Impact of Dyslipidemia in End-Stage Renal Disease

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Abstract. Heart disease is a major cause of morbidity and mortality among patients with renal failure. Premature atherosclerotic coronary heart disease is driven by multiple risk factors, including dyslipidemia and oxidative stress. In the nondialysis population, there is overwhelming evidence that treatment of dyslipidemia can significantly improve cardiovascular outcomes. Accumulating data indicate that dialysis patients have atherogenetic lipid abnormalities. Although LDL cholesterol (LDL-C) levels in patients who undergo hemodialysis are normal or near normal, increased oxidized LDL-C, triglycerides, and lipoprotein (a) [Lp(a)]; decreased HDL cholesterol (HDL-C); and triglyceride-rich VLDL have been noted. Patients who receive peritoneal dialysis have a more atherogenic lipid profile with increased LDL-C, apolipoprotein B, oxidized LDL-C, triglycerides, and Lp(a) and decreased HDL-C. Furthermore, the LDL particles of peritoneal dialysis patients are small and dense. However, there is a dearth of information regarding the goals, efficacy, and safety of dyslipidemia treatment among dialysis patients. Given the strong evidence of risk reduction and the benefits of lipid-lowering treatment in the nondialysis population, the emerging consensus is that dialysis patients should be treated aggressively for dyslipidemia to an LDL-C goal below 100 mg/dl. Although physicians and patients may be reluctant to add medications because of concerns about polypharmacy, potential decreased compliance, and increased cost, the use of agents such as sevelamer that can serve multiple functions, including phosphate control, lipid lowering (decreased LDL-C and total cholesterol), and anti-inflammatory effects (decreased high-sensitivity C-reactive protein), should be explored and considered for patients who would benefit from such treatment.

Epidemiology
Regardless of age, heart disease is a major cause of morbidity and mortality among patients with renal failure. Mortality in dialysis patients is dramatically higher than in the general population, and cardiovascular disease (CVD) is the leading cause of mortality among these patients (1). Atherosclerotic heart disease is believed to account for approximately 55% of mortality and contributes to a 20-fold increase in ischemic heart disease and to a 10-fold increase in risk of stroke among patients with ESRD (chronic kidney disease stage 5) (2). The risk for heart disease or subclinical or clinical disease exists even as patients enter dialysis treatment. In the United States Renal Data System (USRDS) Wave 2 study, for example, the prevalence of ischemic heart disease and cardiac failure was approximately 40% before renal replacement, much higher than the 2 to 26% reported in the general population (3). In a Canadian study, baseline echocardiography identified 74% of patients entering first-time dialysis treatment with left ventricular (LV) hypertrophy (4). In the same study, 32% of patients had LV dilation and 15% had systolic dysfunction. It is likely that both preexisting and new-onset CVD contribute to the high mortality in patients with ESRD. Identifying and reducing the causes of CVD and its associated risk factors in this patient population should go a long way toward improving outcomes in patients with ESRD.

Risk Factors for Coronary Artery Disease among Dialysis Patients
Patients with ESRD are at a particularly high risk for coronary artery disease (CAD) or atherosclerotic coronary heart disease (ASCVD). There are traditional and nontraditional risk factors that contribute to the high incidence of CAD in this population (5). Multiple atherosclerotic risk factors recognized as “traditional” risk factors for ischemic heart disease exist in dialysis patients. These include hypertension, diabetes, dyslipidemia, and hyperhomocysteinemia (Table 1). In addition to these, other risk factors that may be exaggerated in the uremic patient or are unique to uremia must be considered and would be classified as nontraditional. These include disturbances of calcium and phosphate, inflammation, and oxidative stress.

