Are 3-Hydroxy-3-Methylglutaryl-CoA Reductase Inhibitors Renoprotective?

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Statins reduce serum cholesterol and cardiovascular morbidity and mortality. The mechanisms for these beneficial effects are reviewed. Altered inflammatory responses and improved endothelial function mediated by statins are thought to be partly responsible for the reduction of morbidity and mortality as a result of cardiovascular events. In analogy, whether statins confer similar benefits on the kidney has not been established. This review critically considers the available data whereby dyslipidemia mediates renal dysfunction by modulating the inflammatory response to diverse cytokines. Also reviewed is the emerging database indicating that statins may modulate renal function by altering the response of the kidney to dyslipidemia.

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t is well established that 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins) reduce serum levels of cholesterol and cardiovascular morbidity and mortality. Less established is the role of lipids in the progression of kidney disease and the potential beneficial effects of statins in patients with kidney disease. It is also well known that people with chronic kidney disease (CKD), even those in the early stages of the disorder, are at increased risk for cardiovascular disease (CVD) (1). Several nontraditional factors, including oxidant stress and elevated inflammatory markers, are associated with both atherosclerosis and CKD, and two recent reviews suggest that oxidant stress and inflammation may be the primary mediators or the “missing link” that explains the tremendous burden of CVD in CKD (2,3). In this article, we consider emerging evidence that statins, in addition to their cardiovascular effects, may modulate renal function.

Pathophysiologic Concordance of CVD and CKD

CKD is a worldwide problem, and patients with CKD are more likely to die of CVD than the general population. Indeed, the Kidney Disease Outcomes Quality Initiative (K/DOQI) and National Cholesterol Education Program (NCEP) guidelines recognize CKD as a CVD risk equivalent (1). CKD patients frequently have a number of additional risk factors, beyond the traditional risk factors associated with CVD, including proteinuria, electrolyte imbalances, inflammation, increased oxidative stress, and altered nitric oxide (NO) levels, among others (4).

Microalbuminuria or proteinuria is often found in association with hyperlipidemia, especially in patients with diabetes and hypertension, and this may contribute to CVD in these patients. Hemodialysis patients have a characteristic dyslipidemia that further contributes to CVD risk, presenting with very high levels of VLDL and triglycerides, low levels of HDL, and raised levels of small-dense LDL particles (5). Urinary protein loss may increase serum lipoprotein levels. Alternatively, hyperlipidemia may contribute to the progression of CKD by a mechanism similar to atherogenesis (6). Immunostaining of renal biopsies from patients with glomerular disease demonstrated the accumulation of lipoproteins in the glomerular and mesangial cells as well as within the mesangial matrix (7,8). This suggests that the vasculature and the kidney share a number of pathologic features. Atherogenesis depends on interplay of cellular components of the immune system such as monocytes, cytokines, and cell adhesion molecules with lipids, platelets, and endothelial cells. The same interplay of these factors may contribute to progression of kidney disease. Because statins are very effective in retarding pathologic processes that are responsible for CVD, it is conceivable that similar pleiotropic effects may forestall progression of kidney disease.

Inflammation and Progressive Kidney Disease: Role of Statins

In the kidney, mesangial cell proliferation in response to various growth factors such as platelet-derived growth factor (PDGF), insulin, and IGF is important in subsequent mesangial matrix expansion after glomerular injury. Mesangial cells bind both LDL and oxidized LDL cholesterol (ox-LDL). Hyperlipidemia and hyperglycemia increase the production of mesangial matrix and drive recruitment of inflammatory cells into the matrix, thus leading to the progression of CKD. Both LDL and high levels of glucose have been shown to increase the expression of fibronectin mRNA and protein, leading to an increase in the mesangial matrix and cell number in cultured mesangial cells (9,10). LDL stimulates the expression of monocyte chemotactic protein-1 (MCP-1) mRNA, leading to increased amounts of secreted monocyte chemotactic activity (9). When bound to the extracellular matrix, ox-LDL has been shown to be
cytotoxic (10,11). Both LDL and ox-LDL induce the expression of IL-6 and NF-κB, two factors that are important in the inflammatory and proliferative response of mesangial cells. The transcription factor NF-κB has been linked to inflammatory events associated with glomerulonephritis (12).

