measured HDL at 6 months of dialysis initiation. Accordingly, the final study population consisted of 21,074 patients (Fig. 1).

All data were obtained from electronic records of the dialysis organization. To minimize measurement variability, all repeated measures of every relevant variable within each 3-month period starting from the date of first dialysis were averaged to obtain a quarterly mean value. Blood samples were drawn using standardized techniques in all dialysis clinics and were measured using automated and standardized methods in a central laboratory in Deland, Florida. The study was approved by the institutional review board of University of California, Irvine.

Exposure and outcome ascertainment

The exposure of interest was change in HDL-C levels during the first 6 months of dialysis initiation, which was calculated by subtracting values at 6 months (the third patient-quarter) from those at baseline (the first patient-quarter). Given a possible nonlinear relationship with mortality, change in HDL level was treated as a categorical variable and divided into quartiles (<-5, -5 to <1, 1 to <7, and ≥ 7 mg/dL). Quartile 3 (1 to <7 mg/dL) was chosen as the reference because it includes the mean and median values (1.2 and 1.0 mg/dL, respectively) in this study, had the largest sample size, and allowed for the most precise comparison with lower and higher HDL change categories. The primary and secondary outcomes of interest were time to all-cause and CV death, respectively. For mortality analyses, patients remained at risk until death, censoring for loss to follow-up, discontinuation of dialysis therapy, kidney transplantation, transfer to a nonaffiliated dialysis clinic, or end of the study period (December 31, 2011).

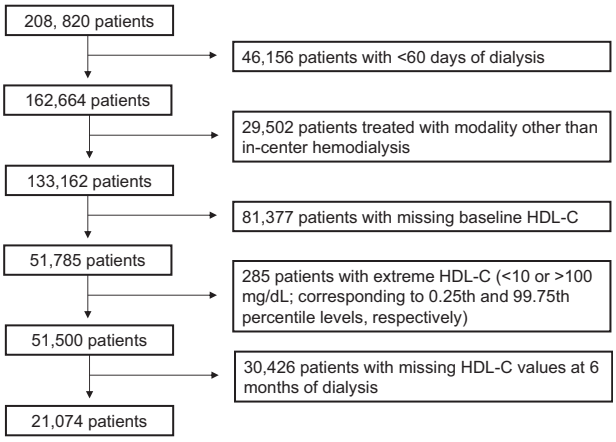

Figure 1 Flow chart of patient selection for the cohort. HDL-C, high-density lipoprotein cholesterol.

Statistical analyses

Data were summarized using proportions, means $\pm$ standard deviation (SD), or median (interquartile range [IQR]) as appropriate and were compared using Student's *t*-test, analysis of variance, Kruskal-Wallis, and chi-square tests, respectively.

Associations between HDL change and mortality were determined in Cox proportional hazard regression models with 3 incremental levels of adjustment based on *a priori* considerations: (1) model 1: unadjusted or minimally adjusted model that included baseline HDL-C values; (2) model 2: case-mix adjusted model that included the aforementioned values plus age, sex, race/ethnicity (white, African American, Hispanic, Asian, or other), primary insurance (Medicare, Medicaid, and others), initial vascular access type (central venous catheter, arteriovenous fistula, arteriovenous graft, or other), comorbid conditions (diabetes mellitus, hypertension, atherosclerotic heart disease, congestive heart failure, other-CV disease, cerebrovascular disease, dyslipidemia, human immunodeficiency virus, chronic obstructive pulmonary disease, and malignancy), alcohol dependence, substance abuse, and dialysis dose as indicated by single-pool Kt/V; (3) model 3: fully adjusted model that included all covariates in the case-mix model plus malnutrition-inflammation-cachexia syndrome variables including serum hemoglobin, white blood cell count, albumin, calcium, phosphorus, intact parathyroid hormone, bicarbonate, total iron binding capacity, ferritin, and LDL-C; (4) model 4: additional adjustment for body mass index (BMI, body weight in kilograms divided by height in meters squared) and statin therapy in addition to the fully adjusted models. In an attempt to mitigate the impact of the regression to the mean phenomena, all multivariate models that examined the "change" as a mortality predictor were also controlled for other laboratory values at sixth month and at baseline because those variables at sixth month could influence and/or may have been influenced by the change in HDL-C during the same period. As CV and non-CV death are competing events, association of HDL change with the 2 outcomes was assessed by means of semiparametric competing risk regression in sensitivity analysis.[21] We additionally explored the continuous, potentially nonlinear relationship between change in HDL over time and mortality by using restricted cubic spline models with 4 knots. All mortality associations were expressed as a hazard ratio (HR) and 95% confidence interval (CI). To test the robustness of our findings, we also performed subgroup analyses based on *a priori* defined variables such as age, gender, race/ethnicity, comorbidities, and laboratory parameters. Subgroups of the continuous variables were created by clinically relevant categories (baseline HDL-C level) or by dichotomization of other variables at the median value.

The frequency of missing data was low ($\leq$0.5%, ascertained at baseline) for most covariates in multivariate adjusted models, except for statin therapy (5.1%). Patients

who were missing statin use data were excluded from analyses without imputation. All analyses were implemented using Stata, version 13.1 (Stata Corporation, College Station, TX).

