Lipid Changes and Statins in Chronic Renal Insufficiency

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It has been known for a long time that chronic kidney disease (CKD) is associated with dyslipidemia, but the full extent of abnormalities has been appreciated only recently, because routine laboratory tests fail to disclose the entire spectrum of lipid abnormalities. Lipids, particularly HDL cholesterol, are predictive of cardiovascular events, but a paradoxical inverse relation between cholesterol concentration and cardiovascular death has been noted in uremic patients. This currently is thought to be explained by the confounding effect of microinflammation and possibly calcification, but this is not definitely proved. Several retrospective analyses that included patients with mild or moderate CKD documented benefit from lowering of cholesterol by statins. In contrast, the Die Deutsche Diabetes Dialyse (4D) study and a small Scandinavian study failed to show a benefit from lowering of cholesterol by statins in ESRD. Pathomechanistically, it is possible that nonclassical pathomechanisms override statin-sensitive mechanisms as also suggested by the observation that statins fail to reduce carotid intima-media thickening. Although, experimentally, exposure to lipids (particularly oxidized lipids) aggravates progression, data on the effect of statins on progression in patients with CKD are not definite. The most likely explanation is that the impact of numerous confounders obscures their effect on progression. The increase in urinary protein excretion of patients who are treated with statins had been a cause of concern, but the underlying mechanism (i.e., interference with proximal tubular reabsorption of protein) meanwhile has been well documented.


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ince the days of Richard Bright, it has been known that in patients with advanced renal disease, the serum is “milky,” pointing to the presence of hyperlipidemia. More recently, interest in hyperlipidemia of renal disease has been raised by the consideration that the known abnormalities in the lipid spectrum of renal patients might predispose to accelerated atherosclerosis (1). Indeed, the Seattle Group found excess death from coronary heart disease in a large proportion of the first cohort of patients who had been started on hemodialysis in Seattle (2).

Lipid Abnormalities in Renal Disease

The magnitude of lipid changes is not disclosed fully by routine laboratory chemistry, which usually shows normal total and LDL cholesterol, low HDL cholesterol, and high triglycerides. As shown in Table 1, more sophisticated analysis shows striking abnormalities: Increased VLDL; remnants and intermediate-density lipoproteins (3); prolonged persistence of postprandial chylomicron remnants (4); accumulation of small dense LDL; modification of apolipoproteins by glycation, oxidation, and carbamoylation (5); increased lipoprotein(a) [Lp(a)] (6); and accumulation of noncardioprotective acute-phase HDL (7,8). An interesting proposal was made by Shoji et al. (9), who showed that intermediate-density lipoproteins were an independent risk factor for aortic atherosclerosis. They also proposed calculation of non-HDL cholesterol (the sum of LDL and VLDL cholesterol). The latter is particularly elevated in renal failure (10).

Prognostic Value of Dyslipidemia in Chronic Kidney Disease

In a prospective study, Degoulet et al. (11) made the unexpected—and at first counterintuitive—observation that in dialysis patients, low cholesterol concentrations were associated with high mortality. This key observation meanwhile was confirmed in numerous studies (12,13). In a cohort of 823 patients who were admitted for dialysis, Liu et al. (13) found in the overall cohort that an increased serum cholesterol was associated with a decreased risk for all-cause mortality, whereas in the absence of inflammation/malnutrition (22% of the cohort with serum albumin >3.6 mg/dl, C-reactive protein <10 mg/L, and IL-6 <3.09 pg/ml), an increment in baseline serum cholesterol was associated with increased mortality, as it is in the general population. This study demonstrates that the predictive value of cholesterol is confounded by concomitant inflammation.

Another controversial issue in the past had been the clinical implications of the changes in Lp(a) concentration. Lp(a) is correlated positively with higher cardiovascular risk in the general population (14) but strongly dependent of the genotype and the concomitant isoproteins of apolipoprotein(a) [apo(a)]. Individuals with low molecular weight isoforms have the highest serum Lp(a) concentrations. In renal patients, the average Lp(a) concentration is particularly increased, but the absolute serum concentration of Lp(a) is less predictive than the isoform itself. The prognosis is particularly adverse in patients with the low molecular weight apo(a) isoform compared with the high molecular weight isoform (15).
Evidence for Accelerated Atherosclerosis in Chronic Kidney Disease

Cross-sectional studies documented the high prevalence of carotid artery atherosclerosis and of atherosclerotic peripheral artery disease (16). Autopsy studies showed an excessive prevalence of advanced coronary atherosclerosis (17), and this has been confirmed by coronary angiography (18) and electron beam computed tomography (19). Coronary calcification is regarded as an index of coronary atherosclerosis. Although in renal patients calcification may not be a specific expression of coronary atherosclerosis (and partially reflect media sclerosis as well), longitudinal studies showed accelerated calcification of the coronaries compared with that in nonrenal control subjects (19,20), and this was true even in early renal disease (21).

In the first description of coronary artery disease of dialyzed patients (2), the authors postulated that in uremic patients, arterogenesis was accelerated. Indeed, several groups showed accelerated aortic atherosclerosis in the experimental model of the apoE knockout mouse with reduced renal function (22–24). This is seen even with minor reduction of renal function (e.g., uninephrectomy [22]) and responds to administration of angiotensin receptor blockers (25).

