Effects of HMG-CoA reductase inhibitors (statins) on progression of kidney disease

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Chronic kidney disease, especially in the setting of proteinuria, is characterized by hyperlipidemia. In animal models, hyperlipidemia causes glomerular foam cells and glomerulosclerosis. Treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) ameliorates kidney disease in these models. The data of the role of hyperlipidemia in progression of human kidney disease are less clear. Data from small studies in glomerular disease suggest that statins decrease proteinuria. Data mainly from cardiovascular studies suggest that statins decrease the loss of glomerular filtration. The benefit of statins may derive from their lipid lowering effects. More recently, data suggest that the benefit of statins is greater than lipid lowering alone. The pleiotropic effects of statins may derive from inhibition of other downstream targets (isoprenoids) of the mevalonic acid pathway that are separate from cholesterol synthesis. Statins inhibits isoprenylation of Ras and Rho GTPases. These effects may lead to decreased monocyte/macrophage infiltration in the glomerulus, decreased mesangial proliferation and decreased accumulation of extracellular matrix and fibrosis. In addition, inhibition of RhoA and Ras may decrease inflammation and increase eNOS activity. These effects could lead to improvement in the progression of kidney disease.

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Diamond[1] proposed analogous pathologic mechanisms between glomerulosclerosis and atherosclerosis, suggesting the similarity of mesangial cells and vascular smooth muscle cells in response to injury and emphasizing the importance of recruitment of monocytes/macrophages that lead to further damage. In this model, hyperlipidemia leads to acceleration of renal damage and interventions that decrease hyperlipidemia or the infiltration of macrophages ameliorate this damage. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins, which lower low-density lipoprotein (LDL) cholesterol and have other pleiotropic effects, have been proposed to be renoprotective, although this remains controversial. This review discusses the evidence of a benefit of statins on kidney injury.

LIPID ABNORMALITIES IN KIDNEY DISEASE

The dyslipidemia of chronic kidney disease is characterized by increased triglycerides and decreased high-density lipoprotein cholesterol.[2] In the absence of proteinuria, LDL and total cholesterol are not typically elevated. However, there are changes in the lipoprotein composition. Decreased triglyceride catabolism leads to increased remnant particles (for example, intermediate-density lipoprotein) and triglyceride enrichment of LDL.[3] These findings are more pronounced in diabetic nephropathy than in nondiabetic nephropathy.[4] There is also an increase in small dense LDL and oxidized LDL, both of which increase atherogenicity.[5,6] In nephrotic syndrome, there is an increase in total cholesterol and LDL.[6] The level of cholesterol is directly correlated with the degree of albuminuria and indirectly correlated with serum albumin level.[7]

ASSOCIATION OF HYPERLIPIDEMIA WITH PROGRESSION OF KIDNEY DISEASE

The finding that the high cholesterol diets induce or exacerbate renal injury in animal models dates back to at least the 1960s.[8,9] In these models, glomerular foam cells are seen and later stages of disease show glomerulosclerosis. Kasiske *et al.*[10] examined the association of a high cholesterol diet with renal injury. Rats were fed either a high cholesterol diet or standard chow. At 10 weeks of age, they underwent either unilateral nephrectomy or sham surgery. At the time of surgery, the glomerular area was 17% greater and the fractional mesangial area was 29% greater in rats fed the

high cholesterol diet. At 25 weeks, the rats fed a high cholesterol diet showed an increase in glomerulosclerosis, mesangial matrix, and cellularity (macrophage infiltration). The effect of diet was greater than the effect of nephrectomy and the effect of the latter on histologic damage was not significant. However, there was a synergistic relationship of nephrectomy and high cholesterol diet on glomerular capillary pressure.

Most tissue culture models of lipids in kidney damage, and later the effect of statins, have focused on the mesangial cell. Lipids can also induce podocyte damage. Joles *et al.*[11] found in models of unilateral nephrectomy that the early markers of hypercholesterolemia and hypertriglyceridemia were podocyte damage with tubulointerstitial cell activation and injury, without mesangial cell proliferation.