In a cross-sectional study of 1041 dialysis patients, the prevalence of atherosclerotic risk factors at the beginning of ESRD was compared with estimates of risk factors in normal adults from the US population derived from the Third National Health and Nutrition Examination (NHANES III) (6). That study found that dialysis patients had a high prevalence of diabetes (54%), hypertension (96%), LV hypertrophy by electrocardiogram (EKG) criteria (22%), low physical activity (80%), hypertriglyceridemia (36%), and low HDL cholesterol (HDL-C; 33%). These patients were also more likely to be older, black, and male when compared with the non-ESRD NHANES III participants. After adjustment for age, race, gender, and atherosclerotic CVD, the prevalence of diabetes, hypertension, LV hypertrophy by EKG, low physical activity,
Table 1. Summary of risk factors for coronary artery disease among dialysis patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>High LDL-C</td>
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<tr>
<td>Lipoprotein (a)</td>
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<tr>
<td>Low HDL-C</td>
</tr>
<tr>
<td>Oxidized LDL</td>
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<tr>
<td>Inflammation</td>
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<tr>
<td>Hypoalbuminemia</td>
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<tr>
<td>Homocysteine</td>
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<tr>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Calcium/phosphate</td>
</tr>
<tr>
<td>?Leptin</td>
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<tr>
<td>Insulin levels</td>
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<tr>
<td>Abdominal obesity</td>
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<tr>
<td>Advanced glycation end products</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Smoking</td>
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<tr>
<td>Family history</td>
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<tr>
<td>Hypertension</td>
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<td>Diabetes</td>
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LDL-C, LDL cholesterol; HDL-C, HDL cholesterol.

low HDL-C, and hypertriglyceridemia were still found to be more common among patients with ESRD than among normal subjects. The projected 5-yr atherosclerotic CVD risk among patients older than 40 yr and without atherosclerotic disease was more than twice as high (13%) for patients with ESRD compared with normal participants (6%).

Other risk factors that often are found to be present in ESRD and that may contribute to increased risk of ASCHD include inflammatory syndromes (7), abnormalities of coagulation (8), hyperhomocysteinemia (9), and disturbance of calcium and phosphate metabolism, which has been linked to increased cardiovascular mortality risk in patients with chronic renal failure (10–12). Thus, patients with ESRD seem to have a greater number and prevalence of risk factors than the general population, and these factors seem to contribute to an increased risk of subsequent atherosclerotic disease. The relative contributions of these risk factors, appropriate treatment strategies, and whether target goals should be different in this population relative to the general population are questions that should be explored further. This article focuses on the quantitative and qualitative changes in lipid profiles as important risk factors for ASCHD among dialysis patients. It also provides an overview of the potential treatments for risk reduction as a result of dyslipidemia and how such treatment should be integrated into the overall care of the patient who is on renal replacement therapy.

The Lipid Hypothesis: Lipids and CVD

Evidence for the importance of lipids as risk factors in CVD has come from animal studies, studies of familial hypercholesterolemia, population studies, and clinical studies. Although these data are not specifically from ESRD populations, they nonetheless serve to illustrate the importance of dyslipidemia as a risk factor for atherosclerosis and highlight how lipid-normalizing treatment can help lower such risk. New Zealand white rabbits that are fed a high-cholesterol (2%) diet develop atherosclerotic lesions more rapidly than those that are fed a normal diet and have long been used as animal models of atherosclerosis. In the Watanabe heritable dyslipidemia (WHHL) model—a model for familial hypercholesterolemia—atherosclerosis develops prematurely from fatty streaks and has been attributed to low LDL receptor levels. Recently, transgenic WHHL rabbits expressing human apolipoprotein (a) have been shown to develop more advanced lesions and vascular calcification than nontransgenic animals (13). Although a detailed review of animal models and the data accrued from them is beyond the scope of this article, this type of data supports the importance of dyslipidemia in the cause of atherosclerotic lesions.

Further understanding of the molecular basis of cholesterol metabolism and its critical effect on atherosclerosis has also come from studies of inborn errors of LDL metabolism, such as familial hypercholesterolemia, an inherited form of hypercholesterolemia that is caused by a mutation of the LDL receptor gene leading to an accumulation of LDL cholesterol (LDL-C) and the development of severe premature atherosclerosis. These patients are at high risk for premature CVD, including myocardial infarction (MI) and death in the third to sixth decades of life (14).

The role of lipids in the cause of atherosclerosis and the importance of therapies in the reduction of risk have been confirmed in population studies and innumerable clinical studies. The United States National Heart, Lung, and Blood Institute’s Framingham study, for example, demonstrated in the early 1960s that high cholesterol increases the risk of heart disease (15). Further studies have defined a negative role for high triglycerides, LDL-C, and lipoprotein (a) (Lp[a]) as risk factors for heart disease. Data have also shown that increasing HDL-C can decrease the risk of death.

