Association Between Cholesterol Level and Mortality in Dialysis Patients

Role of Inflammation and Malnutrition

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Context Total cholesterol level is inversely associated with mortality in dialysis patients, a group at high risk of cardiovascular disease (CVD). This paradox may be explained by systemic inflammation and/or malnutrition, which are associated with lower cholesterol levels and higher mortality.

Objective To determine the relationship between cholesterol level and outcome in patients undergoing dialysis, accounting for inflammation and malnutrition.

Design, Setting, and Participants Prospective study of 823 patients enrolled from October 1995 to June 1998 who recently initiated dialysis, from 79 clinics, classified by absence or presence of inflammation and/or malnutrition (defined as serum albumin levels <3.6 mg/dL, C-reactive protein ≥10 mg/L, or interleukin 6 ≥3.09 pg/mL).

Main Outcome Measures All-cause and cardiovascular disease mortality.

Results During a median follow-up of 2.4 years, 324 deaths (159 CVD deaths), 153 renal transplantations, and 10 losses to follow-up occurred. Average serum cholesterol level was lower in the presence of inflammation/malnutrition than in its absence. In a Cox model adjusted for age, race, and sex, a 40-mg/dL (1.0-mmol/L) increment in baseline total serum cholesterol level was associated with a decreased risk of all-cause mortality overall (relative hazard [RH], 0.92; 95% confidence interval [CI], 0.87-0.98) and in the presence of inflammation/malnutrition (RH, 0.89; CI, 0.84-0.95). In contrast, serum cholesterol level was associated with an increased risk in the absence of inflammation/malnutrition (RH, 1.32; 95% CI, 1.07-1.63). For CVD mortality, an inverse trend was not statistically significant in the presence of inflammation/malnutrition, and a positive association was evident in the absence of inflammation/malnutrition (RH, 1.41; 95% CI, 1.04-1.89). Further adjustment for traditional CVD risk factors, dialysis modality, comorbidity, and inflammatory markers attenuated the inverse association but strengthened the positive association.

Conclusions The inverse association of total cholesterol level with mortality in dialysis patients is likely due to the cholesterol-lowering effect of systemic inflammation and malnutrition, not to a protective effect of high cholesterol concentrations. These findings support treatment of hypercholesterolemia in this population.

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HIGHER CHOLESTEROL LEVELS have been consistently associated with lower mortality in prospective studies[1-4] of dialysis patients, which stands in marked contrast to prospective studies and clinical trial findings in the general population. It has been suggested, but remains unproven, that this paradoxic association is spurious and results from either reverse causation, in which advanced cardiovascular disease (CVD) leads to inflammation and/or malnutrition and lower cholesterol levels, or a confounding effect of inflammation and/or malnutrition, which leads to lower cholesterol levels and higher mortality.[3-5] Detailed examination of this question is important because similar inverse or U- or J-shaped associations have been documented in elderly individuals,[6] smokers,[7] and patients with stroke,[8] heart failure,[9] or coronary heart disease.[10] A better understanding of the mechanisms underlying these associations is needed to develop rational therapeutic goals for dialysis patients, as well as other subpopulations that differ from the general population.

Cardiovascular disease is the leading cause of death in patients with end-stage renal disease (ESRD), accounting for about half of the more than 20% annual mortality rate.[11] The

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inverse association of serum cholesterol level with mortality, combined with a lack of clinical trial data, has dampened enthusiasm for treatment of hypercholesterolemia in dialysis patients.[5] Although 30% of dialysis patients have cholesterol levels higher than 200 mg/dL (5.18 mmol/L), fewer than 10% of these patients are prescribed statins.[2,12]

In patients with renal disease, inflammation and malnutrition are often considered together because a low serum albumin level, a marker of malnutrition, is also influenced by inflammation.[13] Inflammation and malnutrition have been recognized as important contributors to an adverse prognosis in dialysis patients.[14,15]

These factors may explain the inverse association between serum cholesterol level and mortality because they are strongly associated with higher mortality and lower cholesterol levels.[16,17] We evaluated whether the association between cholesterol levels and mortality would be altered by the presence of inflammation or malnutrition.

METHODS

Study Design and Population

The CHOICE (Choices for Healthy Outcomes In Caring for ESRD) study is a national prospective cohort study of 1041 patients who recently initiated dialysis and were aged 19 to 95 years from 81 dialysis clinics associated with Dialysis Clinic, Incorporated (DCI, Nashville, Tenn; n=923 from 79 clinics), New Haven Chronic Ambulatory Peritoneal Dialysis (New Haven, Conn; n=86), or Saint Raphael's Hospital (New Haven, Conn; n=32), described previously.[18] Participants were enrolled from October 1995 to June 1998 a median of 45 days after initiation of dialysis (95% within 3.5 months). Blood was drawn only for participants enrolled at the DCI clinics, of whom 823 (89%; 823/923) had lipid and inflammation profiles measured and formed the final study population. The study was approved by the institutional review board, and participants provided written informed consent.