Hyperlipidemia is not proposed to be a primary cause of human kidney disease. Except for inherited diseases such as lecithin-cholesterol acyltransferase deficiency,[12] kidney disease is not a common characteristic of hyperlipidemia. More plausible is that hyperlipidemia accelerates damage after glomerular injury. The data for this hypothesis in human disease are not very strong. Higher LDL cholesterol has been found to predict the development of microalbuminuria in type I diabetes.[13] In a few small, epidemiologic studies of individuals with glomerular disease or diabetic nephropathy, hyperlipidemia predicted faster loss of kidney function.[14,15] Samuelsson *et al.*,[14] in a study of 73 individuals with nondiabetic kidney disease, found that baseline LDL cholesterol predicted rate of glomerular filtration rate (GFR) change, independent of baseline proteinuria. Krolewski *et al.*[16] evaluated predictors of fast progression (creatinine after 3 years follow-up/baseline creatinine >1.5) in 424 individuals with type I diabetes and proteinuria. The proportion of individuals with fast progression was 29% in those with baseline total cholesterol <180 mg/100 ml, 24% for 180–219 mg/100 ml, 38% for 260–299 mg/100 ml, and 48% for >300 mg/100 ml. This finding persisted after controlling for blood pressure; however, they did not control for degree of proteinuria. In the RENAAL study, baseline total cholesterol (HR (hazard ratio) 1.96 per 100 mg/100 ml higher) and LDL cholesterol (HR 1.47 per 50 mg/100 ml higher) were associated with a higher risk of progression to end-stage renal disease.[17] It is not clear from this report whether they controlled for baseline proteinuria. This issue of whether the prior studies control for proteinuria is relevant, given the strong correlation between serum cholesterol levels and renal albumin clearance,[7] and that the degree of albuminuria is a consistent predictor of progression of kidney disease. Hyperlipidemia could simply be a marker of worse underlying disease, rather than a mediator of progression.

STATINS, PROTEINURIA, AND PROGRESSION

In animal models of kidney disease, treatment with a statin decreases proteinuria and ameliorates pathologic damage. There is a decrease in hypercellularity, including macrophages, decrease in expression of inflammatory markers (for example, interleukin-6, monocyte chemoattractant protein-1, transforming growth factor-β, and intracellular adhesion molecule-1), and decrease in fibrosis. This benefit is seen in varying models of kidney disease including diabetes (streptozotocin and obese Zucker rats), 5/6th nephrectomy, cyclosporine, and ureteral obstruction.[18–21] The benefit has been seen with both hydrophilic (fluvastatin and pravastatin) and lipophilic (atorvastatin, lovastatin, and simvastatin) statins. In one study, however, the statin was needed to be administered prior to or at the same time as the initiation of the renal injury, which would decrease applicability to human disease. Christensen *et al.*,[22] in a model of immune-mediated glomerulonephritis, administered simvastatin 6 days prior, on the same day of, at 1 day after, and at 3 days after the administration of nephrotoxic serum. The greatest benefit on proteinuria was seen in animals who were pretreated, although those treated on the same day as the sera injection also derived a benefit. However, simvastatin was ineffective when administered 1 or 3 days after the sera injection and the histology was similar to untreated mice.

The evidence of the effect of statins on loss of GFR in human studies is suggestive of a modest effect, but the strength of evidence is not very strong. The study showing the largest benefit was the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study.[23] The GREACE Study randomized individuals to structured care with titration of atorvastatin to achieve an LDL <100 mg/100 ml compared with standard care, which could include statins (11% on statins). In the structured treatment arm, creatinine clearance improved by 11.6% (76 ± 13 to 84 ± 8 ml/min over 4 years) compared with a decline in clearance in the usual care arm (77 ± 12 to 74 ± 11 ml/min). This difference was not explained by differences in blood pressure control or use of angiotensin-converting enzyme inhibitors (ACEIs). However, other large studies have not seen such a large benefit and this raises the question whether the findings were related in part to other patient care issues. Sandhu *et al.*,[24] in a meta-analysis of studies investigating statins, found that simvastatin resulted in a reduction in the rate of kidney function loss (1.2 ml/min per year difference between medication and placebo). It is important to differentiate the types of study population (glomerular disease, diabetes, hypertension, and cardiovascular disease). In subgroup analyses, only the cardiovascular disease studies showed a statistically significant difference. This is mainly due to the large sample size of the cardiovascular studies that allowed a modest effect size to be statistically significant. It is unlikely that many of the individuals in the cardiovascular studies had intrinsic kidney disease. The rate of decline in estimated GFR (eGFR) was mainly 1–2 ml/min per year in contrast to the studies in glomerular disease or diabetes where most of the studies had an average rate of decline of >4 ml/min per year. The effect size in the other study populations, especially in the studies >1 year in duration was greater. However, these studies have small sample sizes and are more subject to publication bias,