Statins inhibit the inflammatory response of the kidney through mechanisms similar to those observed in the vasculature. Statins decrease MCP-1, IL-6, PDGF, NF-κB, vascular cellular adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), and fibronectin mRNA and proteins in mesangial cells (9,13–16) and inhibit the proliferative effects of LDL and high levels of glucose and the cytotoxic effects of ox-LDL on mesangial cells (14,15,17). Statins reduce renal tubular epithelial proliferation in vitro (18). In the kidney, statins induce NO synthetase (NOS) and increase NO bioavailability (19), where NO may serve a protective role against inflammation in renal transplant recipients, in nephrotic syndrome-induced glomerulonephritis and autoimmune tubular interstitial nephritis (20,21).

Simvastatin suppressed mesangial cell proliferation, mesangial matrix expansion, and macrophage infiltration into the glomeruli in a rat model of glomerulonephritis (22). Pravastatin decreased the amount of intrarenal C-reactive protein (CRP), macrophages, and tubulointerstitial fibrosis in a rat model of chronic cyclosporine-induced nephropathy (23). Cerivastatin reduced proteinuria and renal injury in stroke-prone spontaneously hypertensive rats independent of BP and cholesterol (24). Lovastatin prevented glomerular macrophage infiltration and attenuated albuminuria in rats with puromycin aminonucleoside nephrosis (25). The combination of atorvastatin and salt restriction normalized aortic endothelial NOS (eNOS) and superoxide, and reduced left ventricular hypertrophy and proteinuria in Dahl salt-sensitive rats, suggesting that upregulation of vascular eNOS and inhibition of oxidative stress may contribute to the pleiotropic protective effects of atorvastatin against end-organ injury (26). This provides a platform for future studies to delineate further the contribution of pleiotropic effects conferred by statins in protection against end-organ injury.

**Effects of Dyslipidemia and Statins on Renal Function**

Evidence suggests that dyslipidemia plays an important role in the initiation and progression of CKD and that lipid-lowering agents may retard the progression of renal disease in patients with CKD. Several studies have found correlations between baseline lipid measures and rate of decline in kidney function (27–29) The Physician’s Health Study assessed the probability of development of renal dysfunction (elevated creatinine) defined as a 60 ml/min per 1.73 m² decrease in creatinine clearance (CrCl), defined as ≤55 ml/min in 4483 healthy male physicians (plasma creatinine levels of <1.5 mg/dl at baseline) who provided blood samples in 1982 and 1996 (29). After 14 years, 134 (30%) men had elevated creatinine and 244 (5.4%) men had reduced CrCl. The relative risk for elevated creatinine was 1.77 (95% confidence interval [CI], 1.10 to 2.86) for total cholesterol ≥240 mg/dl, 2.16 (95% CI, 1.42 to 3.27) for HDL <40 mg/dl, 2.34 (95% CI, 1.34 to 4.07) for the highest quartile of total cholesterol:HDL ratio (≥6.8), and 2.16 (95% CI, 1.22 to 3.80) for the highest quartile of non-HDL cholesterol (≥196.1 mg/dl). The study showed that the odds of progression of renal disease were directly related to blood lipid levels at baseline.

Several studies have suggested that lipid-lowering drugs may preserve renal function in patients with CKD. Fried et al. (30) performed a meta-analysis of 13 small, prospective, controlled trials that examined the effects of antilipidemic agents (primarily statins) on renal function, albuminuria, or proteinuria. Lipid-lowering agents significantly slowed the rate of decline in GFR compared with control subjects (−0.16 ml/min per mg; 95% CI, 0.03 to 0.29 ml/min per mg; P = 0.008). This analysis also showed a trend toward a reduction of proteinuria with lipid-lowering therapy (P = 0.077) and a decreased progression toward end-stage renal disease (ESRD) in treated individuals. Two additional studies showed a 54% reduction in proteinuria with pravastatin 10 mg/d (31) and approximately 35% reduction with simvastatin 20 mg/d (32). It is interesting that the effects of simvastatin on proteinuria seemed to be independent of LDL reductions as a similar benefit was not seen in patients who were treated with cholestyramine despite similar LDL levels (32).

