Beneficial effects of statins on the kidney: the evidence moves from mouse to man

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Introduction

The decline in renal function in healthy humans begins after maturity and is reflected in a fairly constant decrease in glomerular filtration, which in 40–60-year-olds averages 8 ml/min lost glomerular filtration rate (GFR) (6%) per decade as determined by endogenous creatinine clearance (CrCl) [1]. Prevention of the development, or progression, of chronic renal failure is the holy grail of nephrology and while success depends in part on the screening and detection of underlying renal disorders, systemic diseases, namely hypertension and diabetes mellitus, remain the commonest causes of end-stage renal failure. Early detection of renal disease is very feasible in both settings by using microalbuminuria as a marker of cardiovascular and renal risk.

Control of blood pressure (BP) has become the cornerstone of ‘nephroprotection’ [2]. ACE inhibitors and angiotensin receptor blockers have achieved primus inter pares status amongst anti-hypertensives, with suggestions that their actions go further than can be explained by reduction of BP alone [3]. However, there are several other important risk factors that independently or in concert with BP can cause renal functional deterioration [4]. These include gender, smoking, proteinuria and dyslipidaemia [2].

One of the paradoxes in renal medicine has been the abundant nature of experimental, mainly murine, evidence that dyslipidaemia leads to glomerulosclerosis [reviewed in 5,6] but the dearth of epidemiological or trial-based evidence that reversal of dyslipidaemia in man is nephro-protective. Data from conditions such as morbid obesity suggest an association with focal glomerulosclerosis but the North American experience [7] has been difficult to generalize to elsewhere.

This paradox is now closer to resolution following several recent trials in hypertensive/dyslipidaemic cohorts, many of whom had mild to moderate chronic renal impairment. It is the purpose of this review to examine the present state of evidence linking dyslipidaemia and its treatment to renal functional decline.

As we do not have the definitive intervention trial with cholesterol reduction as the intervention, and the primary outcome of renal functional evolution with time and treatment, we have to depend on post hoc analyses, which, though very valuable, are not able to replace a trial with a primary renal objective.

The impact of dyslipidaemia on normal renal function

The Helsinki Heart Study (HHS) involved 2702 dyslipidaemic (non-HDL-cholesterol >5.2 mmol/l)
men screened from 19,000 40–55-year-old male government employees in Finland [8]. Normal renal function was an entry criterion (plasma creatinine <115 μmol/l for inclusion), but in the event, 30 subjects with plasma creatinine between 116 and 135 μmol/l were included. 4081 men were randomized to gemfibrozil (1200 mg/day) or placebo and all were given dietary counselling to lower cholesterol. The study was for 5 years with cardiovascular events as the primary end points. The decline in renal function was estimated from the least squares linear regression of the slope of the reciprocalized plasma creatinine values over time. During the study period there was a monotonous increase in the mean serum creatinine in both gemfibrozil and placebo groups averaging 3% (an increase of ~5–6 μmol/l). Hypertension accelerated renal dysfunction significantly (~8 μmol/l for SBP > 160 mmHg compared with ~5 μmol/l for SBP < 140 mmHg). Subjects with an elevated low- to high-density lipoprotein ratio (> 4.4) had a 20% faster decline than those with a ratio of < 3.2. After multiple regression analyses, both the contribution of the lipoprotein ratio and the protective effect of increased HDL-C remained significant. As expected, hypertension and unfavourable lipoprotein profiles interacted as risk factors for progressive renal decline.

The relationship between lipid abnormalities and renal function has also been evaluated in a recent prospective cohort study among 4483 initially healthy men participating in the Physicians’ Health Study who provided blood samples in 1982 and 1996. Main outcome measures were elevated creatinine, defined as > 1.5 mg/dl (133 μmol/l), and reduced estimated creatinine clearance, defined as < 55 ml/min. Cholesterol parameters included total cholesterol (< 200, 200–239 and > 240 mg/dl), HDL (< 40 mg/dl), total non-HDL cholesterol, and the ratio of total cholesterol to HDL. After 14 years, 134 men (3.0%) had elevated creatinine and 244 (5.4%) had reduced creatinine clearance. The multivariable (smoking, BP, body mass index) age-adjusted relative risk for elevated creatinine was 1.68 for total cholesterol > 240 mg/dl, 2.12 for HDL < 40 mg/dl, 2.22 for the highest quartile of the total cholesterol/HDL ratio (> 6.8), and 2.03 for the highest quartile of non-HDL cholesterol (> 196.1 mg/dl). Therefore, elevated total cholesterol, high non-HDL cholesterol, a high ratio of total cholesterol to HDL, and low HDL in particular were significantly associated with an increased risk of developing renal dysfunction in men with an initial creatinine of <133 μmol/l [9].

