Hyperlipidemia and Long-Term Outcomes in Nondiabetic Chronic Kidney Disease

Varun Chawla,* Tom Greene,† Gerald J. Beck,‡ John W. Kusek,§ Allan J. Collins,‖ Mark J. Sarnak,¶ and Vandana Menon¶

*Department of Medicine, Mount Auburn Hospital, Cambridge, Massachusetts; †Division of Clinical Epidemiology, University of Utah, Salt Lake City, Utah; ‡Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, Ohio; §National Institutes of Health, Bethesda, Maryland; ‖Division of Nephrology, Hennepin County Medical Center, Minneapolis, Minnesota; and ¶Division of Nephrology, Tufts Medical Center, Boston, Massachusetts

Background and objectives: Dyslipidemia confers a paradoxical survival advantage in patients with kidney failure. Data are limited in the earlier stages of chronic kidney disease (CKD).

Design, setting, participants, and measurements: This was a cohort study in 840 subjects with stage 3 to 4 CKD enrolled in the Modification of Diet in Renal Disease study. Cox models were used to examine the relationship of total cholesterol (TC), non-HDL-cholesterol (NHDL-C), triglycerides (TG), and HDL-cholesterol (HDL-C) with all-cause and cardiovascular disease (CVD) mortality and progression to kidney failure.

Results: During a mean follow-up of 10 years, there were 208 deaths, 128 deaths from CVD, and 554 subjects reached kidney failure. There was no association between tertiles of any of the lipid variables and mortality; the lowest HDL-C tertile (1.44, 1.18 to 1.78) had increased risk of kidney failure but covariate adjustment abolished this association. In analyses with lipids as continuous variables, there was a significant association with all-cause mortality for TC (hazard ratio [HR] per 10-mg/dl increase, 95% confidence intervals [CI] = 1.03, 1.0 to 1.06) that disappeared with covariate adjustment; there was no association of TG, HDL-C, and NHDL-C as continuous variables with all-cause or CVD mortality. There was a significant inverse association between HDL-C and kidney failure (HR = 0.93, CI = 0.87 to 0.99) in an unadjusted Cox model that was attenuated after adjustment for covariates (HR = 0.98 CI = 0.91 to 1.06).

Conclusions: In this cohort, with predominantly nondiabetic CKD patients, hyperlipidemia is not an independent predictor of long-term outcomes.

Clin J Am Soc Nephrol 5: 1582–1587, 2010. doi: 10.2215/CJN.01450210

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in chronic kidney disease (CKD) (1–3). Patients with CKD are considered in the highest risk group for development of CVD and, from a risk stratification perspective, equivalent to patients with diabetes or existing coronary heart disease (4,5). Hyperlipidemia, a well established risk factor for CVD in the general population (6–8), is highly prevalent in CKD and is estimated to be over 40% in patients with kidney failure (9–11).

Several studies in patients with kidney failure suggest that higher cholesterol levels are protective for CVD (12–15). These findings represent a paradoxical association of lipid levels with mortality compared to the general population and have been attributed to the inflammation and malnutrition that are common in this patient population (16,17). Data regarding the relationship between hyperlipidemia and outcomes in the earlier stages of CKD before reaching kidney failure are limited and contradictory. Whereas one study found an inverse association between cholesterol levels and risk of all-cause and CVD mortality (16), another found no association between lipid parameters and CVD mortality (18).

Given the high prevalence of hyperlipidemia in CKD, targeting improvement in lipid levels is of particular interest in this high-risk population, especially patients in the earlier stages of CKD who may be most likely to benefit from preventive interventions. We examined the association between lipid levels and mortality in a cohort of patients with predominantly nondiabetic CKD stages 3 to 4.

Materials and Methods

Study Population

The Modification of Diet in Renal Disease (MDRD) study, conducted from 1989 to 1993, was a randomized, controlled trial to study the effects of dietary protein restriction and strict blood pressure (BP) control on the progression of kidney disease (19–21). Enrollment criteria for the study were age 18 to 70 years, mean arterial pressure <125 mmHg, and reduced kidney function with serum creatinine of 1.2 to 7.0 mg/dl in women and 1.4 to 7.0 mg/dl in men. Exclusion criteria were insulin-dependent diabetes mellitus, prior renal transplantation, renal artery stenosis, New York Heart Association class IV or III cardiac failure, and frequent hospitalizations. A total of 585 patients with a

Received February 15, 2010. Accepted May 6, 2010.

