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Inverse Association between Lipid Levels and Mortality in Men with Chronic Kidney Disease Who Are Not Yet on Dialysis: Effects of Case Mix and the Malnutrition-Inflammation-Cachexia Syndrome

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High total cholesterol is associated with lower mortality in dialysis patients, but the relationship between lipid levels and mortality in patients who have chronic kidney disease (CKD) and are not yet on dialysis is poorly described. This study examined the association between lipid levels and all-cause and cardiovascular mortality in 986 male patients (age 67.4 ± 10.9 yr; race 23.7% black) who had CKD and were not yet on dialysis. Associations were determined in fixed-covariate and time-dependent Cox models, before and after adjustment for components of case mix and surrogates for malnutrition-inflammation-cachexia syndrome (MICS). Lower total cholesterol quartiles were associated with higher all-cause mortality in a fixed-covariate model that was adjusted for age, race, and body mass index (hazard ratio [95% confidence interval] for cholesterol <153, 153 to 182, and 183 to 215 versus >215 mg/dl: 1.91 [1.35 to 2.69], 1.36 [0.96 to 1.92], 1.10 [0.78 to 1.57]; P < 0.001 for trend), but this association was attenuated after adjustment for case mix (P = 0.023 for trend) and abolished after additional adjustment for MICS (P = 0.14 for trend), with time-dependent Cox models showing similar results. Similar tendencies also were detected in the association between levels of LDL cholesterol with total and cardiovascular mortality and triglycerides with all-cause mortality in both fixed-covariate and time-dependent analyses. Lower lipid levels are associated with higher mortality in patients who have moderate and advanced CKD and are not yet on dialysis. This inverse association is explained in part by case-mix characteristics and the presence of surrogates for MICS.


The association between lipid abnormalities (higher total cholesterol, LDL cholesterol, and triglycerides and lower HDL cholesterol) and increased mortality is established firmly in the general population (1,2). Contrasting with this, numerous observational studies have documented an increased mortality associated with lower total cholesterol level in patients who had chronic kidney disease (CKD) and received renal replacement therapy (RRT) (3–9). Given the high mortality rate that is experienced by patients with CKD and the preponderance of cardiovascular causes that are responsible for this (10–12), the observed inverse association between total cholesterol and mortality in patients with CKD has become a topic of significant interest (13). Although patients with CKD who are not yet receiving RRT clearly outnumber those who are on RRT (14), there is a paucity of information about the lipid levels that are found in these patients and the outcomes that are associated with these levels. In addition, descriptive studies that have explored the association of a single baseline lipid level with various outcomes cannot account for the longitudinal variation of lipids or for therapeutic interventions that were instituted after the evaluation period but before the occurrence of an outcome. We sought to examine all-cause and cardiovascular mortality as a function of lipid levels in a historical, prospective cohort of patients who had moderate and advanced CKD and were not receiving RRT. We collected data on pertinent clinical and biochemical characteristics and therapeutic interventions longitudinally to capture temporal variations and their effects on outcomes.

Materials and Methods

Study Population

Patients who were evaluated for management of CKD at Salem VA Medical Center (VAMC) between January 1, 1990, and June 30, 2005, were included. After exclusion of patients who were on dialysis and...
those with a kidney transplant, a total of 1012 patients were identified. Ten patients had no lipid measurement and were excluded. Because only five (0.49%) patients were of a race other than black or white and only 11 were female (1.09%) in the cohort, they were excluded from further analyses. The final analysis included 986 patients.

Data Collection

Baseline demographic and anthropometric information; comorbidities; BP measurements; use of hepatic hydroxymethyl glutaryl-CoA reductase inhibitors (statins), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB), and aspirin; and laboratory measures were collected at the time of initial contact with the patients. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Diabetes was defined as the presence of an abnormal fasting glucose level or antidiabetic therapy, and atherosclerotic cardiovascular disease was defined as a previous history of cardiovascular, cerebrovascular, or peripheral vascular disease. Variables that were expected to change during follow-up (BP, BMI, medication use, and laboratory values) then were collected longitudinally, and values for continuous variables were averaged over 6-mo time periods. Fasting or nonfasting levels of total cholesterol, LDL cholesterol, triglycerides, and HDL cholesterol also were collected at baseline and subsequently every 6 mo when available. Of the 986 patients with measurement of total cholesterol level, 870 (88%) had at least one LDL cholesterol measurement, 883 (89%) had at least one triglyceride measurement, and 879 (89%) had at least one HDL measurement available. All measurements were performed in a single clinical laboratory at Salem VAMC. Total cholesterol, LDL cholesterol, triglyceride, and HDL cholesterol were measured on a Beckman LX autoanalyzer using a colorimetric assay (Beckman Industries, Irvine, CA).