Results

Study population

The overall cohort consisted of 21,074 patients who met eligibility criteria (Fig. 1), among whom HDL-C tended to increase during the first 6 months of hemodialysis initiation. The mean ± SD and median (IQR) of observed change in HDL levels were 1.3 ± 10.7 and 1.0 (−4.5, 7.0) mg/dL, respectively. The baseline characteristics of the overall and the subset of patients according to quartiles of change in serum HDL levels are summarized in Table 1. Patients with the higher increments in HDL tended to be older, were less likely to be diabetic, and more likely to have cerebrovascular disease. They also had lower total cholesterol, LDL-C, and intact parathyroid hormone values, but higher ferritin levels. Compared to patients in quartiles 2 and 3 of HDL change, those in the lowest (<−5 mg/dL) and the highest (>7 mg/dL) quartiles were less likely to have arteriovenous fistula as their vascular access, had lower statin use, and had lower serum albumin levels.

During a total time at risk of 32,654 patient-years (PYs), 4810 all-cause deaths occurred (mortality rate, 99.5 per 1000 PYs; 95% CI, 96.7–102.3). Median (IQR) follow-up time was 1.3 years (0.6−2.3 years). Of these, 4304 (89.5%) individuals had data available on primary cause of death, among whom 1710 (39.7%) were attributed to CV mortality (mortality rate, 53.4 per 1000 PYs; 95% CI, 51.0−56.0). Although there were some patients whose cause of death was unknown, when compared to patients who had available information about cause of death, their demographic, comorbidity, and laboratory characteristics were mostly similar (Supplementary Table S1).

All-cause and CV mortality

Table 2 and Figure 2 show the HRs and corresponding 95% CIs for all-cause and CV mortality according to categories of change in HDL over time using Cox proportional regression models. In case-mix models (model 2), there was a J-shaped association between change in HDL and mortality, such that quartiles 1 (<−5 mg/dL) and 4 (≥7 mg/dL) were each associated with higher all-cause (HR, 1.32 [95% CI, 1.21–1.45] and 1.09 [1.01–1.18]) and CV (1.28 [1.06−1.55] and 1.23 [1.04−1.45]) death risk, respectively (reference: 1−7 mg/dL of change in HDL during the first 6 months). However, in fully adjusted models with case-mix and malnutrition-inflammation-cachexia syndrome surrogates (model 3), the higher death risk observed in the lowest quartile was much attenuated, whereas the highest quartile continued to demonstrate significantly higher all-cause (1.11 [1.02−1.20]) and CV mortality (1.15 [1.00−1.32]). Even when BMI and statin therapy were additionally incorporated into the fully adjusted models (model 4), the latter association remained largely unchanged although the difference was no longer statistically significant given the reduced sample size. Moreover, in sensitivity analyses considering non-CV death as a competing event, similar findings were observed (Supplementary Fig. S1), indicating that our findings were not biased by competing risks.

In analyses examining continuous HDL change as a restricted cubic spline adjusted for case-mix variables, we again observed a similar pattern of association between HDL change over time and all-cause and CV mortality in that both decreasing and increasing HDL levels over time were associated with progressively higher mortality risk. On the other hand, in fully adjusted models (including BMI), upward increments of HDL-C were associated with higher death risk, but not decrements over time (Fig. 3). Further subgroup analyses confirmed these associations between incrementally increasing HDL levels (≥7 mg/dL vs −5 to <7 mg/dL of HDL change) and greater all-cause and CV mortality risk across most prespecified subgroups (Fig. 4). It should be noted that in our subgroup analyses, the association of increased HDL-C levels (≥7 mg/dL) with CV mortality did not reach statistical significance. However, there was a strong trend in that direction, and this itself is paradoxical to what is expected based on the observations in the general population.

Discussion

In a large contemporary cohort of 21,074 patients treated with thrice-weekly hemodialysis and followed up for 5 years, we found that increasing concentrations of serum HDL-C over time were paradoxically associated with worse survival. This is contrary to the associations observed in the general population in which higher increments in HDL are associated with improved survival and reduced CV mortality.[4] In this regard, we have previously demonstrated that compared with the HDL from the healthy controls, the HDL from MHD patients exhibits markedly reduced antioxidant activity.[12,13] Furthermore, HDL from patients on MHD not only has reduced antiinflammatory activity but also in a subset of patients may actually be proinflammatory in nature.[17,18] Other investigators have also found that HDL composition and function is significantly altered in patients with CKD and ESRD such that the HDL molecule could become paradoxically proinflammatory.[19,22–24] In fact, a study in a cohort of Japanese MHD patients found that higher HDL-C concentrations were associated with higher levels of oxidized HDL, which were also associated with increased CV mortality.[17] Likewise, we have found that elevated serum HDL-C (>50 mg/dL) levels in prevalent MHD patients were associated with higher all-cause

Table 1 Baseline characteristics of 21,074 patients according to quartiles of change in the serum HDL-C level

