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Editorial

Failure of Statins to Improve Outcomes in Dialysis Patients: Does Peritonitis Modify the Impact of Lipids on Cardiovascular Events?

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See article by Ye et al., pages 92–99 of this issue.

It is well known that cardiac mortality is exceedingly high in chronic dialysis patients. Because disturbances in plasma lipoprotein metabolism are also frequently observed in dialysis patients, it was assumed that they would benefit from lipid-lowering treatment. And indeed, treatment with statins appeared to be safe and to improve lipid profiles of chronic dialysis patients.[1,2] However, 3 large randomized placebo-controlled trials failed to show a reduction in cardiovascular mortality in dialysis patients.[3-6] The absence of reduction of cardiovascular mortality was confirmed by several meta-analyses,[7-9] although some showed a reduction in cardiovascular events.[8] These data lead to the advice of the 2014 Kidney Disease Improving Global Outcomes (KDIGO) group not to prescribe statins to dialysis patients, although they still recommended that statins could be continued in patients who started dialysis and already were treated with these drugs.[10,11] Despite these guidelines, a recent study found that 83% of 77 nephrologists surveyed prescribed statins in dialysis patients for secondary prevention of cardiovascular events.[12]

The question is why low-density lipoprotein cholesterol (LDL-C)–lowering treatment with the use of statins is effective in patients without kidney disease, even in chronic kidney disease, but not in dialysis patients.[13] Standard cardiovascular risk factors do not fully explain the high incidence of cardiovascular events or increased mortality rates.[14] Inflammation and oxidative stress have been linked to the pathogenesis of plaque formation and plaque rupture, and both are linked to worse cardiovascular outcomes. Inflammatory stress also results in statin resistance.[15] Disordered mineral and bone metabolism plays a role in in the pathogenesis of coronary disease and results in increased coronary artery calcification (CAC). A higher CAC score is associated with increased mortality, and statin therapy was associated with greater progression of CAC.[16] That study suggested that we might even harm our dialysis patients by prescribing statins.

In this issue of the *Journal*, Ye et al. describe the relationship between LDL-C at the start of dialysis and cardiovascular events in a large group of patients treated with peritoneal dialysis.[17] As in most previous publications, no relationship was found between LDL-C and cardiovascular events in the entire population. New to this study is that they included the presence or absence of peritonitis in their analysis. They found that low LDL-C was a risk factor for peritonitis. Furthermore, higher LDL-C was associated with increased risk of first cardiovascular events in peritonitis-free patients, whereas in patients who experienced peritonitis, higher LDL-C decreased the risk of first cardiovascular events. Similar results were also observed between LDL-C and mortality. Peritoneal dialysis patients with lower baseline LDL-C had a higher risk of peritonitis.

Because these data were analyzed retrospectively in a cohort of incident patients, no statement can be made about the causality of the data. For the association between LDL-C and peritonitis, the authors suggested 2 possible causes. First, low LDL-C could be linked to malnutrition, which is associated with increased risk of infections. Because the authors in their analysis corrected for serum albumin as a surrogate marker for nutrition, they also speculated on the roles of lipids in the complex host-pathogen relationship.[18] However, peritonitis during peritoneal dialysis is usually considered to be a localized infection, and no data are available on the effects of LDL-C on macrophages present in the peritoneal cavity.

The relationship between LDL-C and cardiovascular events in peritonitis-free patients also remains a puzzle. Although in earlier studies systemic inflammation was suggested as a cause for the absence of a relationship in dialysis patients, not only peritonitis but many other factors, such as carbonyl stress secondary to accumulation of advanced glycosylation end-products present in the dialysate, contribute to inflammation.[19] As the authors also discuss, drop-out due to peritonitis might have influenced the results.

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Despite the fact that the associations found cannot be directly linked to pathophysiologic processes, this study is valuable. Studies on lipids are rare in peritoneal dialysis patients. Only 1 of the 3 studies on which the KDIGO guidelines were based, the AURORA study (**A** Study to Evaluate the **U**se of **R**osuvastatin in Subjects **o**n **R**egular Hemodialysis: An **A**ssessment of Survival and Cardiovascular Events), included 496 peritoneal dialysis patients. The other 2 studies included only hemodialysis patients (**D**ie **D**eutsche **D**iabetes **D**ialyse Studie [4D] study 1255 patients, **S**tudy **H**eart **a**nd **R**enal **P**rotection [SHARP] study 2527 patients and AURORA study 2776 patients). The number of patients included in the cohort of the Ye study[17] was more than 3 times as large, had a long follow-up, and contained a lot of clinical data. Disadvantages of this study were the retrospective analysis of previously obtained data, the fact that it was a single-center study, and the possibility of both patient and doctor biases. Because the occurrence of peritonitis is not a predictable factor, confirming these results in other cohorts seems to be the first step to further analysis. If these data are confirmed, further research into the relationship between lipids and peritonitis would be desirable.

Disclosures

The author has no conflicts of interest to disclose.

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