Measurements

Baseline demographic and clinical data were obtained from hospital and clinic records and questionnaires (TABLE 1). Prevalent CVD was defined as medical record documentation of coronary artery disease, cerebrovascular disease, or peripheral vascular disease. The level of CVD and other comorbidity was assessed by a trained nurse according to medical records and clinic staff reports by using the Index of Co-Existent Disease (ICED), a standardized and validated 4-level scale tested in multiple studies.[19]

Nonfasting blood specimens were drawn before a dialysis treatment at a median of 5.0 months from the initiation of dialysis (95% within 8.7 months), shipped overnight to a central laboratory, and stored at –80°C. Colorimetric methods on an Olympus (Hamburg, Germany) autoanalyzer were used to determine total cholesterol (coefficient of variation [CV], 5.3%), high-density lipoprotein cholesterol (HDL-C; CV, 9.6%), and triglyceride (CV, 12.3%) levels. Non–HDL-C was calculated as total cholesterol level minus HDL-C. Serum albumin levels were measured by using the Bromocresol Green method (CV, 1.1%). Serum high-sensitivity C-reactive protein (CRP), an acute-phase protein, was measured by using a colorimetric competitive enzyme-linked immunosorbent assay (ELISA; CV, 8.9%). Interleukin 6 (IL-6), a central proinflammatory cytokine, was measured in serum by an ultrasensitive ELISA method (CV, 7%).

Outcome Ascertainment

Death from all causes was ascertained by active follow-up through dialysis clinics, as well as passive follow-up by using Centers for Medicare & Medicaid Services (CMS) data. Of 324 deaths, 126 (59% of 214 in-hospital deaths) terminal hospitalization medical records were available and were adjudicated by 2 members of the study's outcomes committee by using a uniformly applied, 16-page diagnostic algorithm modified from the outcome criteria used in the Cardiovascular Health Study[20] and the Hemodialysis (HEMO) Study.[19] The percentage of agreement between reviewers for the attributed underlying cause of death was 86%. For patients whose terminal medical records were unavailable, the cause of death was determined with the CMS death notification form (Form 2746), completed at death by the dialysis-unit staff. The cause of death was considered to be CVD if the death was adjudicated as being due to coronary heart disease, stroke syndrome, or peripheral vascular disease or, for the CMS death notification, if the primary cause of death was coded as 23 (myocardial infarction), 26 (atherosclerotic heart disease), 36 (cerebrovascular accident including intracranial hemorrhage), 44 (mesenteric infarction), 51 (septicemia due to peripheral vascular disease, gangrene), or 29 (sudden death) when a history of CVD was present.

Data Analysis

All analyses were performed using STATA (release 7.0; StataCorp, College Station, Tex) statistical software; $P<.05$ was considered significant. To better distinguish individuals with any evidence of inflammation and/or malnutrition, a composite variable combining serum albumin, CRP, and IL-6 levels was used to categorize the study population into 2 subgroups: presence or absence of inflammation and/or malnutrition. The presence of inflammation/malnutrition was defined as achievement of a priori cutoffs for any of the 3 variables from studies of the general population. For serum albumin levels, the cutoff was less than 3.6 mg/dL, the 10th percentile from the Third National Health and Nutrition Examination Survey (NHANES III); for CRP, 10 mg/L or higher, the 90th percentile for the NHANES III.[21] Interleukin 6 levels were not measured in NHANES, so a cut point of 3.09 pg/mL or higher, the 75th percentile in the Health, Aging, and Body Composition (Health ABC) Study, was used.[22]

The baseline characteristics of the 2 study subgroups were compared with χ^2 statistics, *t* test, and Mann-Whitney

U test as appropriate. In a survival analysis, follow-up time was defined as the period from initiation of dialysis to death, with staggered entry to allow for the various times at which different patients had their cholesterol levels measured. To obtain stable early survival estimates, entry was left truncated at 4.0 months after first dialysis. Individuals were censored because of loss to follow-up (n=10), renal transplant (n=153), or end of follow-up on November 1, 2000 (n=336).

Multivariate Cox proportional hazards models were used to examine the presence, strength, and independence of the association between cholesterol level and either all-cause or CVD mortality. To evaluate potential nonlinear trends, total cholesterol level was categorized into 4 groups (<160, 160-199, 200-239, and ≥240 mg/dL [<4.14, 4.14-5.15, 5.17-6.18, and ≥6.21 mmol/L]), according to the National Cholesterol Education Program (NCEP) guidelines.[23] A sequential multivariate modeling strategy was conducted whereby crude estimates were initially adjusted for demographic information only (model 1), then ad-

Table 1. Baseline Characteristics of Study Sample by Inflammatory and Nutritional Status