Outcomes

Patients were followed until death or loss to follow-up or until April 5, 2006, with the recording of death and RRT. The 30 patients who were lost to follow-up were not different from those with a kidney transplant, a total of 1012 patients were identified. Ten patients had no lipid measurement and were excluded. Because only five (0.49%) patients were of a race other than black or white and only 11 were female (1.09%) in the cohort, they were excluded from further analyses. The final analysis included 986 patients.

Data Collection

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Survival Modeling

The starting time for survival analysis was the date of the initial nephrology encounter, and the outcome measures were total and cardiovascular mortality. Patients were followed until death or until April 15, 2006. Patients who died were censored at the date of death, and patients who were lost to follow-up were censored at the date of the last documented contact with the medical center. Because cause of death was available only for deaths that occurred before January 1, 2005, patients were censored at this date in analyses using cardiovascular mortality as outcome. Event rates were calculated using the person-years approach. Unadjusted and multivariable-adjusted association of total cholesterol, LDL cholesterol, triglycerides, and HDL cholesterol with all-cause and cardiovascular mortality were examined in fixed-covariate and time-dependent Cox models. Multivariable models were created after a priori adjustment for demographic and anthropometric characteristics (age, race, and BMI; model 1), additional case mix excluding surrogates of the malnutrition-inflammation-cachexia syndrome (MICS; comorbidities, smoking, BP, kidney function, proteinuria, calcium, phosphorus, and medication use; model 2), and after adjustment for all of the above plus markers that are associated with MICS (albumin, WBC, hemoglobin, percentage of lymphocytes in WBC, and bicarbonate; model 3). Given the relatively large number of missing values for BMI (17.4% of all patients had no recorded BMI level), we performed analyses with models that included only BMI values that actually were measured and with models that used multiple imputations to account for the missing BMI values. Results are presented for the models that included actually measured BMI values. Nonlinear associations were explored by inclusion of quadratic terms. Effect modification was explored by performing subgroup analyses by age, race, diabetes status, categories of kidney function, and use of statins. Analyses also were repeated in subgroups with and without the presence of markers of MICS, defined as patients with one or more of the following: Serum albumin level <10th percentile, WBC >90th percentile, or percentage of lymphocytes in WBC of <10th percentile. Analyses were repeated with the main outcomes restricted to predialysis events with censoring of patients at the time of initiation of RRT. The proportionality assumption was tested using plots of log (−log [survival rate]) against log (survival time) and by comparing predicted with actual survival curves. P < 0.05 was considered significant. Statistical analyses were performed using STATA statistical software version 8 (STATA Corp., College Station, TX). The study protocol was approved by the Research and Development Committee at the Salem VAMC.

Results

The mean baseline age of the 986 patients was 67.4 ± 10.9 yr, 23.7% were black, and 54.9% had diabetes. The mean baseline estimated GFR (eGFR) was 37.4 ± 17.6 ml/min per 1.73 m². Baseline characteristics for patient groups divided by quartiles of total cholesterol level are presented in Table 1. Patients with lower total cholesterol level were older; had lower levels of BP, albumin, calcium, hemoglobin, and proteinuria; and had higher use of statins, aspirin, and ACEI/ARB. The characteristics of the 30 patients who were lost to follow-up were not different
Table 1. Baseline characteristics of individuals stratified by categories of total cholesterol level