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. Vandana Menon, Division of Nephrology, Tufts Medical Center, 800 Washington Street, Box #391, Boston, MA 02111. Phone: 617-636-8791; Fax: 617-636-8329; E-mail: vmenon@tuftsmedicalcenter.org

ISSN: 1555-9041/509–1582

baseline GFR of 25 to 55 ml/min per 1.73 m^2 were randomly assigned in study A, and 255 patients with a baseline GFR of 13 to 24 ml/min per 1.73 m^2 were randomly assigned in study B. Patients in study A and study B were combined for the analyses presented here. A fasting lipid panel was obtained at the baseline study visit and measurements were performed at the MDRD Central Biochemistry Laboratory, Cleveland Clinic Foundation. Triglycerides were measured as a part of the lipid panel.

We ascertained survival status and date and cause of death from the National Death Index. A death was ascribed to CVD when the primary cause of death was International Classification of Diseases, Ninth Revision codes 390 through 459 ($n = 98$), or when kidney disease or diabetes was listed as the primary cause of death and CVD was the secondary cause of death. We defined survival time as time from randomization to death or end of follow-up (December 31, 2000). We obtained kidney failure outcomes (need for dialysis or transplantation) from the U.S. Renal Data Systems. The Institutional Review Boards of the Cleveland Clinic Foundation and Tufts Medical Center approved all study procedures.

Statistical Analyses

Summary statistics are presented as percentages for categorical data, mean (±SD) for approximately normally distributed continuous variables and as median (interquartile range) for skewed continuous variables by tertiles of total cholesterol. Differences in baseline characteristics between the groups were tested using the χ^2 test for categorical variables, one-way ANOVA for normally distributed continuous variables, and the Kruskall–Wallis test for skewed continuous variables.

We examined the relationship of four lipid parameters (total cholesterol [TC], non-HDL-cholesterol [NHDL-C], triglycerides [TG], and HDL-cholesterol [HDL-C]) categorized into tertiles with the outcomes of all-cause mortality, CVD mortality, and kidney failure (the need for dialysis or transplantation). TG was log-transformed for analysis. Cox proportional hazards models were used to evaluate these relationships initially without adjustment and subsequently adjusting for *a priori* defined confounding variables, including randomization assignments to protein diets and BP strata, age, race, gender, body mass index, systolic BP, history of CVD or diabetes, current cigarette smoking, proteinuria, etiology of kidney disease, and GFR.

The models for the mortality outcomes included patients with kidney failure and were censored only at death or the end of follow-up; models for kidney failure were censored at kidney failure, death, or end of follow-up. We calculated hazard ratios (HR) and 95% confidence intervals (CI). The lowest tertile was the reference for total, NHDL-C, and TG, and the highest tertile the reference for HDL-C.

To maximize statistical power to examine the relationship between each cholesterol measure and outcomes, we repeated the Cox models using continuous forms of the lipid parameters. HRs are per 10-mg/dl increase for TC, HDL-C, and NHDL-C and per unit change in log-transformed TG.

Additional Analyses

Malnutrition and inflammation may modify the relationship between cholesterol and mortality in patients with CKD. Therefore we performed additional multivariable Cox models including C-reactive protein as a marker of inflammation and serum albumin as a marker of malnutrition. Because death is a competing risk for kidney failure, we repeated the Cox models using a composite outcome of death or kidney failure (need for dialysis or transplantation). Covariates and survival time for the composite outcome were the same as those described above for the outcome of kidney failure. We repeated analyses with LDL-cholesterol as a continuous variable.

Results

Characteristics of Study Cohort

The study cohort had a mean ± SD age of 52 ± 12 years and GFR of 33 ± 12 ml/min per 1.73 m^2. The sample was predominantly white (85%), 60% were male, 5% had a history of diabetes, 13% had a history of CVD, and 10% were current smokers. TC ranged from 112 to 402 mg/dl with a mean ± SD of 217 ± 45 mg/dl. HDL-C ranged from 13 to 110 mg/dl, with mean ± SD of 40 ± 14 mg/dl; NHDL-C ranged from 57 to 356 mg/dl, with mean ± SD being 177 ± 45 mg/dl; TG ranged from 25 to 1420 mg/dl, with median ± interquartile range being 140 ± 115 mg/dl. At baseline, 9% ($n = 76$) of the cohort was receiving cholesterol-lowering therapy; of these, 4% ($n = 30$) were on statins.