Dyslipidemia and Progression of Renal Disease

It had been known for a long time that in diverse models of renal damage, high-lipid diets or other maneuvers to induce hyperlipidemia aggravate glomerulosclerosis and progressive renal dysfunction (26–28). Oxidized lipids are particularly injurious in this context (29,30). Although various parameters of dyslipidemia predict accelerated progression in humans (31), a beneficial effect of statins on progression has not been documented beyond doubt. In several studies and meta-analyses that examined the effect of lipid lowering by statins, a trend for slower progression was seen (32), but this finding has not been consistent and significant (33). The most likely explanation is that in renal patients, the adverse effect of dyslipidemia (and the benefit from its reversal), which has been documented clearly in animal experiments, is confounded and overridden by factors that are difficult to control fully even in prospective studies (e.g., BP, proteinuria). In populations with cardiovascular disease, a recent meta-analysis showed that statin therapy seems to reduce proteinuria modestly and results in a small reduction in the rate of kidney function loss (34).

Effect of Statins on Cardiovascular Disease in Patients with Chronic Kidney Disease

In large, prospective statin trials, post hoc analysis of the proportion of the included patients who had impaired renal function (mainly stages 2 and 3 chronic kidney disease [CKD], e.g., in the Anglo-Scandinavian Cardiac Outcomes Trial [ASCOT] [35] or Cholesterol and Recurrent Events [CARE] study [36], suggested a benefit. In the CARE study, this depended on baseline GFR and was seen primarily in the small group of patients with a GFR of <40 ml/min (37).

A similar observation had also been made in patients who received a transplant in the Assessment of Lescol in Renal Transplantation (ALERT) study. There was a tendency for fluvastatin to reduce cardiovascular death (38), including patients with reduced renal function. In a long-term open follow-up observation, the reduction of cardiovascular events became statistically significant (39).

These studies left unresolved the issue of whether statins lowered significantly cardiovascular death in patients with stages 4 and 5 CKD. This possibility was not a priori certain. Fahi et al. (40) drastically lowered LDL cholesterol by atorvastatin in patients with advanced CKD as well as in nonrenal patients with coronary artery disease. As shown in Table 2, this maneuver reduced the maximum intima-media thickness in nonrenal patients with coronary artery disease but failed to affect this index in patients with CKD.

To resolve this issue, in the prospective Die Deutsche Diabetes Dialyse (4D) study, 1255 patients who had type 2 diabetes and had been on hemodialysis for <2 yr were randomly assigned to receive placebo or 20 mg/d atorvastatin (41). In the verum group, LDL cholesterol decreased by 42% from 125 to 72 mg/dl compared with essentially no change (−1.2%) from 121 mg/dl at baseline in the placebo group during the 4-yr observation period. These values correspond to what LaRosa et al. (42) had achieved in his widely known Treating to New Targets (TNT) study, which documented impressive reduction of cardiovascular end points. Although LDL cholesterol was lowered equally effectively in the 4D study, there was a minor trend at best for an improved outcome with respect to the primary composite end point (cardiac death, fatal myocardial infarction, stroke), which failed to reach statistical significance, however. This finding is in full agreement with a recent small Scandinavian study that found significant lowering of cardiovascular end points in patients with pre–end-stage CKD but no effect

### Table 1. Lipid spectrum in renal disease

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Lipoproteins</th>
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<tbody>
<tr>
<td>Abnormal low HDL cholesterol</td>
<td>VLDL remnants/IDL</td>
</tr>
<tr>
<td>high triglyceride</td>
<td>Chylomicron remnants</td>
</tr>
<tr>
<td>Abnormal total cholesterol</td>
<td>small dense LDL modifications (glycation-oxidation-carbamylation)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>AGE-apoB</td>
</tr>
<tr>
<td></td>
<td>High lipoprotein(a)</td>
</tr>
<tr>
<td></td>
<td>Acute-phase HDL</td>
</tr>
</tbody>
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AGE, advanced glycation end products; apoB, apolipoprotein B; IDL, intermediate-density lipoprotein.
The cardiovascular risk is excessive in patients with even minor renal dysfunction (49–51). However, at this stage of CKD, classical cardiovascular risk factors have an impact that is minor renal dysfunction (49–51). However, at this stage of CKD, classical cardiovascular risk factors have an impact that is

The reasons for this unexpected failure to reduce the primary end point despite substantial lowering of LDL cholesterol are unresolved. It might be due to the operation of alternative pathomechanisms such as inflammation or calcification (44), which might override the deleterious effect of dyslipidemia. Certainly cardiovascular death in these patients was due primarily to noncoronary (or nonischemic) causes. For this reason, the power of the study in retrospect was inadequate. Another possibility to consider is that patients who would have been particularly susceptible to statin treatment may have died before reaching ESRD, because a major proportion of renal patients die from cardiovascular causes before reaching ESRD (45). In this context, it is of note (Table 3) that the major cause of death was sudden death and congestive heart failure, in good agreement with data of other studies and the US Renal Data System (www.usrd.org). Indeed, death from confirmed coronary artery disease was lowered by 19% per mmol lowering of cholesterol even in the 4D study, but patients who died from coronary heart disease composed only 9% of the patients who died. We shall have to wait for ongoing studies such as the Study of Heart and Renal Protection (SHARP) (46) and Heart and Renal Protection (HARP) Study (47,48) to be able to make evidence-based recommendations for the treatment of dyslipidemic patients who are in terminal renal failure.

Table 3. Causes of death in the 4D studya

<table>
<thead>
<tr>
<th>Parameter</th>
<th>4D Study</th>
<th>USRDS</th>
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<tbody>
<tr>
<td>Coronary heart disease</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Other cardiac causes</td>
<td>35%</td>
<td>33%</td>
</tr>
<tr>
<td>Stroke</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>50%</td>
<td>51%</td>
</tr>
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</table>

aCAD, coronary artery disease.

References

7. Coetzee GA, Strachan AF, van der Westhuizen DR, Hoppe...
33. Tonelli M, Moye L, Sacks FM, Cole T, Curhan GC: Effect of pravastatin on loss of renal function in people with mod-