Clinical data corroborate the link between serum LDL-C and CAD and support the reduction of cholesterol as a means of reducing congestive heart disease (CHD) mortality and total mortality. Several quantitative angiographic studies have demonstrated a decreased rate of progression—or even regression—of coronary atherosclerotic lesions when LDL-C-reducing treatments are administered (16–20).

In a meta-analysis of 38 studies using cholesterol lowering as an intervention, Gould et al. (21) found that for every 10% decrease in cholesterol, there is a 15% decrease in CHD mortality ($P < 0.001$) and an 11% decrease in total mortality ($P < 0.001$). Even greater benefits have been noted in clinical trials using HMG-CoA reductase inhibitors or statins as lipid-lowering agents. In the Scandinavian Simvastatin Survival Study, cholesterol lowering with simvastatin was found to reduce total cholesterol by 25%. LDL-C by 35%, and triglycerides by 10% and to increase HDL-C by 8% (22). The overall reduction in total mortality as a result of treatment was 30% (relative risk [RR] = 0.70; 95% confidence interval [CI], 0.58 to 0.85; $P = 0.0003$). The study also showed a 34% RR
reduction of a major coronary event with treatment \((RR = 0.66; 95\%\, CI, 0.59 to 0.75; P < 0.00001)\). In the Cholesterol and Recurrent Events trial, pravastatin treatment reduced total cholesterol by 20\%, LDL-C by 28\%, and triglycerides by 14\% and increased HDL-C by 5\% \((23)\). This translated to a reduction in risk of a fatal coronary event or nonfatal MI of 24\% \((P = 0.003)\).

It is clear that there is an association between high LDL-C and CAD in the general population. A combination of elevated LDL-C, elevated triglycerides, and low HDL-C seems to be particularly atherogenic. In addition, high concentrations of Lp(a), a cholesterol-rich lipoprotein with an LDL particle linked to apolipoprotein (a), has been associated with high risk for CAD \((24,25)\). The compelling evidence linking dyslipidemia with CAD and showing benefits of cholesterol reduction or lipid-normalizing strategies led to the recommendation by the American Heart Association that patients with CAD be treated with lipid-lowering agents \((26)\). The Adult Treatment Panel III (ATP III) guidelines recently issued by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults focus on LDL-C as the chief target of lipid-lowering therapy. The ATP III report recommends an LDL-C target of less than 100 mg/dl as optimal for all patients \((27)\).

**Lipid Abnormalities in ESRD**

Among patients with ESRD and uremia, a number of lipid abnormalities have been identified. Although information remains incomplete, accumulating evidence indicates that the kind of dyslipidemia is often related to the type of renal replacement therapy: peritoneal dialysis or hemodialysis \((28)\) (Figure 1).

**Hemodialysis**

Hemodialysis patients often have normal or near-normal levels of total cholesterol and LDL-C \((28)\). Approximately 20 to 40\% of hemodialysis patients have been estimated to have elevated triglycerides and reduced HDL-C \((29,30)\) (Figure 1). In addition, increased oxidized LDL levels \((31–33)\) and increased Lp(a) levels have been reported, with 34\% of patients having levels above the 75th percentile \((34)\). The elevations of Lp(a) levels in hemodialysis patients are smaller than those seen in continuous ambulatory peritoneal dialysis. The triglyceridemia in hemodialysis patients can be explained by the presence of triglyceride-rich VLDL rather than an overproduction of VLDL \((35)\).

**Peritoneal Dialysis**

Peritoneal dialysis seems to be associated with a relatively more atherogenic lipid profile than hemodialysis. In reported studies, 20 to 40\% of peritoneal dialysis patients have been shown to have elevated total cholesterol and LDL-C \((Figure 1)\), and 25 to 50\% of patients have been reported to have elevated triglycerides and apolipoprotein B (apo B) and low HDL-C \((34,36,37)\). The LDL-C has also been shown to be qualitatively different from normal LDL-C in that there is an increased concentration of small, dense particles together with the high apo B \((38)\). In addition, increased oxidized LDL levels \((31–33)\) and increased Lp(a) levels have been reported in peritoneal dialysis patients, with 42\% of patients having levels above the 75th percentile \((34)\). The hypertriglyceridemia in peritoneal dialysis patients may be partially explained by increased hepatic synthesis of VLDL, which binds triglycerides \((38)\).