		Quartiles of changes in HDL-C concentrations			
	Overall	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Characteristics	(n = 21,074)	(n = 4667)	(n = 5353)	(n = 5592)	(n = 5462)
Age, y	62.5 ± 14.6	60.6 ± 15.2	61.9 ± 14.5	63.5 ± 14.1	63.8 ± 14.4
Gender, % women	43.9	47.5	40.3	40.3	47.8
Race, %					
White	45.2	38.1	45.2	50.0	46.3
Black	31.8	36.8	30.3	28.3	32.8
Hispanic	16.3	17.6	17.9	15.6	14.2
Asian	3.0	3.8	2.7	2.7	3.0
Others	3.7	4.2	3.8	3.4	3.6
Primary insurance, %					
Medicare	53.7	52.9	52.9	53.8	55.2
Medicaid	5.9	7.5	5.9	5.2	5.2
Others	40.3	39.6	41.2	41.0	39.6
Initial vascular access type, %					
Central venous catheter	73.4	70.0	69.4	74.0	71.6
Arteriovenous fistula	17.3	15.3	19.4	19.2	14.8
Arteriovenous graft	4.5	4.4	4.1	4.8	4.9
Others and unknown	4.8	10.3	7.1	2.0	8.7
Comorbidities, %					
Diabetes	69.3	72.0	70.2	68.9	66.4
Hypertension	52.7	52.7	52.0	52.0	54.2
Congestive heart failure	41.5	43.8	41.5	40.4	40.9
Atherosclerotic heart disease	20.5	20.4	20.7	20.2	20.7
Other cardiovascular disease	18.2	18.7	17.7	17.9	18.5
Cerebrovascular disease	1.7	1.4	1.7	1.8	1.9
Dyslipidemia	40.6	41.0	41.2	40.3	39.9
HIV	0.4	0.5	0.4	0.3	0.5
COPD	5.1	5.7	5.2	4.8	5.0
History of malignancy	2.0	1.8	1.7	2.4	2.2
Alcohol dependence, %	0.2	0.2	0.2	0.1	0.4
Substance abuse, %	0.3	0.2	0.2	0.2	0.4
Statin use, %	45.4	42.4	48.1	48.2	42.4
Dialysis dose: single-pool Kt/V	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.3
Body mass index, kg/m^2	28.5 ± 7.5	28.0 ± 7.6	29.4 ± 7.7	29.2 ± 7.4	27.5 ± 7.0
Lipid parameters					
Total cholesterol, mg/dL	152.0 ± 43.9	165.9 ± 46.3	152.1 ± 41.4	146.5 ± 40.5	145.7 ± 44.9
LDL-C, mg/dL	79.6 ± 34.9	86.8 ± 37.2	79.8 ± 33.9	76.5 ± 32.6	76.4 ± 35.1
Triglyceride, mg/dL	160.5 ± 91.2	142.6 ± 78.8	168.2 ± 94.9	169.6 ± 96.8	158.7 ± 89.2
HDL-C at baseline, mg/dL	40.6 ± 13.3	50.6 ± 14.4	39.1 ± 11.2	36.6 ± 11.0	37.5 ± 12.2
HDL-C at 6 mo, mg/dL	41.8 ± 13.7	38.2 ± 12.1	37.0 ± 11.1	40.1 ± 11.1	51.4 ± 14.9
Changes in HDL-C over 6 mo	1.3 ± 10.7	−12.4 ± 7.5	−2.1 ± 1.7	3.5 ± 1.7	13.9 ± 7.6
Other laboratory parameters					
Hemoglobin, g/dL	11.2 ± 1.1	11.3 ± 1.1	11.3 ± 1.1	11.2 ± 1.1	11.1 ± 1.2
White blood cells, × 10^3/μL	7.7 ± 2.5	7.8 ± 2.5	7.8 ± 2.8	7.7 ± 2.3	7.6 ± 2.5
Albumin, g/dL	3.5 ± 0.5	3.5 ± 0.5	3.6 ± 0.4	3.6 ± 0.4	3.5 ± 0.5
Calcium, mg/dL	9.1 ± 0.6	9.1 ± 0.6	9.1 ± 0.6	9.1 ± 0.5	9.1 ± 0.6
Phosphorus, mg/dL	5.0 ± 1.1	5.1 ± 1.2	5.0 ± 1.1	4.9 ± 1.1	4.9 ± 1.1
Intact PTH, pg/mL	323 (207–487)	338 (216–510)	331 (214–500)	319 (208–472)	308 (193–466)
Bicarbonate, mEq/L	23.6 ± 2.7	23.6 ± 2.7	23.5 ± 2.6	23.5 ± 2.6	23.7 ± 2.7
TIBC, mg/dL	228.1 ± 47.0	228.2 ± 46.2	231.2 ± 45.9	231.0 ± 46.4	221.9 ± 48.9
Ferritin, ng/mL	271 (160–456)	265 (154–452)	259 (157–436)	269 (159–448)	292 (169–498)

COPD, chronic obstructive pulmonary disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PTH, parathyroid hormone; TIBC, total iron binding capacity.

Data are presented as means ± standard deviations, medians (interquartile ranges), or percentages.

