Statins—beyond lipids in CKD

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Introduction

In the general population, beneficial effects of statin treatment on cardiovascular end points are well established [1]. Chronic kidney disease (CKD) is a status of specific lipid disturbances, i.e. dyslipidaemia with increased levels of triacylglycerides, small dense and oxidized LDL (oxLDL), and lower HDL cholesterol levels. In nephrotic syndrome, also disturbances, i.e. dyslipidaemia with increased levels of triglycerides, small dense and oxidized LDL (oxLDL), and lower HDL cholesterol levels. In nephrotic syndrome, also


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in theory, beneficial systemic and renal effects of lipid lowering in CKD by statins could be expected. In fact, there are indeed well-proven general effects of statins in CKD patients, i.e. lipid-lowering, anti-inflammatory and anti-oxidative effects [5] (Figure 1). In two studies in CKD patients using cardiovascular end points, statin therapy failed to provide a specific benefit [6,7]. This failure may be due to several limitations: firstly, the 4D and the AURORA study were underpowered compared with studies in non-renal patients. Secondly, the follow-up period was probably too short since a more detailed inspection of the survival curves in the 4D study clearly shows that these start to separate after 3 years, possibly indicating that already existing lesions cannot be modified, but the development of new lesions is prevented. A third point might be the results of a sub-analysis which clearly show a benefit from statin therapy (i.e. significantly less events) in those patient whose LDL levels were in the highest quartile. Thus, probably, also LDL levels have to be taken into account when deciding about statin therapy in CKD patients. Moreover, interaction of statins with other drugs usually used in CKD patients was not formally addressed in the
two studies. A more definite answer with respect to potential beneficial effects of statins in CKD patients will most likely be given by the SHARP study, the results of which will be presented at the end of this year.

There is, however, not much data on specific renal effects of statins, and in the existing studies, the analysis of renal end points was not possible due to many confounding factors. In a post-hoc subgroup analysis of the CARE study, a randomized trial of pravastatin versus placebo in 4159 participants with previous myocardial infarction and total plasma cholesterol <240 mg/dL, a beneficial effect of statins on loss of renal function in moderate CKD was found. Here, pravastatin reduced rates of renal loss to a greater extent in participants with than without proteinuria [8]. A systematic meta-analysis found a small beneficial effect of statins on kidney function decline (particularly in patients with cardiovascular disease), and proteinuria [9]. The hereby analysed studies, however, showed several limitations [10]. Another meta-analysis using the data from randomized, placebo-controlled trials of statins reporting baseline and follow-up measurements of albuminuria or proteinuria (15 studies, n = 1384 patients) [11] found a reduction of albuminuria (11 studies) or proteinuria (4 studies) in 13 of 15 studies. Sukhija and co-workers [12] analysed 197 551 patients with 29.5% (58 332 patients) on statins and 70.5% (139 219 patients) without statins. During 3.1 years of follow-up, 3.4% of patients developed renal dysfunction. After adjustment for demographics, risk factors and medication, statins decreased the odds of developing renal dysfunction by 13% (P < 0.0001), and this was independent of the decrease in cholesterol. A more recent meta-analysis [13] also investigated the effects of statins in CKD patients and concluded with respect to potential renal effects: ‘Reno-protective effects of statins are uncertain because of relatively sparse data and possible outcomes reporting bias.’

As the clinical data are obviously controversial, we will provide the reader in the following with some additional aspects from in vitro studies and animal experiments in models of renal disease which are in favour of specific beneficial effects of statins. We are aware, however, that the data from experimental studies do have limitations with respect to extrapolation to CKD patients. They could clarify, however, some principle mechanisms of renal effects of statins which could be important for therapeutic considerations in CKD patients in the future.

Statin therapy in CKD—more than just lipid lowering

Apart from lipid lowering, statins provide a number of additional, so-called ‘pleiotropic effects’ which are due to inhibition of isoprenylation of Ras- and Rho-GTPases [14] (Table 1). Some of these pleiotropic effects may specifically protect the diseased kidney, i.e. anti-inflammatory, anti-oxidant, anti-proliferative, pro-apoptotic and anti-fibrotic effects as well as having beneficial effects on renal

Table 1. Summary of specific renal effects of statins (modified from [14])

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<tr>
<th>Effects on renal cells</th>
<th>Anti-proliferative effect on mesangial cells (inhibition of mesangial cell proliferation)</th>
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<td>Podocyte-protective effects via anti-apoptotic effects, and cytoskeletal and barrier preservation</td>
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<td>Stem cell-activating effects</td>
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<td>Anti-inflammatory effect via inhibition of MCP-1 gene expression and decreased macrophage and T-cell infiltration</td>
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haemodynamics. These potentially renoprotective effects of statins are based on the pathophysiological mechanism of renal damage and progression, i.e. renal inflammation, mesangial cell proliferation and matrix synthesis, interstitial fibrosis, and impaired renal flow. In addition, specific effects of statins on glomerular endothelial cells and podocytes are also likely.