Bianchi et al. (33) conducted what is currently the only study of reasonable size and duration designed to show a statin-mediated reduction in the progression of kidney disease. This prospective, controlled, open-label study demonstrated that treatment with atorvastatin 10 to 40 mg/d reduced proteinuria and the rate of progression of kidney disease in 56 patients with CKD, proteinuria, and hypercholesterolemia. Before randomization to atorvastatin or placebo, all patients had been treated for 1 yr with angiotensin-converting enzyme inhibitors (ACEI), angiotensin AT₁ receptor antagonists (ARB), or a combination of ACEI and ARB. Urine protein excretion decreased from 2.2 ± 0.1 to 1.2 ± 1.0 g/24 h (P < 0.01) in the atorvastatin group versus a nonsignificant decrease from 2.0 ± 0.1 to 1.8 ± 0.1 g/24 h in patients who did not receive atorvastatin in addition to ACEI and/or ARB. CrCl decreased markedly in patients who did not receive atorvastatin (from 50 ± 1.9 to 44.2 ± 1.6 ml/min; P < 0.01) and only slightly (from 51 ± 1.8 to 49.8 ± 1.7; NS) in patients who were treated with atorvastatin.

Secondary or post hoc analysis of kidney function in some landmark statin trials have also suggested potential beneficial effects on kidney function. For example, serum creatinine was assessed as a secondary efficacy measure in the Heart Protection Study of 20,536 people who did and did not have CVD and received simvastatin 40 mg/d or placebo. Serum creatinine levels increased less among simvastatin-treated patients (7.13 μmol/L) compared with the placebo group (8.94 μmol/L; P < 0.0001) (34). A post hoc analysis of nearly 700 participants in the Cholesterol and Recurrent Events study (a randomized, placebo-controlled, secondary prevention trial of pravastatin) with estimated GFR of <60 ml/min per 1.73 m² showed that the rate of GFR decline did not differ between pravastatin and placebo groups (35). However, pravastatin significantly reduced the rate of decline in GFR compared with placebo in individuals with more severe chronic renal insufficiency at baseline: −0.6
ml/min per 1.73 m²/yr slower in those with a GFR of <50 ml/min per 1.73 m² (P = 0.07) and −2.5 ml/min per 1.73 m²/yr slower in those with a GFR of <40 ml/min per 1.73 m² (P = 0.0001).

The Greek Atorvastatin and CHD Evaluation (GREACE) study of dyslipidemic CHD patients recently evaluated the impact of untreated dyslipidemia versus two treatment regimens, usual care and dose titration with atorvastatin (10 to 80 mg/d), on renal function (12). In patients with untreated dyslipidemia and normal renal function at baseline, CrCl declined 5.2% (P < 0.0001) over the 3-yr study period. The usual care group had a 4.9% increase in CrCl (P = 0.003), whereas the atorvastatin group had a 12% increase (P < 0.0001). Thus, statin treatment prevented the decline and significantly improved renal function.

ESRD Patients

Dyslipidemia and CVD are very prevalent among ESRD patients. However, to date, only a few small studies have evaluated the effects of statins on markers of risk or cardiovascular outcome in this patient population. In the US Renal Data Systems Dialysis Morbidity and Mortality Wave-2 study, a retrospective analysis of data from 376 ESRD patients, statin use was associated with a one-third decrease in all-cause and cardiovascular mortality in dialysis patients over a 2-yr period (36). Among statin users, the cardiovascular-specific mortality rate was 61/1000 person-years; the corresponding rate for non-users was 88/1000 person-years.

In an 8-wk randomized study of 44 hypercholesterolemic patients, simvastatin decreased plasma CRP levels and increased serum albumin levels compared with a no-treatment group (31). In an 18-wk trial, 28 ESRD hemodialysis patients with normal LDL and total cholesterol levels and borderline low HDL cholesterol levels were randomized to receive either simvastatin or atorvastatin (37). Treatment with either statin did not affect CRP levels but decreased ox-LDL and remnant lipoprotein cholesterol levels. Treatment also shifted LDL subfractions from small, dense fractions to large, buoyant fractions.