Table 2 Associations of change in high-density lipoprotein cholesterol with all-cause and cardiovascular mortality

	Model 1		Model 2		Model 3		Model 4	
Quartiles of HDL-C changes	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
All-cause mortality								
Quartile 1	1.19 (1.09–1.30)	<.001	1.32 (1.21–1.45)	<.001	1.05 (0.96–1.15)	.316	1.06 (0.96–1.17)	.264
Quartile 2	0.95 (0.87–1.03)	.182	1.02 (0.94–1.10)	.683	0.96 (0.88–1.05)	.369	0.97 (0.89–1.06)	.505
Quartile 3	1.00		1.00		1.00		1.00	
Quartile 4	1.08 (1.00–1.17)	.041	1.09 (1.01–1.18)	.030	1.11 (1.02–1.20)	.016	1.04 (0.96–1.14)	.352
Cardiovascular mortality								
Quartile 1	1.22 (1.05–1.41)	.010	1.30 (1.12–1.52)	.001	1.05 (0.90–1.23)	.532	1.05 (0.89–1.24)	.575
Quartile 2	1.08 (0.94–1.23)	.261	1.15 (1.00–1.31)	.049	1.11 (0.97–1.28)	.137	1.13 (0.98–1.31)	.093
Quartile 3	1.00		1.00		1.00		1.00	
Quartile 4	1.14 (0.99–1.30)	.060	1.16 (1.02–1.33)	.028	1.15 (1.00–1.32)	.048	1.12 (0.96–1.29)	.144

CI, confidence interval; HR, hazard ratio.

Adjustments in model 1: unadjusted; model 2: age, sex, race/ethnicity, primary insurance, vascular access type, comorbid conditions, alcohol dependence, substance abuse, and single-pool Kt/V; model 3: model 2 plus laboratory parameters including serum hemoglobin, white blood cell count, albumin, calcium, phosphorus, intact parathyroid hormone, bicarbonate, total iron binding capacity, ferritin, and low-density lipoprotein cholesterol; and model 4: model 3 plus body mass index and statin therapy.

and CV mortality.[11] Furthermore, Bowe et al.[25] recently reported similar findings in patients with CKD noting a U-shaped association between serum HDL-C levels and mortality across a wide range of estimated glomerular filtration rates. However, these studies were limited by failure to account for changes in HDL levels over time. To the best of our knowledge, this is the first published study to demonstrate the paradoxical association between upward increments in HDL-C over time and higher mortality in the dialysis population. These findings further support the growing body of evidence, which indicate that in some patients with ESRD, HDL may become dysfunctional thereby adding to the CV disease burden.[13–20,23–25]

It is important to note that the association of worse outcomes with decreasing serum HDL levels could be mitigated by controlling for markers of inflammation and malnutrition. However, it is also intriguing to note that controlling for the latter indices did not significantly alter the association of increasing serum HDL levels over time with worse outcomes. Hence, these findings suggest that although inflammation and malnutrition are major contributors to HDL dysfunction in ESRD, they are not the only factors involved in abnormal HDL metabolism, which lead to the paradoxical associations observed in this population. Other alternative mechanisms that can also play a vital role in HDL function need to be considered. In this regard, it should be noted that serum HDL-C level is determined by the rate of HDL-mediated cholesterol uptake from peripheral tissues and disposal of its cholesterol cargo in the liver for conversion to bile acids and secretion in the intestinal tract (ie, reverse cholesterol transport).[1,14,15] HDL-mediated cholesterol uptake from peripheral tissues is markedly impaired by CKD.[23,24] The following factors can contribute to the defective HDL-mediated cholesterol uptake in CKD: (1) reduced production and heightened catabolism of ApoA1, the principle apoprotein constituents of HDL[15]; (2) downregulation of lecithin–cholesterol acyltransferase that is essential for esterification and loading of cholesterol in the core of HDL[26]; (3) upregulation of acyl-CoA cholesterol acyltransferase-1 that, by promoting intracellular esterification of cholesterol, limits the efficacy of HDL-mediated activation of cholesterol ester hydrolase to release free cholesterol for uptake by HDL[27]; and (4) modification of ApoA1 by reactive oxygen species (oxidation), elevated urea level (carbamylation), and systemic inflammation (myeloperoxidase modification), events that limit binding of HDL to the machinery mediating cholesterol efflux, ATP binding casset-A1 and casset-G1 in the peripheral tissues.[28,29] In addition, the aforementioned modifications of HDL protein constituents may also limit the binding of HDL to its hepatic docking receptor (SR-B1) and impair its ability to unload its cholesterol cargo in the liver, thereby leading to impaired cholesterol influx.[28,30] Likewise, systemic inflammation leads to formation of myeloperoxidase-modified albumin, which, via binding to SR-B1, further prevents HDL unloading in the liver.[31] Compromised HDL-mediated removal of surplus cholesterol from peripheral tissues and defective disposal of HDL-C cargo in the liver are equally important in limiting reverse cholesterol transport and promoting CV disease. However, they have opposite impacts on serum HDL-C level, that is, impaired cholesterol uptake from peripheral tissues lowers serum HDL levels, whereas impaired HDL-C disposal in the liver raises serum HDL-C concentrations. Therefore, although the increasing serum HDL-C levels over time may give the impression of improving reverse cholesterol transport and HDL function, these findings, in fact, may be indicating a worsening of these indices. This phenomenon can, in part, account for the worse outcomes observed in our study of ESRD patients with increasing serum HDL-C level over time. The latter mechanisms (HDL-C influx/unloading capacity) will need