Baseline Characteristics by Tertiles of TC

Subjects in the higher TC tertiles were more likely to be older, nonwhite, female, and to have higher body mass index, systolic BP, C-reactive protein, and level of proteinuria than those in the lower tertiles (Table 1). There were no differences between tertiles in prevalence of diabetes and CVD, serum albumin, or level of GFR.

Lipids and All-Cause Mortality

During a median follow-up time of 10 years, there were 208 deaths from any cause. In analyses using tertiles of lipid variables, there was no association between any of the lipid variables and all-cause mortality in unadjusted analyses (Table 2). Adjustment for demographic, CVD, and kidney disease variables did not appreciably alter the observed results.

We repeated these analyses with TC, HDL-C, NHDL-C, and log-transformed TG as continuous variables (Table 3). Each 10-mg/dl increase in TC was associated with a 3% increased risk of all-cause mortality in unadjusted analysis. Adjustment for covariates attenuated this relationship. For HDL-C, NHDL-C, and log-transformed TG, there was no association with all-cause mortality in adjusted or unadjusted analyses.

Lipids and CVD Mortality

During the course of follow-up, 128 (15%) participants died of CVD during follow-up. In analyses using tertiles of cholesterol, there was no association between any of the lipid variables and CVD mortality in unadjusted or adjusted models (Table 2).

We repeated these analyses with each of the lipid parameters as continuous variables. There was no association of TC, HDL-C, NHDL-C, or TG with CVD mortality in unadjusted or adjusted Cox models.

Lipids and Kidney Failure

During follow-up, 554 (66%) participants reached kidney failure. In analyses using tertiles of lipids, the lowest tertile of HDL-C was associated with higher risk of kidney failure in unadjusted models. Adjustment for covariates attenuated this

Table 1. Baseline characteristics by tertiles of TC

Characteristic	Tertile 1, TC < 193 mg/dl (n = 275)	Tertile 2, TC 193 to 232 mg/dl (n = 284)	Tertile 3, TC > 232 mg/dl (n = 281)	P for trend
Age (years)	50.3 ± 13.2	51.6 ± 12.2	53.3 ± 11.6	0.02
White (%)	90.0	84.2	81.1	0.02
Males (%)	68.4	62.7	50.5	<0.01
History of diabetes (%)	4.0	5.3	6.0	0.54
History of CVD (%)	12.7	14.4	12.1	0.7
Current smoking (%)	11.6	8.5	9.6	0.44
Systolic BP (mmHg)	130 ± 16.8	131.8 ± 17.2	134 ± 18.4	0.03
Body mass index (kg/m^2)	26.4 ± 4.5	27.4 ± 4.4	27.6 ± 4.4	<0.01
C-reactive protein (mg/dl)	0.44 (0.5)	0.42 (0.5)	0.55 (0.8)	0.04
Etiology of kidney disease (%)				
polycystic kidney disease	27	28	17	
GN	27	28	39	0.17
other	46	44	44	
GFR (ml/min per 1.73 m^2)	32.4 ± 12.5	32.4 ± 11.9	32.8 ± 11.6	0.85
Serum albumin (g/dl)	4.0 ± 0.3	4.0 ± 0.3	4.0 ± 0.4	0.10
Proteinuria (g/d)	0.8 (1.2)	1.0 (1.4)	1.5 (2.0)	<0.01

Data are mean ± SD or median (interquartile range).

relationship (Table 2). With the lipid parameters as continuous variables, we did not find an association between TC, NHDL-C, or TG with kidney failure. There was a significant inverse association with HDL-C that was attenuated by covariate adjustment.

Additional Analyses

The addition of C-reactive protein and serum albumin to the multivariable Cox models did not alter the nonsignificant associations observed between lipid parameters and the outcomes of all-cause mortality, CVD mortality, and kidney failure (data not shown).