**Statin trials in patients with chronic renal failure**

There are many trials examining renal function and proteinuria as end points after treatment with statins in patients with chronic renal impairment. An important study was undertaken recently by Bianchi et al. [10]. They conducted a prospective controlled open-label study using atorvastatin vs no lipid therapy on the progression of chronic renal impairment and proteinuria in 56 patients with pre-existing renal disease already treated with ACE/ARB therapy. By the end of one year of therapy with atorvastatin 24 h urinary protein losses had fallen from 2.2 to 1.2 g (P < 0.01), and renal function was stable (CrCl 51 and 50 ml/min, respectively, P = NS). This compares with no change in 24 h protein loss (2.0 vs 1.8 g) and a fall in CrCl (50–44 ml/min, P < 0.01) in the lipid placebo group. Similarly, in a publication involving 30 children with ‘early’ IgA nephropathy, therapy with fluvastatin for 12 months had significant beneficial effects on proteinuria, haematuria and serum creatinine levels [11]. A meta-analysis of 13 controlled trials in 404 subjects was undertaken by Fried et al. [12]. Despite the small numbers of subjects in each trial, when the outcomes were pooled it was shown that the use of lipid-lowering therapy (mainly, but not exclusively, statins) was associated with a protective effect on loss of renal function amounting to 1.9 ml/min/year in comparison with controls (95% confidence interval 0.3–3.4), an effect whose magnitude was related to length of treatment. The majority of subjects, however, had either diabetes and/or nephrotic syndrome, and although the degree of renal dysfunction was similar, the rate of renal decline was greater than that seen in hypertensive, dyslipidaemic populations without a primary renal pathology.

The picture with chronic decline of renal allograft function is more complex. There are many factors in the context of ‘chronic allograft nephropathy’ that may be relevant to renal outcome, and these may in certain cases outweigh any putative benefit from statin use. The findings of a small study of fluvastatin use demonstrating a reduction in the decline of renal transplant function (using patients as their own controls [13]) are more than outweighed by the negative report of the ALERT study on renal functional decline [14] (also using fluvastatin). Likewise, 14199 renal transplant subjects showed improvement of endothelial function but not the prognostically more important parameter of large artery stiffness (elastic incremental modulus of the common carotid artery) after 36 months of fluvastatin therapy [15]. One explanation for these disappointing outcomes may be that fluvastatin is a weaker statin than the most modern members of this drug family, achieving ~20% reduction in LDL-C, not the 40–60% reduction seen with atorvastatin and rosuvastatin.

In patients with ADPKD, a double blind cross-over study recently showed potent effects on renal haemodynamics [16]. Ten normocholesterolaemic ADPKD subjects were treated in random order for 4 weeks with 40 mg of simvastatin or placebo daily. The primary end-points were renal blood flow, GFR and endothelial function [using inulin/para-amino hippurate to determine effective renal plasma flow (ERPF) and GFR, as well as forearm vascular reactivity to acetylcholine, l-monomethylarginine and nitroprusside as assessed
by venous occlusion plethysmography). The plasma cholesterol fell from 4.2 to 3.2 mmol/l on simvastatin. Treatment with simvastatin was associated with an increase in GFR from 124 ± 4 to 132 ± 6 ml/min with concomitant increase in ERPF from 494 ± 30 ml/min to 619 ± 67 ml/min. Simvastatin also significantly improved acetylcholine-induced forearm vasodilatation (as statins have been shown to do in the coronary arterial bed). One explanation for these findings would be acutely enhanced nitric oxide production in patients on simvastatin but these functional effects need to be separated from the other more chronic benefits of statin use on structural and morphological parameters in the glomerulus.

Studying ‘nephrological’ rather than ‘hypertensive’ patient cohorts should be a fertile ground on which to test the hypothesis that statins are nephroprotective. The rate of renal functional decline is usually higher, which reduces the number of subjects necessary to follow. However, there is also the risk that the cholesterol/statin effect may be swamped by other factors having an even greater impact on renal function (e.g. immunological). Despite this, evidence from the majority of studies indicates that statin therapy is associated with significant patient benefit in individuals with established chronic renal failure.