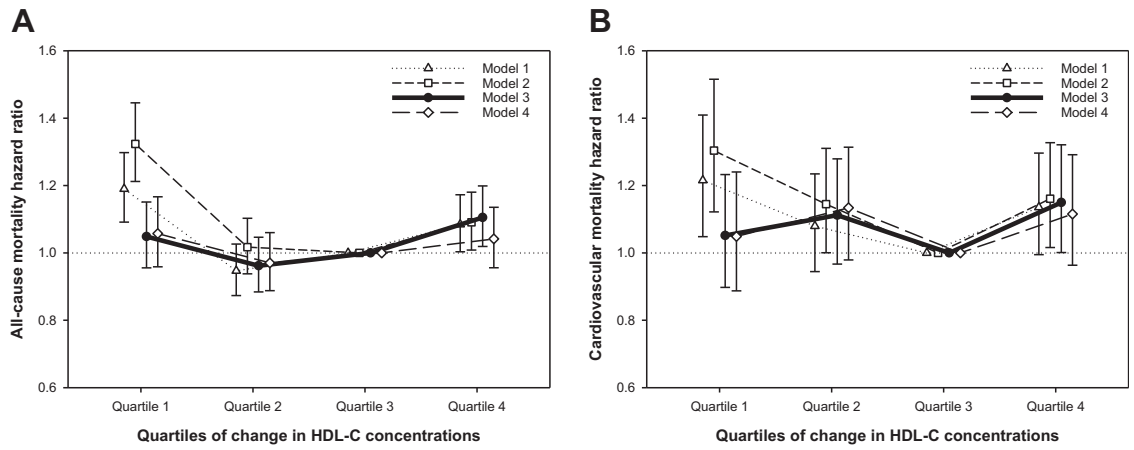

Figure 2 Association of change in high-density lipoprotein cholesterol (HDL-C) levels during the first 6 months of dialysis with all-cause (A) and cardiovascular (B) mortality (hazard ratios and 95% confidence interval error bars). Adjustments in model 1: unadjusted; model 2: age, sex, race/ethnicity, primary insurance, vascular access type, comorbid conditions, alcohol dependence, substance abuse, and single-pool Kt/V; model 3: model 2 plus laboratory parameters including serum hemoglobin, white blood cell count, albumin, calcium, phosphorus, intact parathyroid hormone, bicarbonate, total iron binding capacity, ferritin, and low-density lipoprotein cholesterol; and model 4: model 3 plus body mass index and statin therapy.