We repeated the Cox models for the composite outcome of death or kidney failure. During follow-up, 624 (74%) participants reached the composite outcome. Similar to models with kidney failure as the outcome, there was a significant inverse relationship with HDL-C that disappeared with covariate adjustment (data not shown). Similar to the other cholesterol variables, we did not find a significant relationship between LDL-C and any of the outcomes tested (data not shown).

Discussion

In this cohort of subjects with predominantly nondiabetic stage 3 to 4 CKD, hyperlipidemia does not appear to be independently associated with increased risk for all-cause mortality, CVD mortality, or kidney failure. Although it is a well established traditional risk factor for mortality in the general population, high cholesterol is associated with lower mortality in patients on dialysis. Given the high mortality rates seen in patients with CKD, most of which are related to cardiovascular causes, the role of lipids as modifiable risk factors for CVD is of clinical importance.

Few studies have examined the association between hyperlipidemia and mortality in patients with earlier stages of CKD. In a study of 986 male U.S. veterans, Kovesdy *et al.* (16) found an inverse association of TC and LDL-cholesterol with all-cause and CVD mortality and a direct relationship between TG levels and all-cause mortality in patients with CKD (estimated GFR 37.4 ± 17.6 ml/min per 1.73 m^2). Participants in the lowest quartile of TC had a nearly 2-fold increased risk for all-cause mortality compared with those in the highest quartile. However, adjustments for case-mix and markers of malnutrition and inflammation abolished these associations. This study cohort differed significantly from the MDRD study cohort in being older (mean age 67.4 ± 10 years) and with a high prevalence of diabetes (55%), smoking (25%), and pre-existing CVD (56%).

In another study of 1249 elderly subjects with CKD (GFR 50 ± 10 ml/min per 1.73 m^2) from the Cardiovascular Health Study, none of the lipid parameters examined (LDL-cholesterol, TG, and HDL-C) were associated with CVD mortality (18). In this study, the mean age of the cohort was 75 ± 6 years and mean estimated GFR was 50 ± 10 ml/min per m^2. The average follow-up time was 8.6 years. The cohort had a higher prevalence of diabetes (17%) and CVD (23%) at baseline with mean levels of HDL, LDL, and TG of 51 ± 15 mg/dl, 131 ± 38 mg/dl, and 151 ± 79 mg/dl, respectively.

Our findings suggest that the relationship between hyperlipidemia and long-term outcomes in CKD differs from the general population and patients with kidney failure. Patients in the earlier stages of CKD appear to represent a transition point between the general population and patients with kidney failure with regard to the relationship of hyperlipidemia with survival. It is possible that the effects of hyperlipidemia are masked in the presence of other powerful traditional CVD risk factors. It is also possible that although hyperlipidemia tends to

Table 2. Relationship between tertiles of lipid parameters and long-term outcomes

Parameters	All-Cause Mortality		CVD Mortality		Kidney Failure	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
TC						
tertile 1	1.0	1.0	1.0	1.0	1.0	1.0
tertile 2	1.29, 0.92 to 1.82	1.13, 0.79 to 1.61	1.12, 0.73 to 1.71	0.86, 0.55 to 1.36	1.11, 0.90 to 1.36	0.95, 0.77 to 1.18
tertile 3	1.35, 0.96 to 1.90	1.05, 0.73 to 1.51	1.11, 0.72 to 1.71	0.81, 0.51 to 1.29	1.04, 0.85 to 1.8	0.94, 0.76 to 1.17
NHDL-C						
tertile 1	1.0	1.0	1.0	1.0	1.0	1.0
tertile 2	1.39, 0.98 to 1.97	1.16, 0.80 to 1.66	1.29, 0.89 to 1.98	0.98, 0.62 to 1.53	1.23, 0.99 to 1.51	1.17, 0.94 to 1.45
tertile 3	1.58, 1.12 to 2.23	1.12, 0.78 to 1.60	1.24, 0.80 to 1.93	0.82, 0.52 to 1.30	1.18, 0.96 to 1.45	1.01, 0.80 to 1.25
TG						
tertile 1	1.0	1.0	1.0	1.0	1.0	1.0
tertile 2	1.03, 0.73 to 1.44	0.91, 0.64 to 1.29	1.32, 0.87 to 2.03	1.27, 0.82 to 1.97	0.88, 0.72 to 1. 09	0.89, 0.71 to 1.10
tertile 3	1.18, 0.85 to 1.65	0.94, 0.66 to 1.34	1.11, 0.71 to 1.74	0.96, 0.60 to 1.54	1.04, 0.85 to 1.27	0.99, 0.80 to 1.23
HDL-C						
tertile 1	1.38, 0.98 to 1.95	1.17, 0.78 to 1.74	1.26, 0.82 to 1.91	1.04, 0.64 to 1.70	1.44, 1.18 to 1.78	1.10, 0.85 to 1.42
tertile 2	1.39, 0.99 to 1.96	1.34, 0.93 to 1.95	1.03, 0.67 to 1.60	0.98, 0.61 to 1.57	1.17, 0.95 to 1.44	1.04, 0.87 to 1.38
tertile 3	1.0	1.0	1.0	1.0	1.0	1.0