**Statin trials in patients with hypertension or dyslipidaemia and normal/near-normal renal function**

Most trials of anti-hypertensives and lipid-lowering drugs go to some lengths to exclude patients with chronic kidney disease. This is most often done on the basis of plasma creatinine values. Fortunately, as we nephrologists know, this is an unsophisticated approach, and as a result many subjects are included whose creatinine clearance is significantly reduced. As a result of this, we can examine the effect of these interventions on large cohorts.

The CARE study was a randomized trial of pravastatin vs placebo in 4159 subjects with hyperlipidaemia and a previous history of myocardial infarction [17]. Patients were prospectively followed-up for 60 months with end-points being major adverse cardiovascular events. From this large study it was possible to undertake a post hoc subgroup analysis. Participants with estimated GFR (MDRD-GFR) < 60 ml/min per 1.73 m² body surface area at baseline were considered to have moderate chronic renal insufficiency. Multivariate regression was used to calculate rates of decline in MDRD-GFR for individuals receiving pravastatin and placebo, controlling for prospectively determined covariates that might influence rates of renal function loss. A change in renal function could be calculated in 3384 individuals, of whom 690 (20.4%) had MDRD-GFR < 60 ml/min per 1.73 m² and were eligible for inclusion.

Among all individuals with MDRD-GFR < 60 ml/min per 1.73 m², the MDRD-GFR decline in the pravastatin group was not significantly different from that in the placebo group (0.1 ml/min per 1.73 m²/year slower; 95% CI –0.2 to 0.4; \( P = 0.49 \)). However, there was a significant stepwise inverse relation between MDRD-GFR before treatment and slowing of renal function loss with pravastatin use, with more benefit in those with lower MDRD-GFR at baseline \( (P = 0.04) \). Rate of change in MDRD-GFR in the pravastatin group was 0.6 ml/min per 1.73 m²/year slower than placebo (95% CI –1.0 to 1.2; \( P = 0.07 \)) in those with MDRD-GFR < 50 ml/min, and 2.5 ml/min per 1.73 m²/year slower (95% CI 1.4 to 3.6; \( P = 0.0001 \)) in those with MDRD-GFR < 40 ml/min per 1.73 m²/year.

Pravastatin also reduced rates of renal loss to a greater extent in participants with than without proteinuria at baseline \( (P = 0.006) \). Proteinuria at baseline was also associated with a much greater protective effect of pravastatin [18].

One of the largest statin-based cardiovascular disease (CVD) prevention trials was the Heart Protection Study [19]. Adults aged 40–80 years of age with previous CVD or diabetes were allocated 40 mg of simvastatin daily or placebo. All-cause mortality was significantly reduced (12.9% deaths among 10 269 allocated simvastatin vs 14.7% among 10 267 allocated placebo; \( P = 0.0003 \)) due to a highly significant 18% reduction in the coronary death rate (5.7 vs 6.9%; \( P = 0.0005 \)). Impressive reductions of about one-quarter in the first event rate for non-fatal myocardial infarction or coronary death, non-fatal or fatal stroke, and coronary or non-coronary revascularization were also observed. The 5903 diabetic subjects in this large trial were further studied and compared in more detail with the 14 573 non-diabetic subjects. Unadjusted serum creatinine concentrations increased for all patients, with or without diabetes, over a period of 4.6 years. However, allocation to simvastatin significantly reduced the observed rise with time in serum creatinine in both diabetic and non-diabetic subjects [20].

A large secondary CVD prevention trial (GREACE) examined the use of atorvastatin at doses aimed to achieve marked reductions in LDL-cholesterol in 1600 Greek patients with established coronary heart disease [21]. 800 were allocated to atorvastatin (median dose 24 mg), and 95% of these subjects achieved the lipid-reduction goals (LDL-cholesterol falling by 45–50% and HDL-cholesterol rising by 7%). The use of atorvastatin reduced, in comparison with ‘usual’ care, total mortality (RR 0.57, CI 0.39 to 0.78, \( P = 0.0021 \)), coronary mortality (RR 0.53, CI 0.29 to 0.74, \( P = 0.0017 \)), coronary morbidity and stroke. Renal function was examined in this study (once again using a post hoc analysis) using Cockcroft–Gault derived CrCl values [22]. The mean CrCl at entry was 77 ml/min. Patients on atorvastatin showed a 12% rise in CrCl, patients on other statins a 4.9% rise in CrCl and statin-free patients a 5.2% fall in CrCl over a 36 months follow-up. The effect on CrCl was evident from as early as 6 weeks, there was a clear dose–response relationship and those with the lowest CrCl at entry showed the greatest improvement with atorvastatin therapy.
Other potentially important factors such as BP, anti-hypertensives, gender and smoking were well balanced across the two groups.