Characteristics	Overall (N = 823)	Presence of Inflammation/Malnutrition (n = 634)	No Inflammation/Malnutrition (n = 189)	*P* Value*
Demographics				
Age, mean (SD), y	57.2 (15)	58.2 (14)	53.7 (16)	<.001
Sex, female, No. (%)	386 (46.9)	296 (46.7)	90 (47.6)	.82
Race, No. (%)				
White	532 (64.6)	420 (66.3)	112 (59.3)	.21
Black	247 (30.0)	181 (28.6)	66 (34.9)	
Clinical variables				
Smoking, No. (%)				
Former	366 (44.5)	294 (46.3)	73 (38.7)	.12
Current	128 (15.5)	99 (15.6)	29 (15.1)	
Hemodialysis, No. (%)	666 (80.9)	512 (80.8)	154 (81.5)	.82
BMI, median (IQR)	25.7 (22.6-30.4)	25.8 (22.7-30.7)	25.3 (22.1-28.5)	.03
Systolic blood pressure, mean (SD), mm Hg	150 (18)	150 (19)	151 (16)	.63
Comorbidity, No. (%)				
ICED comorbidity score				
Level 0-1	200 (24.3)	190 (30.0)	92 (48.7)	<.001
Level 2	304 (36.9)	233 (36.8)	70 (37.0)	
Level 3	237 (28.8)	210 (33.2)	27 (14.3)	
Prevalent CVD	355 (43.1)	294 (46.4)	61 (32.3)	.001
Diabetes	456 (55.4)	373 (58.8)	83 (43.9)	<.001
Congestive heart failure	385 (46.8)	317 (50.0)	69 (36.5)	.009
Statin use	108 (13.1)	88 (13.9)	20 (10.6)	.24
Lipid levels, mean (SD), mg/dL				
Total cholesterol	188.5 (50)	186.4 (51)	195.3 (48)	.03
Non-HDL	145.4 (49)	143.8 (49)	150.9 (47)	.08
HDL	43.1 (15)	42.8 (15)	44.4 (15)	.19
Total cholesterol, No. (%), mg/dL*				
<160	249 (30.3)	206 (32.5)	43 (22.8)	.04
160-199	278 (33.9)	213 (33.6)	65 (34.4)	
200-239	182 (22.1)	130 (20.5)	52 (27.5)	
≥240	114 (13.9)	85 (13.4)	29 (15.3)	
Non-HDL cholesterol, No. (%), mg/dL				
<130	342 (41.6)	274 (43.2)	68 (36.0)	.11
130-159	198 (24.1)	153 (24.1)	45 (23.8)	
160-189	151 (18.4)	106 (16.7)	45 (23.8)	
≥190	132 (16.0)	101 (15.9)	31 (16.4)	
Inflammation and malnutrition				
CRP, median (IQR), mg/L	3.8 (1.6-9.4)	4.6 (2.2-13.1)	1.8 (1.0-3.7)	<.001
IL-6, median (IQR), pg/mL	4.0 (2.5-7.1)	5.1 (3.5-8.2)	2.0 (1.6-2.5)	<.001
Albumin, mean (SD), g/dL	3.7 (0.4)	3.5 (0.4)	3.9 (0.2)	<.001

Abbreviations: BMI, body mass index (measured as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; CVD, cardiovascular disease; HDL, high-density lipoprotein; ICED, Index of Co-Existent Disease; IL-6, interleukin 6; IQR, interquartile range.
SI conversion factor: To convert values for cholesterol to mmol/L, multiply by 0.0259.
*By χ^2, *t*, or Mann-Whitney *U* test.

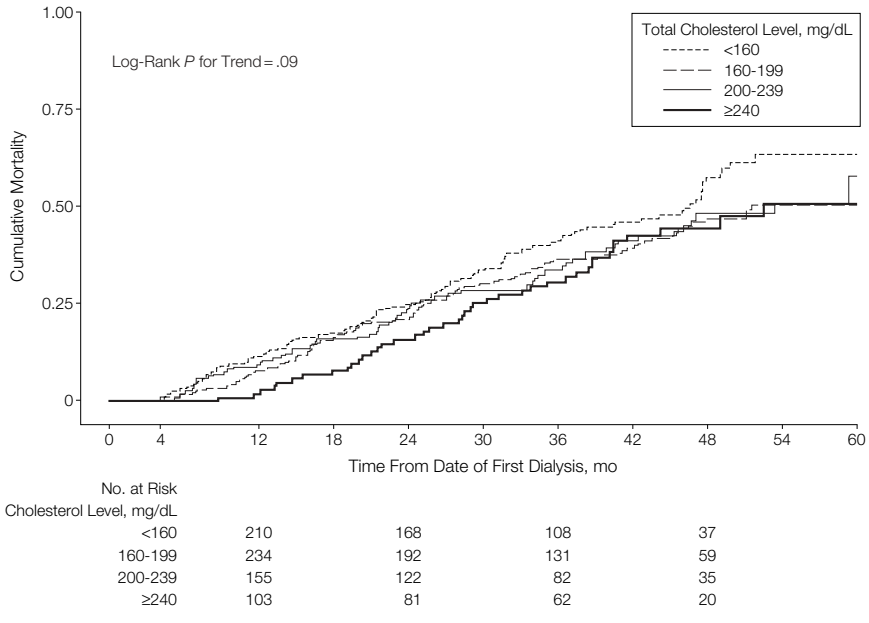
justed for traditional CVD risk factors, dialysis modality, and comorbidity (model 2), and then adjusted for the above variables plus baseline serum albumin levels, IL-6, and CRP level (model 3). To allow for potential dialysis-clinic–specific practices, all the analyses were adjusted for clustering within clinics by using robust variance methods.[24] Cholesterol was also modeled as a continuous variable with a fifth-order polynomial to allow for the possibility of a nonlinear relationship with mortality. The adjusted 3-year mortality, predicted from Cox models adjusted for age, sex, race, modality, and cigarette-smoking status of the entire study group at each cholesterol level, was plotted as a function of serum cholesterol level.[25] Analyses were also performed with non–HDL-C in place of total cholesterol levels. The a priori cutoffs for serum non–HDL-C were less than 130, 130-159, 160-189, and at least 190 mg/dL (<3.36, 3.36-4.11, 4.14-4.89, and ≥4.91 mmol/L), corresponding to NCEP guidelines. For all survival analyses, the proportionality assumption of the Cox model was confirmed by inspection of log (–log[survival function]) curves and Schoenfeld residuals.