**Effect of statins on mesangial cells**

Already more than 10 years ago, beneficial effects of statins on mesangial cell (MC) proliferation were documented in *in vitro* as well as *in vivo* models of renal disease. Using the anti-Thy1 rat model of mesangiproliferative glomerulonephritis (GN), marked anti-proteinuric and renoprotective effects due to selective anti-proliferative and anti-inflammatory actions of statins were documented [15]. In this model, the anti-proliferative effect of simvastatin was also associated with reduced CDK2 expression in MC, and these effects were independent of lipid lowering. In another animal model of renal disease, i.e. nephrotic rats, also significant anti-proteinuric and anti-inflammatory effects of statins were shown [16]. Apart from lowering serum cholesterol and proteinuria, lovastatin significantly reduced glomerular macrophage influx and expression of MCP-1 mRNA [16]. *In vitro* as well as *in vivo*, the anti-proliferative and anti-fibrotic effects of statins on MC have been attributed to the inhibition of Rho and Ras pathways [17] as well as to the inhibitors of ccn2 (ctgf) mRNA expression [18].

**Effect of statins on podocytes**

In recent years, podocytes have moved into the focus of basic and clinical research in nephrology. Using podocyte cultures, oxLDL was shown to dose dependently induce podocyte apoptosis, decrease Akt activity, phosphorylation and nephrin expression, and disturb the F-actin cytoskeleton [19]. These negative effects of oxLDL could be completely prevented by different statins in a dose-dependent manner. Here, statins exert protective effects on podocytes by stabilizing the podocyte cytoskeleton and barrier function via PI3k. Cormack-Aboud et al. [20] studied the effect of rosuvastatin on puromycin aminonucleoside (PAN)- and adriamycin-induced apoptosis in p21<sup>+/+</sup> and p21<sup>−/−</sup> conditionally immortalized mouse podocytes and found a protection of podocyte apoptosis through a p21-dependent pathway.

In the rat DOCA-salt model of hypertension, fluvastatin showed a selective beneficial effect on glomerular damage and particularly on injured podocytes, whereas tubulointerstitial inflammation and proliferation were not affected [21]. Interestingly, the marked anti-proteinuric effect of the statin was independent of blood pressure or cholesterol lowering. In the rat model of PAN-induced nephrosis, fluvastatin significantly prevented PAN-induced proteinuria and serum creatinine elevation, and dramatically mitigated podocyte injury [22]. In contrast to the DOCA-salt study [21], fluvastatin also prevented tubulointerstitial damage with the repression of PAN-induced NF-kappaB and activator protein-1 activation. Additionally, fluvastatin inhibited glomerular and podocytic RhoA-GTPase expression which was markedly increased in PAN, indicating that the beneficial effects of fluvastatin are attributable to direct modulation of excessive RhoA activity. Of note, beneficial effects of statin on podocyte damage were also shown in HIV-associated nephropathy [23] as well as in a mouse model of early-stage type 2 diabetes mellitus, i.e. high-fat diet in C57BL/6.

**Effects of statins on renal endothelium**

In the hypertensive Dahl salt-sensitive rat, a beneficial effect of atorvastatin on endothelial relaxation and vasoconstriction in parallel with decreased O<sub>2</sub> production and increased eNOS activity was documented [24]. In a recent paper of the same group [25], statins were found to lower blood pressure, attenuate proteinuria and glomerulosclerosis due to anti-oxidative effects (increased cNOS and NOS3 protein expression), and decrease LOX-1 mRNA and MCP-1 mRNA expression. Using the animal model of the spontaneously hypertensive rat (SHR), Ito et al. [26] confirmed that atorvastatin upregulates NO synthases in the kidney by Rho-kinase inhibition and Akt activation. In an animal model of obesity and hypertension (WKY and SHR, high-fat diet), simvastatin reduced oxidative stress, thereby protecting against endothelial dysfunction and renal injury [27].

In summary, the aforementioned *in vivo* studies showed marked renal anti-oxidative as well as vasodilative effects of statins.

**Beyond the kidney—immunomodulatory effects of statins**

In addition to the nephroprotective effects on glomerular cells and renal endothelium, a completely novel role of statins was recently documented. Using atorvastatin in the mouse anti-GBM GN model, Eller et al. [28] showed lipid-lowering, anti-proteinuric and anti-fibrotic effects together with an interesting renal and systemic immunomodulatory effect. Atorvastatin decreased interstitial and glomerular T-cell, macrophage, neutrophil, and Th17-cell infiltration in the kidney and the draining lymph nodes. Atorvastatin also lowered the systemic Th1 and Th17 response as well as the amount of intracellular IL-17 in CD4<sup>+</sup> T cells whereas IL-17 production of regulatory T cells was increased.

**Conclusion and outlook—statins beyond the horizon**

Apart from the glomerular and immunomodulatory effects of statins, other currently less well-investigated effects of statins may become interesting in the near future: already
some years ago, statins were found to increase the number of endothelial progenitor cells (EPCs) and haematopoietic stem cells (HSCs) via PI3k and Akt [29]. Evidence was provided that the increased pool of circulating EPCs originates from bone marrow thus enhancing neovascularization. Statins also induced differentiation of CD34+ EPCs similar to VEGF [29]. In the hypertensive hypercholesterolaemic pig model, simvastatin decreased EPC apoptosis, thereby rescuing renal repair mechanisms and counteracting renal damage [30]. These statin effects may become important for supportive therapy in renal damage in the future.

Conflict of interest statement. None declared.

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