where negative studies are less likely to be published. The dose of the statin might also be related to benefit. A recent cardiovascular study that was published since the publication of the meta-analysis was an analysis of the Treatment to New Targets (TNT) Study.[25] This trial randomized 10,001 individuals with coronary heart disease to 10 or 80 mg of atorvastatin. In both groups, there was an improvement in eGFR, but the change was greater in those who received the higher dose (3.5 ± 0.14 vs 5.2 ± 0.14 ml/min per 1.73 m^2). In addition, few individuals in the higher dose arm developed incident chronic kidney disease (eGFR <60 ml/min per 1.73 m^2; 6.6 vs 9.2%).

A second recent meta-analysis analyzing the association of statin use with reduction in albuminuria suggested that statins did not change albuminuria in individuals with low levels of albuminuria at baseline (<30 mg/day).[26] In this study, the weighted mean difference between statin and placebo was 2 (95% CI: -32, $+35$) for those with baseline albuminuria <30 mg/day vs -48 (-71, -25) and -47 (-67, -26) for individuals with baseline albuminuria 30–299 and $\geqslant 300$ mg/day, respectively. This is also consistent with the analysis of the CARE Study data by Tonelli *et al.*,[27] who found that the improvement in slope of decline of kidney function is greater in individuals with proteinuria (trace or greater on dipstick). The benefit was also greater in individuals with lower eGFR at baseline (<40 ml/min). This study was not able to quantify whether the improvement in slope was related to the degree of proteinuria.

These results suggest that the renal benefit of statins may depend on the presence of intrinsic kidney disease. They also suggest that statins are more likely to be beneficial in proteinuric disease (that is, glomerular disease). This could relate to the mechanism of benefit.

EFFECT OF STATINS ON PROTEINURIA IN INDIVIDUALS ON ANGIOTENSIN-CONVERTING ENZYME INHIBITORS OR ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) reduce proteinuria and slow the progression of proteinuric kidney disease, making them the standard of care. Therefore, the clinical question is whether statins lower proteinuria above the effect of an ACEI or ARB. Table 1 summarizes the results from four randomized studies that evaluated the effect of statins on proteinuria in individuals on ACEI or ARB. The Atthobari Study in Table 1 was from PREVEND-IT, a randomized 2×2 study of fosinopril and pravastatin in individuals with high-normal albuminuria or microalbuminuria.[30] In this study, fosinopril decreased proteinuria, but pravastatin did not. Two of the studies were in individuals with overt proteinuria.[28,29] In both of these studies, statin lowered proteinuria to a greater degree than placebo. Interestingly, Lee *et al.* recently published a follow-up study where they withdrew the pravastatin in one-half of the treated individuals and continued the pravastatin for an additional 6 months in the other half.[32] The proteinuria on those whose statin was withdrawn returned to baseline values, while it remained stable in those who continued on treatment.

POTENTIAL MECHANISMS OF BENEFIT OF STATINS

A number of mechanisms have been proposed to explain the renal benefit of statins in kidney disease (Table 2). It is not clear whether the potential renal benefits of statins relate to lipid lowering or to other pleiotropic effects of statins. Mesangial cells bind and uptake LDL, oxidized LDL, intermediate-density lipoprotein via specific receptors.[33] LDL also binds to extracellular matrix when the concentration is high where it might be subject to oxidation.[34] Coritsidis *et al.*

Table 1 | Effect of statins on proteinuria in individuals on ACEIs or ARBs in randomized studies