Table 2. Dialysis Patients and Levels of Markers (N = 823)

Markers of Inflammation/Malnutrition	No. (%) of Patients			
	CRP ≥10 mg/L	IL-6 ≥3.09 pg/mL	Albumin <3.6 mg/dL	Total
One only	8 (<1)	209 (25)	80 (10)	297 (36)
Two				
CRP ≥10 mg/L		88 (11)	4 (<1)	242 (29)
IL-6 ≥3.09 pg/mL			150 (18)	
All				95 (12)
None				189 (23)
Total with marker	195 (24)	542 (66)	329 (40)	

Abbreviations: CRP, C-reactive protein; IL-6, interleukin 6.

Figure 1. Unadjusted Cumulative All-Cause Mortality by Cholesterol Level



To convert cholesterol from mg/dL to mmol/L, multiply values by 0.0259.

RESULTS

Baseline characteristics are presented in Table 1. Age, sex, race, and dialysis modality distributions were similar to that of the 1997 US dialysis population.[26] Overall, 77% (n=634) of the dialysis patients had evidence of inflammation/malnutrition. TABLE 2 lists the overlap of persons with high levels of IL-6 and CRP and low levels of albumin. Presence of inflammation/malnutrition was associated with older age, higher comorbidity score, prevalent CVD, diabetes, heart failure, higher body mass index (BMI), and lower total cholesterol level.

During a median follow-up of 2.4 years (range, 0.1-4.8 years) and 1875 person-years, 324 deaths occurred (49% CVD deaths). FIGURE 1 and FIGURE 2 show that lower cholesterol levels were associated with higher mortality in the overall cohort (*P* for trend=.09) and in the presence of inflammation/malnutrition (*P* for trend=.03), respectively. However, in the absence of inflammation/malnutrition, the association was in the opposite direction, with higher total cholesterol level categories associated with higher mortality (*P* for trend=.02).

The inverse association of total cholesterol level with all-cause mortality, overall and in the presence of inflammation/malnutrition, was also seen in Cox proportional hazards analysis adjusting for age, race, sex, and clinic (TABLE 3, categorical measure) and in analyses with serum cholesterol level as a continuous measure (Table 3, continuous measure, model 1). This association was attenuated and no longer statistically significant after adjustment for traditional CVD risk factors, dialysis modality, and comorbidity (model 2) or further adjustment for albumin level and inflammatory markers (model 3). In the absence of inflammation/malnutrition, total cholesterol level was positively associated with all-cause mortality in model 1 and even more strongly so with further adjustment. In the full model (model 3), the adjusted relative hazard of all-cause mortality associated with a 40-mg/dL (1.0-mmol/L) higher cholesterol level was 1.51 (95% confidence interval, 1.12-

2.04) in the absence of inflammation/malnutrition ($P = .007$ and P for interaction = .04). Further adjustment for statin intake, dialysis dose (Kt/V), and type of vascular access did not change the results materially (data not shown).