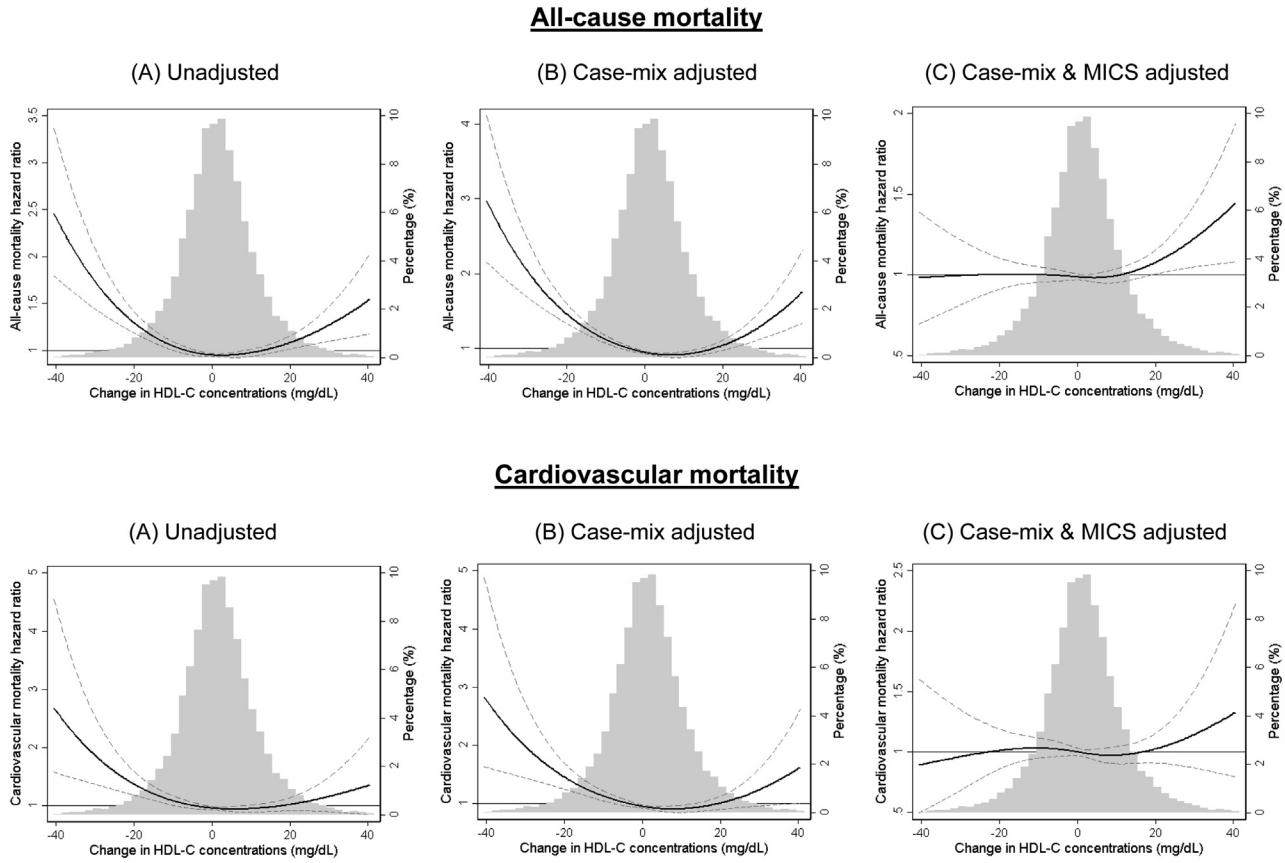

Figure 3 Cubic spline models of the Cox proportional regression analyses reflecting 3 incrementally adjusted all-cause and cardiovascular mortality predictability (with 95% confidence intervals) according to increments in serum high-density lipoprotein cholesterol (HDL-C) levels over time. Adjustments in (A) model 1: unadjusted; (B) case-mix model: age, sex, race/ethnicity, primary insurance, vascular access type, comorbid conditions, alcohol dependence, substance abuse, and single-pool Kt/V; (C) case-mix plus malnutrition-inflammation-cachexia syndrome (MICS) model: case-mix adjusted model plus laboratory parameters including serum hemoglobin, white blood cell count, albumin, calcium, phosphorus, intact parathyroid hormone, bicarbonate, total iron binding capacity, ferritin, low-density lipoprotein cholesterol, and body mass index.

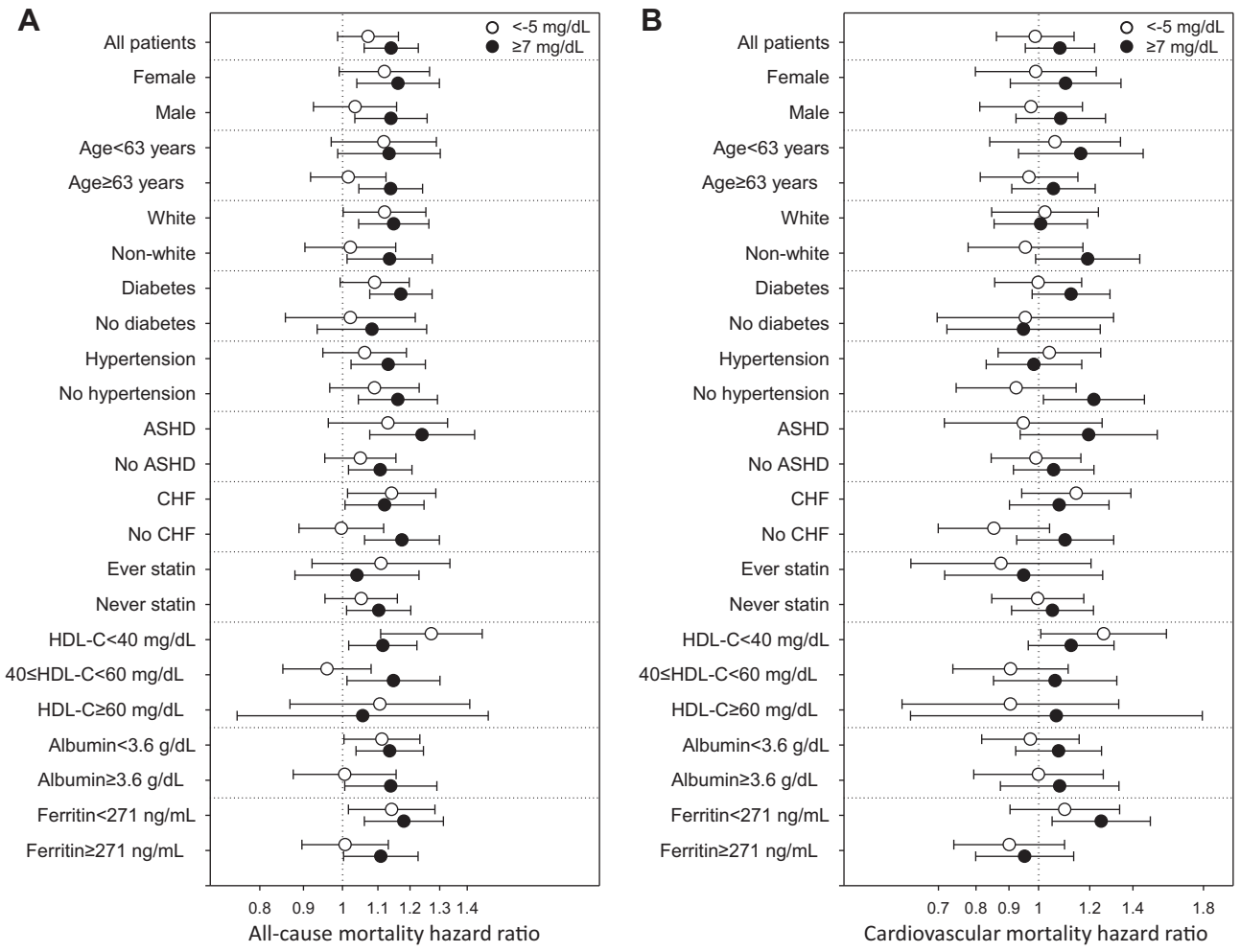

Figure 4 Multivariate adjusted hazard ratios of all-cause (A) and cardiovascular (B) mortality for the lowest (<−5 mg/dL) and the highest (≥7 mg/dL) quartiles vs the reference group with interquartile range (−5 to <7 mg/dL) of change in serum HDL concentrations over time, overall and in selected subgroups. Models were adjusted for age, sex, race/ethnicity, primary insurance, vascular access type, comorbid conditions, alcohol dependence, substance abuse, single-pool Kt/V, serum hemoglobin, white blood cell count, albumin, calcium, phosphorus, iPTH, bicarbonate, total iron binding capacity, ferritin, and low-density lipoprotein cholesterol. ASHD, atherosclerotic heart disease; CHF, congestive heart failure; HDL-C, high-density lipoprotein cholesterol; iPTH, intact parathyroid hormone.