**Development of Coronary Artery Plaque and Treatment Implications**

What are the implications of atherogenic lipid profiles among patients with uremia or ESRD? To answer this question, the overall cause and development of atherosclerotic plaques and the superimposition of factors unique to uremic patients must be considered. In general, plaque formation in CAD involves oxidation of LDL-C, inflammation, and calcification. Thus, any strategy to reduce risk of ASCHD should consider reduction of LDL-C, reduction of oxidative risk, and reduction of risk of calcification, particularly because abnormal calcium and phosphorus metabolism and vascular calcification are significant contributors to mortality in patients with ESRD \((10–12)\). Strategies for the reduction of hyperphosphatemia and calcification involve the use of phosphate binders, and available phosphate binders have different effects on the two therapeutic goals \((39)\).

For reduction of oxidative stress, high-dose supplementation with 800 IU/d \(\alpha\)-tocopherol (vitamin E) can be useful. It has been shown to reduce cardiovascular risk in the Secondary Prevention with Antioxidants of Cardiovascular Disease in End-Stage Renal Disease study of hemodialysis patients with preexisting CVD \((40)\). In that study, the primary end point was a composite variable of MI, ischemic stroke, peripheral vascular disease (excluding arteriovenous fistula), and unstable angina, and it showed a 54\% reduction with treatment \((RR = 0.46; 95\%\, CI, 0.27 to 0.78; P = 0.014)\). Confirmation of these results, as well as information regarding the utility of other

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**Figure 1.** Diagrammatic view of lipoprotein profiles in normal subjects versus patients on hemodialysis and peritoneal dialysis. Note: The arrows show increasing atherogenicity from normal health to hemodialysis to peritoneal dialysis.
antioxidant agents, is needed to recommend their use conclusively. In ESRD, antioxidant therapy may be especially valuable in hemodialysis patients, who show greater evidence of oxidative stress than the general population and peritoneal dialysis patients (41).

Despite increased antioxidant defense, there seems to be a relationship between the degree of lipid peroxidation and the severity of CVD in hemodialysis patients (41). Lipid-lowering therapies are important in patients with ESRD and should be included whenever diet and exercise are not sufficient to achieve target lipid goals. However, use of antilipid therapies remains low in dialysis patients. It is clear that dialysis patients have a myriad of lipid abnormalities, with peritoneal dialysis patients having a more atherogenic lipid profile than hemodialysis patients. By extension of the compelling data in the general population and the high risk for lipid abnormalities and CVD in the dialysis population, most patients with ESRD should be treated with lipid-lowering agents. Supporting evidence for this approach comes from a recently published analysis of data from the USRDS Dialysis Morbidity and Mortality Wave 2 study that shows that statin use is associated with a reduction in cardiovascular mortality (RR = 0.64; 95% CI, 0.45 to 0.91) and total mortality (RR = 0.68; 95% CI, 0.54 to 0.87) (42). Further prospective studies are needed to confirm the use of this strategy in dialysis patients. Large-scale, prospective, randomized trials (4-D Trial, HARP) to determine the effects of statins on cardiovascular complications in diabetic and nondiabetic patients on hemodialysis are ongoing and should provide further information on the effects of lipid lowering on reducing the risk of CVD in this patient population (43). Currently, there are no specific trials examining cholesterol reduction in dialysis patients.

Both the European Joint Task Force and the US National Cholesterol Education Program (27,44) have issued lipid guidelines for the general population. In addition, specific recommendations on the management of dyslipidemias in chronic kidney disease (CKD) have recently been published through the National Kidney Foundation’s Kidney Disease Outcome Quality Initiative (45). In comparing these guidelines with the ATP III guidelines (27), patients with CKD should be considered to be in the highest risk category, meaning that the target LDL-C level for CKD patients is below 100 mg/dl.

Lipid-Lowering Therapy in ESRD: The Reality

Let us examine the reality of lipid management in current practice. Are patients with ESRD receiving lipid-lowering treatment? Assuming that at least 50% of patients who initiate dialysis have clinical or subclinical ASCHD and that at least 80% of these patients have dyslipidemia, it may be expected that at least 40% of dialysis patients should be receiving lipid-lowering therapy. In fact, the data show far less usage of lipid-lowering treatments. In a Canadian study of patients with ESRD, a lipid-lowering agent was used in 9.5% of patients with no ASCHD and in 29.4% of patients with ASCHD (46); USRDS data indicate that as few as 15% of peritoneal dialysis patients and 8% of hemodialysis patients are on lipid-lowering treatments (47).