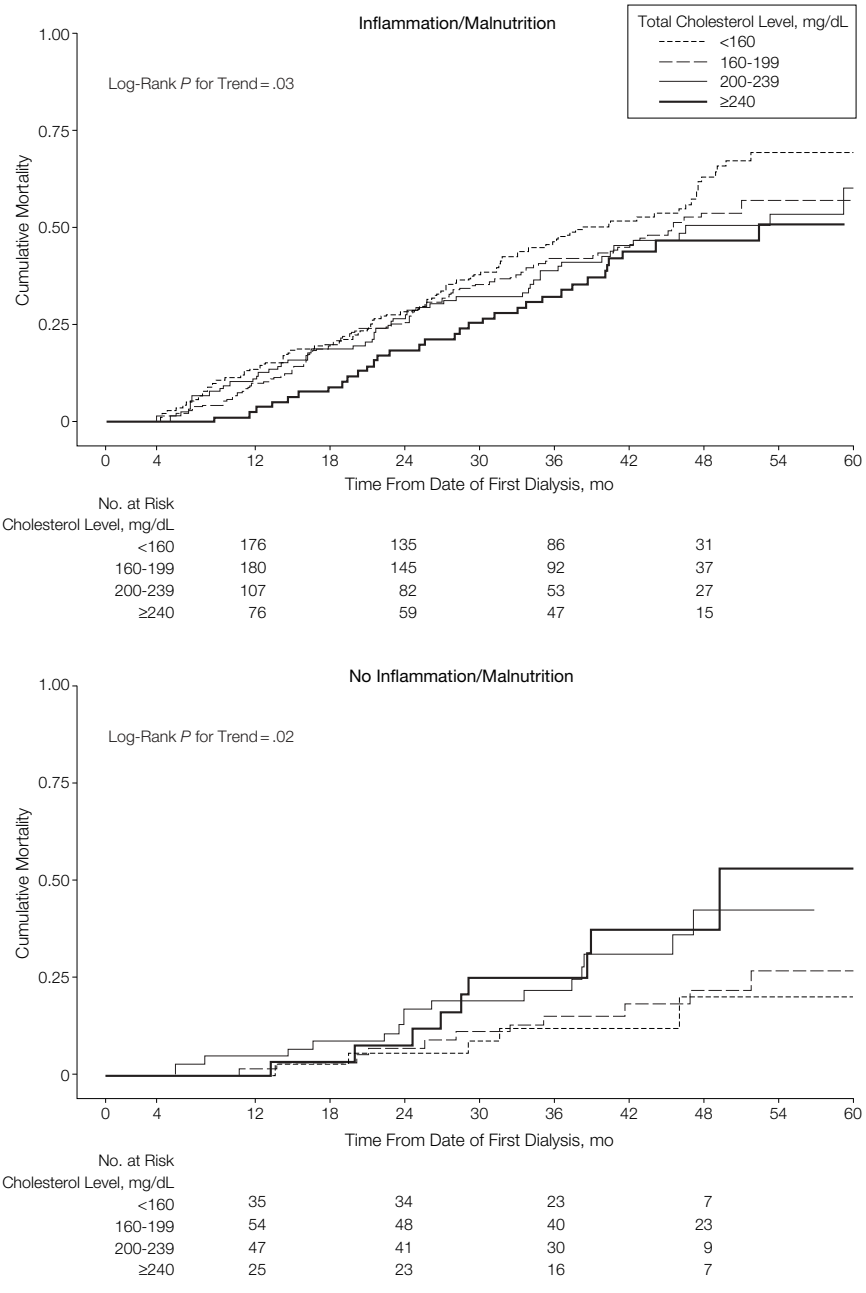
To further assess the role of early mortality in explaining the association of low cholesterol level with increased risk of mortality, survival analyses excluding the first 6 or 12 months of follow-up were conducted. The results of these analyses were similar to the results in the overall group. Model 2 was also repeated after stratification of the overall group by age (<60 vs ≥60 years), race, sex, current smoking, dialysis modality, and presence of diabetes or CVD. An inverse association was observed in individuals with a history of CVD (relative hazard, 0.89; $P = .03$) but not in individuals without a history of CVD (relative hazard, 1.06; $P = .32$). Limiting the analysis to hemodialysis patients yielded results similar to those reported in the overall group. No significant interaction was present for the rest of the subgroups.

In assessing cause-specific mortality, the association of serum cholesterol level with non-CVD mortality was similar to that observed for all-cause mortality (data not shown). For CVD mortality, an inverse trend was present but was not statistically significant in the presence of inflammation/malnutrition (Table 3). In the absence of inflammation/malnutrition, however, serum cholesterol level was even more strongly positively associated with CVD mortality than with all-cause mortality.

FIGURE 3 shows the relationships between serum cholesterol levels and predicted 3-year all-cause and CVD mortality for the entire study group. The absolute risk of mortality is high in the overall group, ranging from approximately 45% at lower serum cholesterol levels to 30% at higher serum cholesterol levels. A similar relationship with highest mortality at lower serum cholesterol levels, which then plateaus at a serum cholesterol level of about 180 mg/dL (4.65 mmol/L), is seen in individuals with inflammation/malnutrition. In contrast, the association between serum cholesterol level and mortality is positive and nearly linear among the minority of dialysis patients without any sign of inflammation/malnutrition.

A similar pattern was observed for the 3-year CVD mortality (Figure 3). A U-shaped association of cholesterol level with mortality was observed in the overall group and in the presence of inflammation/malnutrition, whereas a positive association was seen in the absence of inflammation/malnutrition.

Figure 2. Unadjusted Cumulative All-Cause Mortality by Presence of Inflammation/Malnutrition, by Cholesterol Level



To convert cholesterol from mg/dL to mmol/L, multiply values by 0.0259.