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Cholesterol (mg/dl)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;152</td>
<td>152 to 215</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>68.7 ± 10.9</td>
<td>68.8 ± 10.4</td>
</tr>
<tr>
<td>Race (% black)</td>
<td>60 (24.1)</td>
<td>50 (20.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>151 (60.6)</td>
<td>130 (53.5)</td>
</tr>
<tr>
<td>ASCVD</td>
<td>165 (66.3)</td>
<td>152 (62.5)</td>
</tr>
<tr>
<td>Smoking</td>
<td>60 (25.6)</td>
<td>60 (26.3)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.5 ± 5.8</td>
<td>28.3 ± 5.3</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>144.5 ± 24.8</td>
<td>154.0 ± 26.6</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>71.3 ± 15.9</td>
<td>74.2 ± 14.9</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m²)</td>
<td>36.7 ± 16.0</td>
<td>37.2 ± 17.6</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.5 ± 0.5</td>
<td>3.6 ± 0.4</td>
</tr>
<tr>
<td>Bicarbonate (mg/dl)</td>
<td>25.5 ± 3.8</td>
<td>25.4 ± 3.6</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.1 ± 0.6</td>
<td>9.1 ± 0.6</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>3.8 ± 0.8</td>
<td>3.8 ± 0.7</td>
</tr>
<tr>
<td>Hgb (g/dl)</td>
<td>12.3 ± 1.9</td>
<td>12.6 ± 1.8</td>
</tr>
<tr>
<td>WBC count (1000/mm³)</td>
<td>7.1 (6.8 to 7.4)</td>
<td>7.3 (7.0 to 7.5)</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>22.4 ± 10.1</td>
<td>22.8 ± 8.0</td>
</tr>
<tr>
<td>Proteinuria (mg/24 h)</td>
<td>586 (495 to 692)</td>
<td>745 (610 to 910)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>102 (45.9)</td>
<td>101 (40.3)</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>162 (73.0)</td>
<td>156 (62.9)</td>
</tr>
<tr>
<td>Statins</td>
<td>116 (46.6)</td>
<td>103 (42.4)</td>
</tr>
</tbody>
</table>

aData are means ± SD, n (% of total), or geometric means (95% confidence interval). Comparisons are made by ANOVA or χ² test. ACEI/ARB; angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; DBP, diastolic BP; Hgb, hemoglobin; SBP, systolic BP; WBC, white blood cell.

(design not shown). Table 2 presents baseline and time-averaged total cholesterol, LDL cholesterol, triglyceride, and HDL cholesterol levels by categories of baseline levels of eGFR. Patients with higher eGFR had significantly higher total cholesterol and triglyceride levels, but their levels of LDL and HDL cholesterol were not different from those with lower eGFR. A total of 478 (48.4%) patients died (46.4% of them from cardiovascular causes), and 218 patients (22.7%) started dialysis over a median follow-up of 3.0 yr (total time at risk 3499 patient-years). The overall mortality rate (95% CI) was 136.6 deaths/1000 patient-years (124.9 to 149.4).

Figure 1 shows the hazard ratios (HR; 95% CI) of all-cause and cardiovascular mortality in groups divided by quartiles of total cholesterol in fixed-covariate Cox models, with incremental adjustments for demographic and anthropometric characteristics, case mix, and MICS. Lower total cholesterol was associated with higher all-cause mortality in the fixed-covariate model that was adjusted for age, race, and BMI (HR [95% CI] for 1 ln-unit lower cholesterol level: 2.74 [1.69 to 4.44]; P < 0.001) but with attenuation of this association after adjustment for case mix (2.02 [1.25 to 3.23]; P = 0.004) and after additional adjustment for MICS (1.71 [1.08 to 2.72]; P = 0.022). Similar tendencies were apparent in the association of cholesterol with cardiovascular mortality (HR [95% CI] for 1 ln-unit lower cholesterol level in the three models: 2.38 [1.00 to 5.62], 1.98 [0.84 to 4.62], and 1.62 [0.70 to 3.73]). Time-dependent Cox models also yielded results that were analogous to the fixed-covariate models.

