Experimental Evidence for a Role of Dyslipidemia in Renal Injury and for a Renal Protective Effect of Statins

The presence of lipids in renal cells upregulates intracellular signaling pathways involved in inflammatory and fibrogenic responses, both of which are components of progressive renal injury. Lipids activate various growth factors that cause mesangial cell proliferation. Mesangial cells bind both LDL and oxidized LDL (ox-LDL), leading to yet more cell proliferation via multiple downstream effects. LDL stimulates the expression of monocyte chemoattractant protein-1 (MCP-1) mRNA, which increases monocyte chemotactic activity (1). LDL also stimulates the expression of fibronectin mRNA, which induces proliferation of mesangial matrix cells. In the extracellular matrix, ox-LDL induces podocyte apoptosis, decreases Akt activity, depletes nephrin (an adhesion molecule specific to the glomerular slit membrane), and induces the retraction of cultured podocytes, which leads to alterations in the glomerular barrier and increased albumin diffusion (2). Both LDL and ox-LDL induce the expression of NF-κB, which has been associated with inflammation in glomerulonephritis and the progression of chronic kidney disease (CKD) (3). It has also been found to induce the expression of genes that encode other cytokines, chemokines, interferons, growth factors, cell adhesion molecules, and MHC proteins involved in inflammation and proliferation (4).

Inhibitors of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase (i.e., statins) reduce renal injury in several experimental models (5–7). Statins also exert immunomodulatory and antiinflammatory effects (8–10) because mevalonate also serves as a precursor for isoprenoids—farnesylpyrophosphate (F-PP) and geranylpyrophosphate (G-PP)—that normally attach posttranslationally to intracellular signaling proteins (10). By blocking the synthesis of F-PP and G-PP, statins prevent the anchoring of growth factors to the cell membrane and cytoskeleton, thus hindering signal transduction to the nucleus, activation of transcription factors, and cell proliferation in the vascular endothelium.

Among their antiinflammatory and antiproliferative effects, statins reduce levels of MCP-1, IL-1β, TNF-α, TGF-β1, IL-6, PDGF, NF-κB, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, fibronectin mRNA, and mesangial proteins (8,10–14). Dichtl and colleagues (15) found that statins downregulate the activation of NF-κB, activator protein-1, and hypoxia-inducible factor-1α. NF-κB inhibition decreases the release of MCP-1 and stimulates apoptosis of vascular smooth muscle cells (15,16). Statins reduce the proliferation of renal tubular epithelium by impairment of activator protein-1 binding (17) and prevent monocytes from maturing into macrophages while inducing apoptosis of these cells (18). Other investigators (19) have shown that by downregulating surface integrin adhesion molecules and inactivating Rho GTPases, statins prevent monocytes from adhering to endothelial cells, thus blunting the earliest manifestations of atherosclerosis.

Additionally, statins exert a positive influence on nitric oxide (NO), a potent vasodilator with apparent antiinflammatory actions and beneficial effects on platelet aggregation, neutrophil adhesion, and cell proliferation (20). Statins have been shown to upregulate and stabilize endothelial NO synthase (eNOS) while increasing the bioavailability of NO (8,10,21–25). Statins also protect against the oxidation of LDL and thereby reduce oxidative stress (22,23) and inhibit the proliferative effects of ox-LDL on mesangial cells (26). Finally, statins stabilize eNOS mRNA by inhibiting the geranylgeranylation of Rho GTPase (27,28), which in turn reduces the level of surface protein endothelin-1, a potent vasoconstrictor and mitogen (23).

Effects of Statins on Kidney Function in CKD Patients

Epidemiologic and clinical evidence support the notion that dyslipidemia is a risk factor for CKD initiation, and that lipid lowering may slow disease progression. In the Physician’s Health Study (29), researchers traced the probability of ensuing renal dysfunction in 4483 apparently healthy males (baseline plasma creatinine level 1.5 mg/dl). After 14 yr, the odds of renal disease progression were directly related to baseline blood lipid levels (30). The Helsinki Heart Study documented an association between dyslipidemia and progressive kidney disease in 2702 middle-aged dyslipidemic men (30). The decline in renal function over 5 yr was faster by 20% in men with an LDL:HDL ratio >4.4 than in those with a ratio <3.2. Renal biopsies from patients with glomerular disease indicate that lipoproteins accumulate in both glomerular and mesangial cells and within the mesangial matrix (31), and oxidized lipids are frequently found in biopsy specimens from patients with renal disease (32).