Study (reference)	*N*	Study duration	Study population	Statin	ACEI/ARB	Change in proteinuria statin treated	Change in proteinuria placebo
Lee *et al.*[28]	40	6 months	Hypertension; proteinuria, 300–3000 mg/day; nondiabetic, creatinine, <1.5 mg/100 ml	Pravastatin, 10 mg	Losartan (average dose >50 mg)	-752 ± 399 mg/day	-64 ± 216 mg/day
Bianchi *et al.*[29]	56	12 months	Idiopathic GN; proteinuria >1 g/day	Atorvastatin, 10–40 mg; titrated to LDL <120 mg/100 ml or decline $\geqslant 40\%$	ACEI, ARB or both—doses not stated	-45.5% 2.2 ± 0.1 to 1.2 ± 1.0 g/day	-10% 2.1 ± 0.1 to 1.85 ± 0.1 g/day
Atthobari *et al.*[a 30]	396	4 years, 2×2 design	Albuminuria 15–300 mg/day	Pravastatin 40 mg/day	Fosinopril, 20 mg/day	-11.9 (95% CI: -21.1, -1.7)	-23.9 (95% CI: -32.3, -14.6)
Tonolo *et al.*[31]	86	4 years	Type II diabetes, baseline GFR decline >1 ml/min per 1.73 m^2 per year	Simvastatin, 40 mg/day, vs cholestyramine, 3 g/day	Ramipril, 5 mg/day, or lisinopril, 20 mg/day	77 (31–259) to 40 (10–319)	(cholestyramine) 88 (34–261) to 81 (17–399)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; GFR, glomerular filtration rate; GN, glomerulonephritis; LDL, low-density lipoprotein.
[a]Data presented are for those treated with fosinopril ± pravastatin.

Table 2 | Potential mechanism of statin benefit in kidney disease

Inhibit mesangial proliferation
Inhibit induction of TGF-β and increase in extracellular matrix
Inhibition of induction of MCP-1
Decrease in macrophage infiltration
Decrease in inflammation and oxidative stress
Ameliorate podocyte damage
Hemodynamic effects on endothelial function and vasodilation
Ameliorate renal vascular disease

MCP-1, monocyte chemoattractant protein-1; TGF-β, transforming growth factor-β.

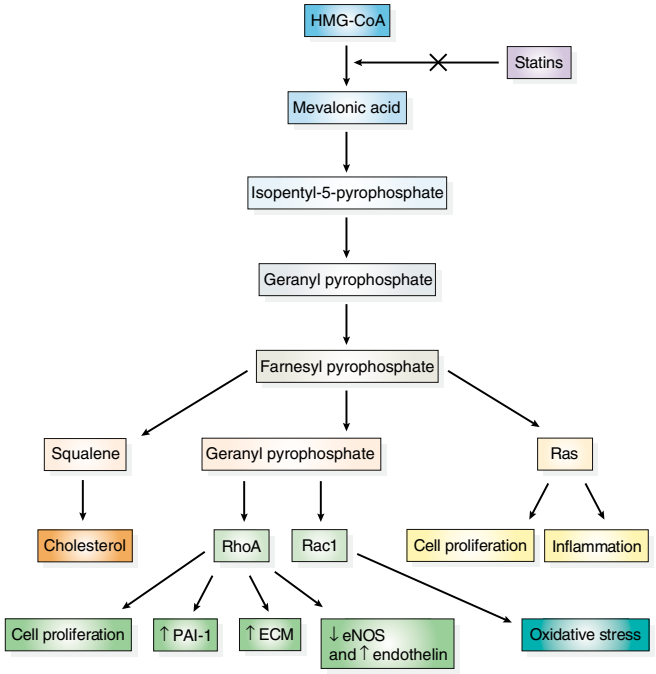

Figure 1 | Mevalonic acid pathway and implications for kidney disease. ECM = extracellular matrix. Data from Liao,[37,38] Kim *et al.*,[39] Rikitake and Liao,[40] Vecchione *et al.*,[41] Gojo *et al.*,[42] Toblli *et al.*,[43] Xu *et al.*,[44] and McTaggart.[45]

found that LDL stimulated mesangial proliferation, while oxidized LDL was cytotoxic in tissue culture.[33,35] Rovin *et al.*[36] found that mesangial cells treated with LDL increase expression of fibronectin and monocyte chemoattractant protein-1 messenger RNA and secretion in a dose-dependent fashion. Therefore, it is possible that beneficial effects of statins are related to their effect on lipoprotein concentration.