Figure 2 shows the HR of all-cause and cardiovascular mortality associated with various quartiles of LDL cholesterol in fixed-covariate Cox models. The association of LDL cholesterol level with all-cause and cardiovascular mortality was similar to that found for total cholesterol, with lower LDL cholesterol quartiles showing an association with higher mortality in the models that were adjusted for age, race, and BMI and an attenuation of this association in the models that were adjusted further for case mix and MICS. Fixed-covariate Cox models with LDL cholesterol as a continuous variable showed similar tendencies (HR [95% CI] of 1 ln-unit lower LDL cholesterol level in the three models for all-cause mortality: 1.72 [1.23 to 2.43], 1.36 [0.95 to 1.96], and 1.26 [0.87 to 1.81]; for cardiovascular mortality: 1.85 [1.03 to 3.33], 1.61 [0.85 to 3.03], and 1.42 [0.74 to 2.77]). Time-dependent Cox models yielded similar results.
Table 2. Baseline and time-averaged levels of total cholesterol, LDL cholesterol, triglycerides, and HDL cholesterol by categories of baseline eGFR\(^a\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline eGFR (ml/min per 1.73 m(^2))</th>
<th>15 to 30</th>
<th>31 to 60</th>
<th>&gt;60</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>baseline</td>
<td>191 (177 to 207);</td>
<td>184 (178 to 189);</td>
<td>184 (180 to 189);</td>
<td>199 (187 to 211);</td>
</tr>
<tr>
<td></td>
<td>time averaged</td>
<td>164 (159 to 170);</td>
<td>175 (173 to 176);</td>
<td>183 (182 to 185);</td>
<td>193 (189 to 196);</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>baseline</td>
<td>124 (103 to 148);</td>
<td>106 (101 to 111);</td>
<td>105 (101 to 109);</td>
<td>108 (98 to 119);</td>
</tr>
<tr>
<td></td>
<td>time averaged</td>
<td>104 (91 to 119);</td>
<td>103 (100 to 106);</td>
<td>104 (102 to 106);</td>
<td>104 (100 to 108);</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>baseline</td>
<td>177 (138 to 227);</td>
<td>167 (155 to 180);</td>
<td>175 (165 to 185);</td>
<td>215 (181 to 254);</td>
</tr>
<tr>
<td></td>
<td>time averaged</td>
<td>176 (152 to 204);</td>
<td>168 (161 to 176);</td>
<td>178 (173 to 183);</td>
<td>209 (194 to 225);</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>baseline</td>
<td>36 (30 to 43);</td>
<td>37 (36 to 38);</td>
<td>36 (35 to 37);</td>
<td>36 (34 to 40);</td>
</tr>
<tr>
<td></td>
<td>time averaged</td>
<td>37 (34 to 41);</td>
<td>36 (35 to 37);</td>
<td>36 (35 to 37);</td>
<td>36 (35 to 37);</td>
</tr>
</tbody>
</table>

\(^a\)Data are geometric means (95% confidence interval) with the number of patients in each category (for baseline values) and number of total measurements in each category (for time-averaged values) shown. Comparisons are made by ANOVA. eGFR, estimated GFR.

As shown in Figure 3, lower triglyceride quartiles were associated with higher all-cause mortality (with an attenuation of the association after sequential adjustments for case mix and MICS), but no significant association was apparent between triglyceride levels and cardiovascular mortality. Analyzing triglycerides as continuous variables yielded concordant results in both fixed-covariate and time-dependent Cox models. There was no significant association between HDL cholesterol level and all-cause or cardiovascular mortality (Figure 4). The results remained consistent in subgroup analyses that were performed in categories that were divided by age, race, diabetes status, eGFR, and treatment with statins or when examined in patients with or without the presence of MICS. Inclusion of imputed data points for BMI also did not alter the outcomes significantly. The results also were similar when only mortality before the initiation of RRT was analyzed.

**Discussion**

We describe the association of lower total and LDL cholesterol with higher all-cause and cardiovascular mortality and of lower triglyceride levels with higher all-cause mortality in patients who had CKD and were not yet on dialysis. We found that although this association was significant after adjustment for demographic and anthropometric characteristics, it was attenuated after adjustments for both case mix and for surrogates of MICS.

Several observational studies have documented an association between lower total cholesterol and higher mortality in patients who have CKD and receive RRT (3–9). This phenomenon represents a seemingly paradoxical reversal of the well-established association of higher lipid levels with mortality in the general population (1,2). Given the extremely high mortality rates that were observed in patients who had CKD and were on RRT, the majority of which are related to cardiovascular causes (10), the role of lipid levels as causative factors in this mortality has been a matter of great interest and controversy. In an attempt to explain the inverse association between total cholesterol level and mortality in patients who are on dialysis, Liu et al. (6) showed that higher total cholesterol, in fact, was associated with increased mortality in a subset of patients without evidence of inflammation and malnutrition, whereas patients with such evidence retained the inverse association that was the characteristic of their overall patient cohort. A similar interaction was described by Iséki et al. (5), who showed higher mortality with higher total cholesterol only in dialysis patients with serum albumin levels >4.5 g/dl. These results suggested that lower total cholesterol was in fact a surrogate marker of inflammation and/or malnutrition; therefore, therapy that is directed toward lowering cholesterol should not be withheld, especially given the additional, potentially beneficial non-lipid-related effects of statins (the most widely used cholesterol-lowering drugs) (17,18). Surprising, however, the only completed clinical trial aimed at improving outcomes through lipid...
lowering with a statin in patients who had diabetes and were on dialysis (19) did not show a significant reduction in the composite outcome of death from cardiac causes, nonfatal myocardial infarction, and stroke. An alternative explanation for the inverse association between cholesterol and mortality is a true protective effect of higher lipid levels. The hypothesis championed by Rauchhaus et al. (20,21) suggests that binding of lipoproteins to bacterial endotoxins may result in reduced inflammation; therefore, higher lipoprotein levels may be of benefit. Indeed, contrasting the studies by Liu et al. and Iseki et al., other studies in patients who were on RRT could not account for the inverse association between total cholesterol and mortality by adjusting for surrogates of MICS (7,8).