Evidence suggests that lipid-lowering agents might help pre-
serve renal function in patients with CKD (33–40). A meta-analysis of 13 small, prospective, controlled trials examining the effects of antihyperlipidemic medications (primarily statins) on renal function, albuminuria, or proteinuria showed that treatment significantly slowed the rate of decline in GFR (0.16 ml/min per mo; 95% CI 0.03–0.29 ml/min per mo; \( P = 0.008 \) versus controls) (33). There was also a trend toward reduced proteinuria (\( P = 0.077 \)) and less progression toward ESRD in treated subjects. Tono et al. (41) found that simvastatin decreased urinary albumin excretion, which was largely independent of LDL cholesterol reduction. Similarly, Chang and coworkers (37) observed that simvastatin therapy resulted in a significant increase in serum albumin levels in patients undergoing hemodialysis.

A meta-analysis of renal function data from the rosuvastatin clinical development program, in which a diverse group of >10,000 persons received recommended doses for up to 3.8 yr, showed that treated subjects had lower serum creatinine levels as well as increased eGFR compared with baseline, both early and later in the course of treatment (40). In a prospective, controlled, open-label study, atorvastatin (10 to 40 mg/d) reduced proteinuria and the rate of progression of kidney disease in 56 patients with CKD, proteinuria, and hypercholesterolemia who had been treated with angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, or a combination of the two before random assignment to supplemental atorvastatin or placebo (38).

Secondary and post hoc analyses of renal function in statin trials have also implicated the renoprotective effects of statins. A post hoc analysis of nearly 700 participants in the Cholesterol and Recurrent Events (CARE) study, for example, demonstrated parity in the rate of GFR decrease between pravastatin and placebo in patients with moderate chronic renal insufficiency (estimated GFR [eGFR] <60 ml/min per 1.73 m\(^2\)) but a significant difference in the rate of decline with pravastatin (2.5 ml/min per 1.73 m\(^2\) per year slower than in placebo recipients; \( P = 0.0001 \)) in those with severe CKD at baseline (eGFR <40 ml/min per 1.73 m\(^2\)) (34). Similarly, a subgroup analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) found that statin treatment either prevented a decline in renal function or significantly improved renal function (39). In GREACE, the effects of dose-titrated atorvastatin (10 to 80 mg/d) on renal function were compared with those of usual care (i.e., lifestyle changes and lipid-lowering agents, including various statins) in previously untreated dyslipidemic patients with coronary heart disease. At study end, CrCl had increased by 12% (\( P < 0.0001 \)) in the atorvastatin group and by 4.9% (\( P = 0.003 \)) in the usual care patients who were given statins, whereas it had declined by 5.2% (\( P < 0.0001 \)) in patients from both groups who had either stopped taking statins or never received them at all.

In the subanalysis of the Treating to New Targets (TNT) study in this issue of CJASN, James et al. (42) investigated how intensive lipid lowering with 80 mg atorvastatin affects renal function when compared with 10 mg atorvastatin in patients with coronary heart disease (CHD). A total of 10,001 patients with CHD and LDL cholesterol levels of <130 mg/dl were randomized to double-blind therapy with 10 mg/d or 80 mg/d atorvastatin. eGFR values determined using the Modification of Diet in Renal Disease (MDRD) equation were compared at baseline and at the end of follow-up in 9656 participants with complete renal data. Mean eGFR at baseline was 65.6 ± 11.4 ml/min per 1.73 m\(^2\) in the 10-mg atorvastatin group and 65.0 ± 11.2 ml/min per 1.73 m\(^2\) in the 80-mg atorvastatin group. At the end of approximately 5 yr follow-up, mean change in eGFR showed an increase of 3.5 ± 0.14 ml/min per 1.73 m\(^2\) with 10 mg atorvastatin and 5.2 ± 0.14 ml/min per 1.73 m\(^2\) with 80 mg atorvastatin (\( P < 0.0001 \) for treatment difference). The expected 5-yr decline in renal function was not observed in the TNT study. eGFR improved in both TNT treatment groups but was significantly greater with 80 mg atorvastatin than with 10 mg atorvastatin, suggesting that this benefit may be dose-related.

This study adds further evidence that statins may exert renal protective effects. However, some caveats remain in the interpretations of this and other similar studies. Estimation of GFR using the MDRD formula has limitations. These studies do not rule out the possibility that statins might affect renal tubular secretion or the metabolism of creatinine, leading to changes in serum levels independent of effects on GFR. Large, prospective, randomized trials with measurements of true (not estimated) GFR are necessary to definitely prove a beneficial effect of statins on CKD progression.

Disclosures
None.

References


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See the related article, “Effect of Intensive Lipid Lowering with Atorvastatin on Renal Function in Patients with Coronary Heart Disease: The Treating to New Targets (TNT) Study” on pages 1131–1139.