When the analysis was repeated with non–HDL-C as the independent variable, results similar to those described for the primary analysis that used total cholesterol levels were observed (TABLE 4). In the presence of inflammation/malnutrition, non–HDL-C was significantly and inversely associated with all-cause mortality, but the association with CVD mortality was not statistically significant. In contrast, non–HDL-C was positively associated with CVD and all-cause mortality in the absence of inflammation/malnutrition.

COMMENT

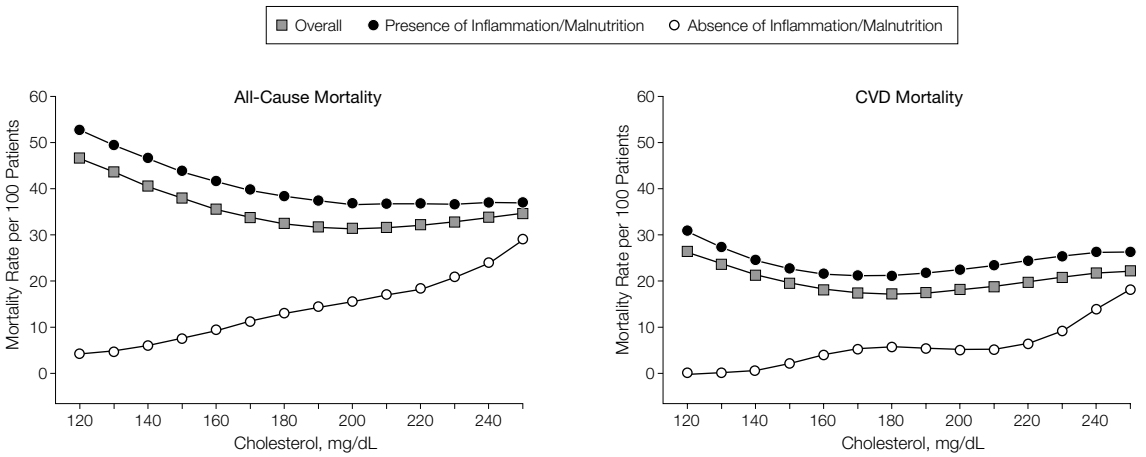
More than a decade ago, in a study of more than 12 000 hemodialysis patients, Lowrie and Lew[1] noted that overall mortality risk was significantly lower at higher total serum cholesterol levels. Since then, many prospective studies in

Table 3. Risk of All-Cause and CVD Mortality Associated With Total Cholesterol, Stratified by Inflammatory and Nutritional Status

Total Cholesterol Level, mg/dL	Overall (N = 823)	Presence of Inflammation/Malnutrition (n = 634)	No Inflammation/Malnutrition (n = 189)	*P* Value for Interaction
All-Cause Mortality RH (95% Confidence Interval)				
Categorical measure*				
<160	1.00	1.00	1.00	<.001
160-199	0.74 (0.54-1.00)	0.76 (0.58-1.01)	1.23 (0.49-3.12)	
200-239	0.74 (0.56-0.99)	0.71 (0.54-0.93)	2.33 (0.91-6.00)	
≥240	0.71 (0.52-0.98)	0.62 (0.44-0.88)	3.22 (1.07-9.70)	
Continuous measure (per 40 mg/dL)				
Model 1*	0.92 (0.87-0.98)	0.89 (0.84-0.95)	1.32 (1.07-1.63)	.001
Model 2†	0.94 (0.87-1.02)	0.92 (0.84-1.00)	1.53 (1.11-2.11)	.03
Model 3‡	0.97 (0.90-1.04)	0.93 (0.86-1.00)	1.51 (1.12-2.04)	.04
CVD Mortality RH (95% Confidence Interval)				
Categorical measure*				
<160	1.00	1.00	1.00	.11
160-199	0.80 (0.54-1.18)	0.85 (0.58-1.26)	1.67 (0.24-11.79)	
200-239	1.16 (0.77-1.76)	0.97 (0.62-1.51)	3.14 (0.64-15.35)	
≥240	0.87 (0.55-1.38)	0.72 (0.44-1.19)	4.60 (0.68-31.33)	
Continuous measure (per 40 mg/dL)				
Model 1*	0.99 (0.90-1.08)	0.92 (0.83-1.00)	1.41 (1.04-1.89)	.11
Model 2†	0.99 (0.87-1.14)	0.96 (0.83-1.05)	2.00 (1.27-3.16)	.17
Model 3‡	1.01 (0.88-1.15)	0.94 (0.83-1.05)	2.73 (1.37-5.46)	.20

Abbreviations: CVD, cardiovascular disease; RH, relative hazard.
SI conversion factor: To convert values for cholesterol to mmol/L, multiply by 0.0259.
*Adjusted for age, race (black, white, other), sex, and clinic.
†Adjusted for model 1 and smoking status, body mass index, dialysis modality, comorbidity score, diabetes, prevalent CVD, congestive heart failure, and systolic blood pressure.
‡Adjusted for model 2 and serum albumin, interleukin 6, and C-reactive protein levels.