It is unclear whether findings from studies of patients who are on dialysis or other patient populations can be extrapolated to patients who have CKD and are not yet on dialysis. In 807 participants with eGFR of 15 to 60 ml/min per 1.73 m² from the Atherosclerosis Risk in Communities (ARIC) study, Muntner et al. (22) showed a higher relative risk for incident coronary heart disease with higher total cholesterol and triglyceride levels, compared with patients with no CKD. Conversely, in 1249 elderly patients who had moderate CKD (eGFR 50 ± 10 ml/min per 1.73 m²) and participated in the Cardiovascular Health Study, none of the lipid parameters examined (LDL cholesterol, triglycerides, and HDL cholesterol) was associated with cardiovascular mortality (23). Our study is, to our knowledge, the first to examine associations of all components of the lipid panel with all-cause and cardiovascular mortality in a patient population with moderate and advanced CKD. We examined the associations between single baseline values of the components of the lipid panels (fixed-covariate models) but also conducted time-dependent analyses to account for the effects of temporal changes in lipid levels, therapeutic agents, and various clinical and biochemical characteristics, the last yielding similar results to the fixed-covariate models. We found that both case-mix characteristics and MICS play a significant role in the observed inverse association between lipid levels and mortality. The inverse association between total cholesterol, LDL cholesterol, and triglycerides and mortality was weakened after adjustment for case mix and was attenuated further (and mostly rendered nonsignificant) after adjustment for MICS. We did not detect interactions with markers of MICS; therefore, we
cannot claim that lower lipid levels are merely surrogates of MICS. Although better powered observational studies in the future may be able to discern more precisely the relative contribution of various patient characteristics (including MICS) to the inverse association between lipids and mortality, the ultimate answer should be provided by the completion of several randomized, controlled trials that currently are examining the effect of lipid-lowering therapy on clinical outcomes in patients with CKD (24,25).

Several shortcomings of our study need to be emphasized. This being an observational study, we cannot establish causality, only associations from our results. We examined an exclusively male patient group from a single medical center; therefore, our results may not be generalizable to women or to patients from other geographic areas. Given the retrospective nature of our study, we could not establish whether lipid measurements were performed in a fasting state. Not all of the patients with measurements of total cholesterol levels had LDL, triglyceride, or HDL measurements available, and this may have limited the power of our analyses relating to these components, especially when examining cardiovascular outcomes, given the lower number of cardiovascular events combined with the shorter follow-up period for this outcome. Although we attempted to account for several potential confounders, residual confounding cannot be ruled out. Most important, we did not have direct measurements of inflammation (e.g., C-reactive protein, IL-6) available to confirm the presence or absence of MICS. We used instead a combination of widely available markers that have been shown to be associated with MICS (26–28), but we cannot rule out the presence of residual confounding and resulting misclassification of patients with inflammation. We enrolled patients over an extended period of time; therefore, changes in therapeutic practices over time may have influenced our outcomes. We tried to minimize the impact of this by using data from a single center and by accounting for temporal changes in the application of certain therapeutic agents (e.g., statins, ACEI/ARB) as well as clinical and biochemical characteristics that may reflect the changing practices (e.g., BP, cholesterol level, hemoglobin level).

**Conclusion**

Our study shows an association between lower total and LDL cholesterol with higher all-cause and cardiovascular mortality and between lower triglyceride levels and higher all-cause mortality in patients who have CKD and are not yet on RRT. This association seems to be explained in part by case-mix...

*Figure 3. HR (95% CI) of all-cause and cardiovascular mortality associated with various levels of triglycerides in a fixed-covariate Cox model. Adjustments were made for age, race, and BMI (model 1); age, race, BMI, comorbidities, smoking, BP, kidney function, proteinuria, calcium, phosphorus, and medication use (model 2); and age, race, BMI, comorbidities, smoking, BP, kidney function, proteinuria, calcium, phosphorus, medication use, albumin, WBC count, hemoglobin, percentage of lymphocytes in WBC, and bicarbonate (model 3). The group with triglyceride level of >258 mg/dl served as reference.*
characteristics of the studied population and by the presence of surrogates of the MICS. We caution against translating results of observational studies into therapeutic practice, no matter how compelling those results might be. Results from clinical trials that currently are under way (24,25) could provide definitive answers.

Disclosures
None.

References
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