Data presented as HR, 95% CI. HRs are per mg/dl increase for TC, HDL-C, and NHDL-C and per unit change in log-transformed TG.

[a]Models adjusted for randomization assignments to protein diets and BP strata, age, race, gender, body mass index, systolic BP, history of CVD or diabetes, current cigarette smoking, proteinuria, etiology of kidney disease, and GFR.

Table 3. Relationship between lipid parameters as continuous variables and long-term outcomes

Parameter	All-Cause Mortality		CVD Mortality		Kidney Failure	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
TC	1.03, 1.0 to 1.06	1.02, 0.98 to 1.05	1.02, 0.98 to 1.06	1.0, 0.96 to 1.04	1.01, 0.99 to 1.03	1.01, 0.98 to 1.03
NHDL-C	1.04, 1.01 to 1.07	1.01, 0.98 to 1.05	1.02, 0.98 to 1.06	0.99, 0.95 to 1.03	1.02, 0.996 to 1.03	1.01, 0.99 to 1.03
TG	1.23, 0.99 to 1.53	1.02, 0.79 to 1.31	1.13, 0.83 to 1.50	0.97, 0.70 to 1.32	1.06, 0.92 to 1.21	1.02, 0.86 to 1.19
HDL-C	0.92, 0.83 to 1.02	1.02, 0.91 to 1.14	0.98, 0.86 to 1.1	1.09, 0.95 to 1.26	0.93, 0.87 to 0.99	0.98, 0.91 to 1.06

Data presented as HR, 95% CI. HRs are per 10-mg/dl increase for TC, HDL-C, and NHDL-C and per unit change in log-transformed TG.
[a]Models adjusted for randomization assignments to protein diets and BP strata, age, race, gender, body mass index, systolic BP, history of CVD or diabetes, current cigarette smoking, proteinuria, etiology of kidney disease, and GFR.

lead to large-vessel coronary disease, the CVD burden in CKD may be due to other types of CVD such as cardiomyopathies, arteriosclerosis, and small-vessel coronary disease (22).

Our study has several strengths. This is a large cohort of patients with CKD spanning a wide range of kidney function and consists of subjects who are predominantly nondiabetic, not acutely ill, or appreciably malnourished. Statins reduce mortality by pathways other than lipid lowering (23,24); however, the number of patients using statins in our cohort was low, thus limiting their confounding effect. The limitations include single baseline measurement of lipids to predict several events in the future. However there are several precedents for the use of a single baseline measure to predict future events. Also, although we had a wide range of lipid values and a large number of events, a lack of statistical power may have prevented us from detecting associations.

In conclusion, hyperlipidemia does not appear to be an independent risk factor for long-term outcomes in patients with stage 3 to 4 CKD. Results from ongoing trials such as the Study of Heart and Renal Protection will provide definitive data regarding utility of cholesterol lowering in this patient population.

Acknowledgments

This study was supported through grants K23 DK067303, K23 DK02904, and K24 DK078204 from the National Institute of Diabetes and Digestive and Kidney Diseases. Part of this material was presented in abstract form at the annual meeting of the American Society of Nephrology; November 4 through 9, 2008; Philadelphia, PA.

Disclosures

None.

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