It has been recognized that statins have pleiotropic effects that may be mediated by downstream targets of the mevalonic acid pathway that are separate from cholesterol synthesis (Figure 1).[37,38] Statins decrease the synthesis of other isoprenoids (for example, farnesyl pyrophosphate and geranyl geranyl pyrophosphate) which inhibits isoprenylation of Ras and Rho GTPases.[38,39] In vascular tissue, this leads to increased endothelial nitric oxide synthase activity, decreased oxidative stress and decreased expression of inflammatory markers.[38,40,41] The beneficial effects of statins on mesangial proliferation, expression of transforming growth factor-β with decrease in extracellular matrix, monocyte chemoattractant protein-1 expression and macrophage infiltration in the kidney and decrease chemokine and inflammatory marker expression may be mediated through inhibition of Ras and RhoA.[39,42,43,46–49] They also suggest other potential targets for treatment of kidney disease.[42]

A more recently described mechanism of renal protection of statins focuses on the podocyte, rather than the mesangial cell. Podocyte damage causes proteinuria and glomerulosclerosis.[50] It has been proposed that the degree of podocyte damage determines whether the glomerulus can undergo repair compared with glomerulosclerosis (podocyte depletion hypothesis).[51] Statins ameliorate podocyte damage and decrease podocyte apoptosis in animal models,[52,53] which could therefore decrease glomerulosclerosis. In a small randomized study or 40 patients with chronic glomerulonephritis, treatment with cerivastatin decreased the number of podocytes found in the urine, whereas there was no change in the placebo group.[54]

ISSUE OF TUBULAR PROTEINURIA WITH STATINS

The Food and Drug Administration (FDA) approval of rosuvastatin raised the controversy of statin-induced proteinuria. In the initial preapproval studies, the incidence of proteinuria was higher in treated subjects, and the increase in proteinuria was mainly seen in those taking 80 mg (not an FDA-approved dose), but there was a trend for the 40-mg dose as well.[55] The proposed mechanism of the proteinuria is tubular inhibition of protein uptake.[55] In a tissue culture model using human kidney tubular cells, simvastatin, pravastatin, and rosuvastatin decreased receptor-mediated protein endocytosis of albumin in proximal tubular cells in a dose-dependent fashion.[56] There was no effect on cell viability. Whether there are differences between statins in *in vivo* models is not clear, as most prior studies of statins in nonkidney disease populations have not systematically evaluated for proteinuria. If the medication needs to act from the luminal surface to inhibit the uptake of proteinuria, it is theoretically possible that rosuvastatin would have a greater effect as a larger proportion of the medication is filtered and excreted unchanged. However, it is important to recognize that the increase in proteinuria with rosuvastatin has not led to a greater risk of acute injury or progression of kidney disease.[57,58] The National Lipid Association Statin Safety Task Force recent conclusions were that in the absence of rhabdomyolysis, statins do not cause acute renal failure or insufficiency.[59,60] The ongoing PLANET studies will compare 10 mg rosuvastatin 80 mg with atorvastatin on change in proteinuria in individuals with diabetic (PLANET I) and nondiabetic (PLANET II) over 1 year (Clinicaltrials.gov; NCT 00296400, NCT 00296374).

CONCLUSION

Statins are effective cholesterol-lowering medications that decrease cardiovascular disease. They may also have beneficial effects on ameliorating the damage from kidney disease. This benefit may be secondary to the pleiotropic effects of statins

and not solely to lipid lowering. The current data on renal benefit are not clear and, at this time, statins should be prescribed for cardiovascular disease. The future results of the Study on Heart and Renal Protection (SHARP) should help define the role of statins on progression of kidney disease, as well as cardiovascular disease in individuals with chronic kidney disease.

DISCLOSURE

Dr Fried has served as a consultant for and received honoraria from Pfizer and research support from Merck (pending).

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