to be examined in future investigations, especially given the fact that increasing HDL-C efflux activity has not been associated with improved outcomes in hemodialysis and renal transplant patients.[32–34]

The strengths of our study include its examination of a large, nationally representative cohort of incident hemodialysis patients, a relatively long follow-up period of up to 5 years, serial HDL measurements in one single laboratory with optimal quality-assurance monitoring that enabled to account for the change in HDL over time, various subgroup analyses, and granular data on comorbidities and laboratory variables. However, several limitations of our study should be mentioned. First, the present findings should be qualified given the observational nature of our study design, which precludes conclusions about causality. In addition, we cannot completely rule out the possibility of the regression to the mean phenomena playing a role in our findings, although we have excluded subjects with extreme values of HDL-C and have adjusted our analyses for baseline and HDL-C levels at sixth month. Moreover, it should be mentioned that we did not have data available on the cause of death in all of our patients, as 10% of patients did not have data available on CV mortality. However, we did compare all baseline characteristics between the subjects with and without data on cause of death and found no meaningful differences between the 2 groups (Supplementary Table 1). Finally, given that we did not have complete data on traditional and nontraditional CV disease risk factors including oxidative status, inflammatory markers, or relevant life style factors such as weight changes or smoking status, our findings may have been limited by residual confounding. Nonetheless, we did try to address this shortcoming at least in part by vigorous adjustment for measured covariates such as demographic, clinical, and laboratory parameters.

In conclusion, increasing serum HDL-C over time was paradoxically associated with worse survival and higher CV mortality in incident hemodialysis patients. Although malnutrition and some markers of inflammation may explain the increased risk of mortality in patients with decreasing serum HDL concentrations, these indices do not mitigate the elevated risk in patients with increasing serum HDL-C. Future studies will need focus on evaluating the role of HDL properties and function on mortality rather than mere levels.

Acknowledgments

The authors thank DaVita Clinical Research (DCR) for providing the clinical data for this research.

Funding source: Kamyar Kalantar-Zadeh is supported by NIH (NIDDK) grants K24-DK091419, R01-DK078106, and philanthropic grants from Mr. Harold Simmons, Mr. Louis Chang, Joseph Lee, and AVEO, Inc. Csaba P. Kovesdy is supported by NIH (NIDDK) grants R01-DK096920 and U01-DK102163, and Connie M. Rhee is supported by NIH (NIDDK) grants K23-DK102903. Hamid Moradi is supported by a career development award from the Office of Research and Development of the Department of Veterans Affairs (1 IK CX 001043-01A2). Elani Streja is supported by a career development award from the Office of Research and Development of the Department of Veterans Affairs (IK2-CX001266-01).

Authors' contribution: Tae Ik Chang, Elani Streja, Kamyar Kalantar-Zadeh, and Hamid Moradi contributed to the study concept and design. Kamyar Kalantar-Zadeh acquired the data. Tae Ik Chang, Hamid Moradi, and Elani Streja conducted statistical analyses and interpretation with advice from Melissa Soohoo, Connie M. Rhee, Csaba P. Kovesdy, Moti L. Kashyap, Nosratola D. Vaziri, and Kamyar Kalantar-Zadeh. Tae Ik Chang and Hamid Moradi drafted the manuscript. Elani Streja, Gang Jee Ko, Melissa Soohoo, Connie M. Rhee, Csaba P. Kovesdy, Moti L. Kashyap, Nosratola D. Vaziri, and Kamyar Kalantar-Zadeh critically revised it for important intellectual content.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jacl.2018.01.010.