In examining the possible reasons for the underimplementation of lipid-management strategies among dialysis patients, the following factors may be intuitively considered as potential reasons: polypharmacy, cost, compliance, lack of published evidence, side effects, and normal LDL-C levels. It is hoped that a case has been made here for the severity of consequences (ASCHD) in the absence of lipid control in the general population and, by extension, in the dialysis or uremic population. Although more studies of dyslipidemia in ESRD are certainly needed, the potential risk of nontreatment clearly indicates that more aggressive lipid-lowering strategies need to be implemented for these patients. In considering such therapy, LDL-C measurements alone are not sufficient to determine whether treatment is warranted. As we have seen, quantitative differences in apo B protein, oxidized LDL-C, HDL-C, and Lp(a) as well as qualitative differences in VLDL particles exist in dialysis patients relative to nondialysis subjects.

Finally, dialysis patients are among a group of chronically ill patients who remain on long-term multiple pharmacotherapies, and it is understandable that there may be reluctance, on the part of both the physician and the patient, to add one more medication to the regimen. This reluctance may be related to cost and/or compliance, as well as fear of side effects and drug interactions. Any strategy to reduce the number of medications would only serve to improve compliance, reduce cost, and reduce risk of adverse events. In this regard, it is interesting to note that the calcium-free, metal-free phosphate binder sevelamer hydrochloride (mean dose, 6.5 g/d) has been shown in a randomized trial (n = 200) to reduce serum LDL-C concentrations by 37% (37 mg/dl) and total cholesterol by 22% (40 mg/dl; P < 0.0001 versus calcium binders for both) in addition to decreasing serum phosphate levels by 33% (Figure 2) (48). Sevelamer did not seem to affect HDL-C or triglyceride levels in this study, although a separate open-label study has shown a 30% reduction in LDL-C and an 18% increase in HDL-C relative to baseline (P < 0.0001 for both) after 46 wk of sevelamer treatment (49). In contrast, calcium-based phosphate binders were not shown to have any effect on total cholesterol or LDL-C levels (Figure 2) (48).

Sevelamer treatment has also been shown to produce a reduction in highly sensitive C-reactive protein, a key marker of inflammation. In contrast, calcium-containing binders may...
increase highly sensitive C-reactive protein levels. Thus, data indicate that sevelamer may have additional benefits beyond phosphate reduction in patients who undergo hemodialysis: namely, LDL-C reduction and anti-inflammatory effects. The contribution of either or both of these effects to a reduction in calcification or atherosclerosis in sevelamer-treated patients is currently unclear. Additional studies are needed to elucidate further these benefits of treatment with sevelamer. However, this medication may be especially useful in meeting lipid targets in patients with ESRD without the need for additional specific lipid-lowering agents.

Conclusion

Dyslipidemia is an important risk factor for ASCHD. In the general or nonuremic population, there is overwhelming evidence that the treatment of lipid abnormalities markedly improves cardiovascular outcomes. Emerging data indicate that dialysis patients also have a number of lipid abnormalities and that the specific abnormalities often differ between patients who receive hemodialysis versus peritoneal dialysis. In either case, the abnormal lipid profiles are atherogenic, with the dyslipidemia being more atherogenic in peritoneal dialysis patients. However, there is a dearth of information regarding the goals, efficacy, and safety of treatment for lipid optimization among dialysis patients. No prospective randomized studies have examined lipid-lowering strategies in this specific patient population. One analysis of USRDS data indicates that statin therapy can reduce cardiovascular mortality and total mortality among hemodialysis patients (42). Given the strong evidence showing the benefit of lipid-lowering therapy in the general population, the current consensus is that until further data are available, dialysis patients should be treated aggressively—with an LDL-C goal less than 100 mg/dl—to reduce the risk of CVD. Although shortcomings of added medications, compliance issues, and increased cost may hinder the addition of lipid-lowering therapies to the overall treatment strategy of dialysis patients, the use of a single medication such as sevelamer to control hyperphosphatemia, reduce lipid levels, and reduce some aspects of inflammatory processes is an interesting option that should be explored further. Preliminary data in this regard are encouraging and should be confirmed.

References

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