Renal Transplant Patients

Dyslipidemia and atherosclerotic vascular diseases are common among renal transplant recipients. Lipid-lowering drugs are used extensively in these patients. However, there are no studies available to demonstrate a beneficial impact of these drugs on cardiovascular outcome. Several observational studies also suggest that hyperlipidemia may play a role in chronic allograft nephropathy (38).

In vitro studies suggest that HMG-CoA reductase inhibitors may inhibit the growth and proliferation of lymphocytes (39,40). This has led to speculation that these agents might reduce rejection of solid-organ transplants. Indeed, two prospective studies have shown that HMG-CoA reductase inhibitors started immediately after transplantation of orthotopic hearts reduce graft vascular disease and improve patient survival (41,42). One study of 48 renal transplant recipients who were randomized to receive either pravastatin or placebo showed lower rate of acute rejection among patients who were treated with statin (25 versus 58%; P < 0.01) (43). However, another study with simvastatin did not confirm this finding (44). In summary, the available studies are scant and conflicting. Additional studies encompassing determination of the role of HMG-CoA reductase inhibitors in transplant recipients is necessary.

Mechanisms of Action of Statins

The mechanisms for the beneficial effects of statins on CVD and kidney disease have been studied extensively (Table 1).

![Table 1: Pleiotropic effects of statins](image-url)

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<th>Decrease</th>
<th>Immunomodulation</th>
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<tr>
<td>ET-1</td>
<td>Decrease</td>
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<td>IL-6</td>
<td>IFN-γ-induced MHC class II expression</td>
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<td>VCAM-1 and ICAM-1</td>
<td>T cell activation</td>
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<td>PDGF</td>
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<td>NF-κB activation</td>
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<td>proinflammatory cytokines, MCP-1 in particular</td>
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<td>apolipoprotein A1 expression</td>
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*ET-1, endothelin-1; VCAM-1, vascular cellular adhesion molecule-1; ICAM-1, intracellular adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; CRP, C-reactive protein; NO, nitric oxide; PPAR-α, peroxisome proliferator–activated receptor-α. Modified in part from references 50–52.
The current view of atherogenesis is that of an inflammatory process, irrespective of the initial insult to the vascular wall (45). This hypothesis is supported by the association of inflammatory markers, in particular CRP, with increased risk for coronary disease (46). Interactions between the vascular endothelium and the immune system drive the development of plaques (47,48).

ox-LDL stimulates chemotaxis of monocytes and their transformation into macrophages that engulf the lipids (48,49). The lipid-engorged macrophages become foam cells that die and form the lipid-rich core of the plaque. A collagen cap, preventing contact between the prothrombotic lipids and the blood, covers this core. However, inflammatory cells may also secrete metalloproteinases that digest the collagen cap, causing plaque rupture, acute thrombotic complications, and clinical events (48).

Statins reduce cholesterol synthesis by inhibiting HMG-CoA reductase, the rate-limiting step in its synthesis. A significant consequence of the HMG-CoA reductase inhibition by statins is interference with the synthesis of the isoprenoid compounds farnesylpyrophosphate and geranylpyrophosphate. It is through the inhibition of isoprenylation that statins exert a considerable number of non–lipid-dependent effects. Normally, the isoprenoid compounds become attached posttranslationally to intracellular signaling proteins such as the GTPases Ras, Rac, and Rho. These intracellular signaling molecules facilitate communication between growth factor receptors and the cellular cytoskeleton to influence cell motility, membrane transport, and transcription factor activation (50). Some of these transcription factors, such as NF-κB, induce cell proliferation and activation of a variety of cytokines and chemokines, such as MCP-1, VCAM, and ICAM to mention a few. Statins interfere with the anchoring of growth factors to the cell membrane and cytoskeleton and with signal transduction to the nucleus, thus preventing the activation of transcription factors and cell proliferation.