Data concerning renal function from the recently reported ASCOT-LLA trial [23] are not yet generally available but will be of great interest as they will add significantly to the evidence base in this area.

Conclusions

There is not only abundant experimental evidence from a wide variety of animal models that a combination of nephroprotective measures is highly effective [24], but now rapidly emerging data from diverse clinical sources support this assertion in man. Statin use for dyslipidaemia (and achieving significant reduction in LDL-cholesterol) does seem to slow down age-related renal functional decline, especially in concert with BP and anti-proteinuria measures, at least as far as the post hoc analyses of large intervention trials go. The reasons to favour the use of statins in chronic renal disease include beneficial effects on renal haemodynamics, endothelial function, monocyte recruitment, mesangial cell proliferation and mesangial matrix accumulation. Many of these effects have cardiovascular benefits at the same time. Even if there were no good evidence for beneficial renal outcome by using statins in patients with mild-moderate chronic renal failure, it is clearly known that mild CRF, and separately but additively, microalbuminuria, is associated with a marked increase in susceptibility to CVD [25,26]. Indeed, CRF and proteinuria, likewise to LVH and diabetes, confer the same CVD risk as a positive history of previous cardiovascular events. In other words, the ‘primary’ event is development of proteinuria or renal impairment and interventions subsequent to that are a form of ‘secondary’ renal and cardiovascular prevention.

Are all statins the same? The answer is probably yes. Negative studies may be explained by lack of potency in reducing LDL-cholesterol and/or raising HDL-cholesterol. Certainly, with the presently available statins there is no good evidence for any additional safety concerns using these drugs in chronic renal failure [17], in dialysis patients [27] or in renal transplant recipients [14]. On this basis the question should be asked of someone in chronic renal failure—why is this patient not on a statin?

Unanswered questions, though, include at what level should we start a statin (as so many renal patients have reduced cholesterol values due to malnutrition) and to what extent should we bear down on LDL-cholesterol, or should we titrate to another target, e.g. CRP or IL-6 levels? Certainly, both lipid-lowering effects and pleiotropic/anti-inflammatory effects seem valuable, as shown by de Zeeuw’s group [28] examining the relationship between CRP and GFR in 7317 non-diabetic subjects with mild chronic renal impairment. Their findings indicated that elevated CRP was positively associated with cardiovascular and renal risk factors, namely age, body mass index, BP, serum cholesterol level, smoking, plasma glucose level and elevated urinary albumin excretion. They also describe an association between inflammation, as measured by CRP, and hyperfiltration.

This is a similar dilemma to that in treatment of hypertension and proteinuria with ACE-I/ARB, where the dose–response curves for BP and protein reductions may not coincide. Thus, the call for a placebo-controlled trial of statins in dialysis patients with patient survival as an outcome is justified at present [29], as there is some confusion, through co-localization of risk factors and reverse epidemiology [30], about the benefits of statins in this population [31]. ACE-I and statins have direct effects on their primary targets—BP and lipids, respectively—but both have additional evidence for pleiotropism (benefits not entirely explicable by reference to the primary target). Both seem to benefit the renal population with its greatly increased risk of de novo or recurrent CVD and progression to ESRD.

We still would benefit from a primary renal-outcome lipid-lowering therapy study; however, it is not likely that we shall see one anytime soon. Until we do, we favour a more systematic use of statins in chronic kidney disease patients than is typically the case today.

Conflict of interest statement. None declared.

References

Recurrent focal glomerulosclerosis in the era of genetics of podocyte proteins: theory and therapy

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**Keywords:** focal segmental glomerulosclerosis; inherited nephrotic syndrome; podocin; post-transplant recurrence of proteinuria; proteinuria

**Introduction**

Focal segmental glomerulosclerosis (FSGS) is the most frequent cause of intractable proteinuria in children and adults and is emerging as a major glomerular cause of chronic kidney disease [1]. Most of the aspects related to its pathogenesis remain unknown, one major issue being post-transplant recurrence. Recent advances in