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 chemoattrant 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 of renal injury (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-β, 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 GTPases (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 progressing 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 re-
duced proteinuria \( (P = 0.077) \) and less progression toward
ESRD in treated subjects. Tonolo et al. (41) found that simva-
statin 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 GFR 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) re-
duced 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 combi-
nation 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, demon-
strated parity in the rate of GFR decrease between pravastatin
and placebo in patients with moderate chronic renal insuffi-
siciency (estimated GFR [eGFR] <60 ml/min per 1.73 m²) but
a significant difference in the rate of decline with pravastatin (2.5
ml/min per 1.73 m² per year slower than in placebo recipients;
\( P = 0.0001 \)) in those with severe CKD at baseline (eGFR <40
ml/min per 1.73 m²) (34). Similarly, a subgroup analysis of the
Greek Atorvastatin and Coronary Heart Disease Evaluation
(GREACE) found that statin treatment either prevented a de-
cline 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
various statins) in previously untreated dyslipidemic patients
and lifestyle changes and lipid-lowering agents, including
GFR are necessary to definitely prove a beneficial effect of
statins on CKD progression.

Disclosures

None.

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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.