Figure 3. Estimated 3-Year All-Cause and Cardiovascular Disease (CVD) Mortality by Cholesterol Level



Serum cholesterol is modeled as a fifth-order polynomial, and all values are predicted from Cox models adjusted to age, sex, race, modality, and smoking status of the entire study group at each cholesterol level. To convert cholesterol from mg/dL to mmol/L, multiply values by 0.0259.

the ESRD population have replicated this inverse association. This paradoxic association raises some critical questions. Is there a different biological effect of cholesterol in dialysis patients compared with the general population? Should patients be advised to increase their nutrient intake to increase their cholesterol levels? Should new standards be considered for their lipid management?

Our data demonstrate an inverse association of cholesterol levels with all-cause mortality and a U-shaped relationship with CVD mortality in the presence of inflammation/malnutrition. In marked contrast, there was a strong, graded, positive association of serum cholesterol level with overall and CVD mortality in the absence of inflammation/malnutrition. Thus, some ESRD patients with low serum cholesterol levels are at low risk of mortality, as in the general population, whereas others are at high risk because they are in an inflammatory and/or malnutrition state that lowers cholesterol levels and increases risk of death. These findings corroborate the hypothesis that hypercholesterolemia is a risk factor for all-cause and CVD mortality among persons with ESRD and that this association is masked among individuals with inflammation and/or malnutrition.

Several studies support the notion that high cholesterol level contributes to higher risk of CVD or mortality in dialysis patients.[4] A recent study of 520 Japanese patients receiving hemodialysis reported that non–HDL-C positively predicts CVD mortality.[27] This study population has a much lower annual mortality than the US dialysis population, 4.6% vs 20%,[11] and is almost certainly much healthier. In another recent Japanese study,[2] higher cholesterol levels were associated with lower mortality in persons with low serum albumin levels but were associated with higher mortality in a subgroup with serum albumin values higher than 4.5 g/dL (10% of the study population). Furthermore, an association of statin use with reduced mortality in ESRD patients was reported by Seliger et al.[12]

The mechanism by which systemic inflammation and malnutrition may confound the association between cholesterol and mortality is not entirely clear. A cytokine-mediated acute-phase reaction to acute or chronic inflammation may partially account for hypocholesterolemia in dialysis patients by increasing catabolism and decreasing appetite.[16,28,29] Inhibition of lipoprotein lipase by cytokines increases macrophage uptake of lipids and results in a delayed catabolism of triglyceride-rich apolipoprotein B and a decrease in HDL-C in ESRD patients.[30,31] Low albumin level, a marker for inflammation and malnutrition, has been shown to increase susceptibility to infection and death in dialysis patients.[15] The acute-phase response decreases hepatic synthesis of albumin and increases its catabolism.[32] Thus, much of the observed association of albumin level with outcomes may be attributed to inflammation rather than malnutrition in the ESRD population.[13] Chronic underlying illnesses and acute-phase inflammation may contrib-

Table 4. Risk of All-Cause and CVD Mortality Associated With Non–HDL-C, Stratified by Inflammatory and Nutritional Status

Non–HDL-C, mg/dL	Overall (N = 823)	Presence of Inflammation/Malnutrition (n = 634)	No Inflammation/Malnutrition (n = 189)	*P* Value for Interaction
All-Cause Mortality RH (95% Confidence Interval)				
Categorical measure*				
<130	1.00	1.00	1.00	.003
130-159	0.88 (0.67-1.17)	0.89 (0.66-1.19)	0.91 (0.28-3.00)	
160-189	0.89 (0.67-1.18)	0.83 (0.60-1.15)	2.07 (0.98-4.35)	
≥190	0.83 (0.64-1.06)	0.69 (0.50-0.95)	2.74 (1.06-7.12)	
Continuous measure (per 40 mg/dL)				
Model 1*	0.92 (0.87-0.99)	0.89 (0.83-0.96)	1.33 (1.06-1.66)	.001
Model 2†	0.94 (0.86-1.02)	0.91 (0.83-1.00)	1.50 (1.10-1.96)	.02
Model 3‡	0.96 (0.89-1.03)	0.91 (0.85-0.99)	1.43 (1.09-1.89)	.02
CVD Mortality RH (95% Confidence Interval)				
Categorical measure*				
<130	1.00	1.00	1.00	.23
130-159	1.04 (0.69-1.56)	1.05 (0.69-1.60)	1.06 (0.17-6.40)	
160-189	1.14 (0.76-1.72)	1.16 (0.74-1.82)	2.12 (0.66-6.86)	
≥190	0.91 (0.61-1.36)	0.82 (0.51-1.30)	3.04 (0.67-13.80)	
Continuous measure (per 40 mg/dL)				
Model 1*	0.95 (0.87-1.04)	0.94 (0.85-1.03)	1.27 (0.93-1.74)	.22
Model 2†	0.97 (0.85-1.10)	0.97 (0.85-1.11)	1.72 (1.06-2.81)	.56
Model 3‡	0.97 (0.86-1.10)	0.95 (0.84-1.07)	2.09 (1.02-4.27)	.62