Via interference with isoprenylation, statins exert significant anti-inflammatory and immunomodulatory effects. Some of the more significant effects are a decrease in adhesion molecule expression on vascular endothelial cells; a decrease in circulating CRP; reduced synthesis of inflammatory cytokines IL-1β, TNF-α, TGF-β, and IL-6; reduced synthesis of inducible cyclooxygenase-2; and inhibition of NF-κB, a DNA-binding protein that controls the expression of genes encoding other cytokines, chemokines, interferons, MHC proteins, growth factors, and cell adhesion molecules (46,49–57). Statins may also block the differentiation of monocytes into macrophages and induce apoptosis of these cells (58).

Of importance, statins cause an upregulation and stabilization of eNOS and an increase in NO production (49–52,54,59,60), and NO plays regulatory and modulatory roles in inflammatory conditions, inhibiting platelet aggregation, neutrophil adhesion, and cell proliferation and slowing cellular proliferation after cytokine exposure (61–66).

The multiple pleiotropic effects cited above have the potential to have a significant impact on the atherogenic processes at several points, reducing vascular inflammation and improving endothelial function. A number of in vitro and in vivo studies have investigated the effects of statins on the cells of the general vasculature. In cultured vascular smooth muscle cells (VSMC) or endothelial cells, statins downregulated the activation of the transcription factors NF-κB, activator protein-1, and hypoxia-inducible factor-1α (20). Inhibition of the activation of NF-κB led to decreased secretion of MCP-1, a chemoattractant for monocyte inflammatory cell and a mitogen for VSMC (67). In turn, the decreased secretion of MCP-1 caused by administration of atorvastatin, lovastatin, simvastatin, and fluvastatin stimulated apoptosis of VSMC (25,68). Statins also inhibit monocyte adhesion to endothelial cells via downregulation of surface integrins through inactivation of Rho GTPase (69). Thus statins could reduce the progression of arteriosclerosis via reducing the activation and infiltration of immune cells into plaque lesions (70).

Antioxidant effects may improve vascular function. Statins prevent Rac GTPase activation of NAD(P)H oxidase, reducing O2− generation in VSMC (71). In endothelial cells, ox-LDL contributes to the progression of atherosclerosis by decreasing levels of eNOS mRNA and protein. Statins affect this process first by protecting against the oxidation of LDL (19,72,73) and second by stabilizing eNOS mRNA through blocking geranylgeranylation of Rho GTPase (19). Blocking geranylgeranylation of Rho GTPase by statins also decreases the levels of the surface protein endothelin-1, a potent vasoconstrictor and mitogen (72,74). These changes help to normalize vascular reactivity.

In vivo studies in animal models of atherosclerosis provide additional support that these mechanisms are important to reducing atherogenesis. Inflammatory markers such as intimal macrophages, metalloproteinase expression, and IL-6 expression were decreased in plaques from statin-treated monkeys (75). Atherosclerotic plaques in these statin-treated monkeys had substantially more VSMC and collagen within the plaques, suggesting that the plaques were more stable and less likely to rupture (75). Furthermore, less endothelial dysfunction was observed as demonstrated by a decreased vasodilatory response to acetylcholine and a less pronounced expression of VCAM-1 (75).

Treatment with statins normalizes endothelium-dependent vasodilatory responses in patients with hypertension, hypertriglyceridemia, or atherosclerosis and decreases levels of CRP and other inflammatory markers in patients with hyperlipidemia, mixed dyslipidemia (similar to that characterizing patients with renal disease), acute coronary syndrome, or type 2 diabetes (45,76–81). The recently completed REVERSAL trial suggests that the differential reduction of CRP achieved with atorvastatin versus pravastatin, at comparable levels of LDL reduction, contributes to improved outcomes as demonstrated by halting plaque progression (82). However, it is still unclear whether all statins are equally effective at reducing CRP and whether they have an impact on other markers of inflammation. In addition, available data are insufficient to demonstrate a correlation between statins’ effects on CRP levels and on lipids or cardiovascular outcomes (53).

In conclusion, available evidence supports a substantial role
of dyslipidemia in the progression of kidney disease. Statins may modulate renal function by altering the response of the kidney to dyslipidemia.

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