References

1. Vaziri ND, Moradi H. Mechanisms of dyslipidemia of chronic renal failure. *Hemodial Int*. 2006;10:1–7.
2. Keane WF, Tomassini JE, Neff DR. Lipid abnormalities in patients with chronic kidney disease. *Contrib Nephrol*. 2011;171:135–142.
3. Vaziri ND. Role of dyslipidemia in impairment of energy metabolism, oxidative stress, inflammation and cardiovascular disease in chronic kidney disease. *Clin Exp Nephrol*. 2014;18:265–268.
4. Olsson AG, Schwartz GG, Szarek M, et al. High-density lipoprotein, but not low-density lipoprotein cholesterol levels influence short-term prognosis after acute coronary syndrome: results from the MIRACL trial. *Eur Heart J*. 2005;26:890–896.
5. Bloomfield Rubins H, Davenport J, Babikian V, et al. Reduction in stroke with gemfibrozil in men with coronary heart disease and low HDL cholesterol: The Veterans Affairs HDL Intervention Trial (VA-HIT). *Circulation*. 2001;103:2828–2833.
6. Assmann G, Schulte H, von Eckardstein A, Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis*. 1996;124 Suppl:S11–20.
7. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302:1993–2000.
8. AIM-HIGH Investigators, Boden WE, Probstfield JL, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365:2255–2267.
9. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357:2109–2122.
10. Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomisation study. *Lancet*. 2012;380:572–580.
11. Moradi H, Streja E, Kashyap ML, et al. Elevated high-density lipoprotein cholesterol and cardiovascular mortality in maintenance hemodialysis patients. *Nephrol Dial Transplant*. 2014;29:1554–1562.
12. Moradi H, Pahl MV, Elahimehr R, et al. Impaired antioxidant activity of high-density lipoprotein in chronic kidney disease. *Transl Res*. 2009;153:77–85.
13. Moradi H, Ganji S, Kamanna V, et al. Increased monocyte adhesion promoting capacity of plasma in end-stage renal disease - response to antioxidant therapy. *Clin Nephrol*. 2010;74:273–281.
14. Moradi H, Vaziri ND, Kashyap ML, et al. Role of HDL dysfunction in endstage renal disease: a double-edged sword. *J Ren Nutr*. 2013;23:203–206.
15. Vaziri ND, Navab M, Fogelman AM. HDL metabolism and activity in chronic kidney disease. *Nat Rev Nephrol*. 2010;6:287–296.
16. Holzer M, Birner-Gruenberger R, Stojakovic T, et al. Uremia alters HDL composition and function. *J Am Soc Nephrol*. 2011;22:1631–1641.
17. Honda H, Ueda M, Kojima S, et al. Oxidized high-density lipoprotein as a risk factor for cardiovascular events in prevalent hemodialysis patients. *Atherosclerosis*. 2012;220:493–501.
18. Vaziri ND, Moradi H, Pahl MV, et al. In vitro stimulation of HDL anti-inflammatory activity and inhibition of LDL pro-inflammatory activity in the plasma of patients with end-stage renal disease by an apoA-1 mimetic peptide. *Kidney Int*. 2009;76:437–444.
19. Yamamoto S, Yancey PG, Ikizler TA, et al. Dysfunctional high-density lipoprotein in patients on chronic hemodialysis. *J Am Coll Cardiol*. 2012;60:2372–2379.
20. Weichhart T, Kopecky C, Kubicek M, et al. Serum amyloid A in uremic HDL promotes inflammation. *J Am Soc Nephrol*. 2012;23:934–947.
21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of competing risk. *J Am Stat Assoc*. 1999;94:496–509.
22. Yamamoto S, Kon V. Chronic kidney disease induced dysfunction of high density lipoprotein. *Clin Exp Nephrol*. 2014;18:251–254.
23. Holzer M, Schilcher G, Curcic S, et al. Dialysis modalities and HDL composition and function. *J Am Soc Nephrol*. 2015;26:2267–2276.
24. Kopecky C, Haidinger M, Birner-Grünberger R, et al. Restoration of renal function does not correct impairment of uremic HDL properties. *J Am Soc Nephrol*. 2015;26:565–575.

25. Bowe B, Xie Y, Xian H, et al. High density lipoprotein cholesterol and the risk of all-cause mortality among U.S. Veterans. *Clin J Am Soc Nephrol*. 2016;11:1784–1793.
26. Vaziri ND, Liang K, Parks JS. Down-regulation of hepatic lecithin: cholesterol acyltransferase gene expression in chronic renal failure. *Kidney Int*. 2001;59:2192–2196.
27. Liang K, Vaziri ND. Upregulation of acyl-CoA: cholesterol acyltransferase in chronic renal failure. *Am J Physiol Endocrinol Metab*. 2002; 283:E676–E681.
28. Holzer M, Gauster M, Pfeifer T, et al. Protein carbamylation renders high-density lipoprotein dysfunctional. *Antioxid Redox Signal*. 2011; 14:2337–2346.
29. Hewing B, Parathath S, Barrett T, et al. Effects of native and myeloperoxidase-modified apolipoprotein a-I on reverse cholesterol transport and atherosclerosis in mice. *Arterioscler Thromb Vasc Biol*. 2014;34:779–789.
30. Marsche G, Hammer A, Oskolkova O, et al. Hypochlorite-modified high density lipoprotein, a high affinity ligand to scavenger receptor class B, type I, impairs high density lipoprotein-dependent selective lipid uptake and reverse cholesterol transport. *J Biol Chem*. 2002;277:32172–32179.
31. Binder V, Ljubojevic S, Haybaeck J, et al. The myeloperoxidase product hypochlorous acid generates irreversible high-density lipoprotein receptor inhibitors. *Arterioscler Thromb Vasc Biol*. 2013;33:1020–1027.
32. Annema W, Dikkers A, de Boer JF, et al. HDL cholesterol efflux predicts graft failure in renal transplant recipients. *J Am Soc Nephrol*. 2016;27:595–603.
33. Bauer L, Kern S, Rogacev KS, et al. HDL cholesterol efflux capacity and cardiovascular events in patients with chronic kidney disease. *J Am Coll Cardiol*. 2017;69:246–247.
34. Kopecky C, Ebtehaj S, Genser B, et al. HDL cholesterol efflux does not predict cardiovascular risk in hemodialysis patients. *J Am Soc Nephrol*. 2017;28:769–775.