Abbreviations: CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; RH, relative hazard.
SI conversion factor: To convert values for cholesterol to mmol/L, multiply by 0.0259.
*Adjusted for age, race (black, white, other), sex, and clinic.
†Adjusted for model 1 and smoking status, body mass index, dialysis modality, comorbidity score, diabetes, prevalent CVD, congestive heart failure, and systolic blood pressure.
‡Adjusted for model 2 and serum albumin, interleukin 6, and CRP levels.

ute to or cause malnutrition, and some adverse effects of malnutrition, such as wasting and frailty, are mediated by inflammation factors; in this sense, malnutrition and inflammation are often interdependent and difficult to disentangle. Although the acute-phase response causes muscle and weight loss, adipose tissue synthesizes high levels of cytokines. This synthetic capability may explain the slightly higher BMI in persons with inflammation/malnutrition in this study. Another explanation is the high prevalence of diabetes and obesity in the dialysis population. Although patients with inflammation can become malnourished and lose lean body weight, they may stay overweight for a long period, which may explain why high BMI or weight for height percentile was not sufficient to isolate a "healthy" group with a positive relationship between cholesterol and mortality.

It is surprising that total cholesterol level was not positively associated with mortality after serum CRP, IL-6, and albumin levels were controlled for in the overall group or in the subgroup with evidence of inflammation/malnutrition. Residual confounding may still exist. Inflammatory markers were measured only once and are subject to measurement error and physiologic variability because of infection and other acute events. We also may not have accounted for potential confounding effects such as type of dialyzer membrane, other unmeasured or unknown CVD risk factors, and clinical or subclinical illness. Measuring the exact level and nature of inflammation and associated pathophysiologic abnormalities may be more difficult than merely identifying the absence or presence of inflammation. Furthermore, inflammation may interact with other risk factors. For example, inflammation may change lipoprotein structure and function by oxidatively modifying low-density lipoprotein.[33]

Numerous prospective studies have reported a J- or U-shaped relationship between total cholesterol level and mortality in the older and general populations,[6,7,34-37] as well as in various patient populations.[8-10] The Framingham Study[38] reported that spontaneously decreasing cholesterol levels were associated with elevated all-cause mortality and CVD mortality. Excess deaths at low cholesterol levels are thought to have mainly noncardiovascular causes, such as cancer, hemorrhagic stroke, liver disease, suicide, and alcohol dependence syndrome.[35] In the Honolulu Heart Study, Iribarren et al[37] demonstrated that the presence of cancer, liver disease, and hemorrhagic stroke partially explains the inverse association of low cholesterol level and high mortality. Also, they found that the inverse association was seen only in the presence of smoking, high alcohol consumption, or untreated hypertension. Our results imply that inflammation and malnutrition status may also explain the paradoxic association of cholesterol with mortality in populations with evidence of other clinically significant pathophysiologic states.

The present study has a number of limitations. Total cholesterol levels in this study were measured in the nonfasting state. However, similar results were obtained when analyses were repeated with non–HDL-C, the measurement of which is reliable in nonfasting serum.[39] The underlying cause for 198 of the 324 deaths was determined by using the CMS death notification form in the absence of medical records. If individuals with malnutrition and low cholesterol levels were more likely to be assigned as CVD death, a bias would result, leading to an inverse association between cholesterol level and CVD death. Furthermore, analyses were not conclusive for peritoneal dialysis patients because of a relatively small sample size (n=165).

In summary, our data demonstrate that hypercholesterolemia is an independent risk factor for all-cause and CVD mortality in a subgroup of ESRD patients without serologic evidence of inflammation or malnutrition. These data provide evidence of confounding and effect modification of the association of serum cholesterol with mortality by inflammation and/or malnutrition. Not taking into account the effect of inflammation may lead to an incorrect conclusion that high cholesterol is not harmful in ESRD patients and a failure to control cholesterol levels as aggressively as in the general population. Given new observations that statins affect inflammation, in addition to cholesterol, our findings support full implementation of current guidelines for use of statins in preventing CVD in dialysis patients.[4] Large-scale clinical trials to evaluate the mortality benefit of even more aggressive lowering of cholesterol levels and inflammation with statins in this population are warranted, given evolving rationale that the aggressiveness of cholesterol lowering should be driven by overall patient risk rather than cholesterol levels.[40,41] Finally, the possibility that an observed association between a risk factor and outcome is distorted by inflammation and malnutrition should be evaluated in the general population, particularly in smokers, elderly individuals, and those with chronic diseases.

Author Contributions: Drs Coresh and Liu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Liu, Coresh, Eustace, Longenecker, Fink, Powe, Klag.
Acquisition of data: Liu, Coresh, Longenecker, Jaar, Fink, Tracy, Powe, Klag.
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Drafting of the manuscript: Liu.
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