

Atorvastatin improves tubular status in non-diabetic patients with chronic kidney disease — placebo controlled, randomized, cross-over study

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Background. There is evidence that dyslipidemia is associated with chronic kidney disease (CKD) and it has been implicated in the progression of renal damage. Optimal management of dyslipidemia should therefore lead to renal benefits. A number of experimental models demonstrate a beneficial effect of statins in ameliorating renal damage. However, the exact mechanism by which statins protect against renal damage remains unclear. **Methods.** In a placebo-controlled, randomized, cross-over study we evaluated the influence of atorvastatin (ATO) 40 mg/day added to the renin-angiotensin-aldosterone system (RAAS) blockade on proteinuria and surrogate biomarkers of tubular damage or injury in 14 non-diabetic patients with proteinuria (0.4–1.8 g per 24 h) with normal or declined kidney function (eGFR 55–153 ml/min). In the eight-week run-in period, therapy using angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin II subtype 1 receptor antagonists (ARB) was adjusted to achieve a blood pressure below 130/80 mm Hg. Next, patients were randomly assigned to one of two treatment sequences: ATO/washout/placebo or placebo/washout/ATO. Clinical evaluation and laboratory tests were performed at the randomization point and after each period of the study. The primary end point of this study was a change in proteinuria measured as 24-h urine protein excretion (DPE). Secondary end points included urine *N*-acetyl- β -D-glucosaminidase (NAG) and α 1-microglobulin (α 1m) excretion. **Results.** The ATO therapy significantly reduced urine excretion of α 1m ($P=0.033$) and NAG ($P=0.038$) as compared to placebo. There were no differences in proteinuria, blood pressure, eGFR and serum creatinine between the ATO and placebo groups. **Conclusion.** Atorvastatin treatment is safe and improves biomarkers of tubular damage or injury in non-diabetic patients with CKD.

Keywords: Atorvastatin, kidney, chronic kidney disease, proteinuria, tubular injury

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INTRODUCTION

Despite recent progress, there is still no optimal therapy that stops progression of renal disease. Therefore, it is necessary to search for alternative therapeutic

strategies which can further improve renal outcome (Renke *et al.*, 2010). There is evidence that dyslipidemia is associated with chronic kidney disease (CKD) (Gujarro & Keane, 1993; Samuelsson *et al.*, 1997). Experimental studies have established that lipids are damaging to the kidney (Keane *et al.*, 1988; Rutkowski *et al.*, 2003). The administration of various statins has been reported to exhibit beneficial effects in a number of experimental models of chronic kidney diseases suggesting that lipids may represent important therapeutic targets to halt or attenuate renal injury (Tylicki *et al.*, 2003). The benefits of statins can be explained not only by their lipid-lowering potential but also by non-lipid related mechanisms, the so called “pleiotropic effects”. Several studies have evaluated the effects of statins on the progression of CKD in human subjects but the results are controversial (Chan *et al.*, 1992; Fuiano *et al.*, 1996; Bianchi *et al.*, 2003; Strippoli *et al.*, 2008; Banach *et al.*, 2009). Considering the prognostic impact of proteinuria reduction on long-term renal outcome, in the present study we evaluated the effects of addition of atorvastatin (ATO), a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, to background nephroprotective therapy consisting of angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin II subtype 1 receptor antagonists (ARB). ATO, in contrast to many other statins, does not require dosage modification at any level of renal function (K/DOQI 2003). The patients were then evaluated for proteinuria, inflammation, renal function, and surrogate biomarkers of tubular injury. The primary end point of this study was a change in proteinuria measured as 24-h urine protein excretion (DPE), in measurements available for each patient. Secondary end points included urine *N*-acetyl- β -D-glucosaminidase (NAG) and α 1-microglobulin (α 1m) excretion.

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Abbreviations: α 1m, α 1-microglobulin; ACEI, angiotensin converting enzyme inhibitors; ALAT, alanine aminotransferase; ARB, angiotensin II subtype 1 receptor antagonists; ASAT, aspartate aminotransferase; ATO, atorvastatin; BMI, body mass index; BP, blood pressure; CK, creatine phosphokinase; CKD, chronic kidney disease; CVD, cardiovascular diseases; DPE, 24-h urinary protein excretion; eGFR, estimated glomerular filtration rate; hsCRP, high sensitive C-reactive protein; NAG, *N*-acetyl- β -D-glucosaminidase; RAAS-rennin, angiotensin-aldosterone system

METHODS

Patients were selected from a cohort that attended our renal outpatients' department. The inclusion criteria were as follows: age 18–65 years, chronic non-diabetic proteinuric nephropathy without dyslipidemia, normal or slightly impaired stable renal function expressed as estimated glomerular filtration rate (eGFR) above 45 ml/min, stable proteinuria above 300 mg/24 h, and no steroids or other immunosuppressive treatment for a minimum of six months before the study. Stable renal function and proteinuria were defined as a variability of serum creatinine and proteinuria less than 25% during six months before the start of the study. Patients with total cholesterol less than 200 mg/dl, low-density lipoprotein (LDL) cholesterol < 130 mg/dl, and triglycerides < 150 mg/dl were included. Exclusion criteria were as follows: nephritic syndrome, diabetes mellitus, cardiovascular disease (CVD), potassium serum level > 5.1 mmol/l, history of malignancy including leukemia and lymphoma, fertile women who were not taking oral contraceptives, pregnant or lactating women, patients with active liver disease, i.e., aspartate aminotransferase (ASAT) or alanine aminotransferase (ALAT) values more than three times the upper reference values, and known or suspected contraindications to the study medications, including a history of adverse reactions to statins, ACEI or ARB.

General protocol. The study was a prospective, placebo-controlled, randomized, two-period cross-over trial in which the renal effects of adding ATO (Sortis; Parke-Davis, Pfizer Polska) to background nephroprotective therapy with ACEI and/or ARB (Xartan; Adamed Polska) were evaluated. At the beginning, subjects entered an eight week run-in period during which the background nephroprotective therapy using pharmacological blockade of RAAS was adjusted to give a target blood pressure (BP) below 130/80 mm Hg (Table 1). At the end of the run-in period, patients were randomly assigned to one of two treatment sequences: twelve-week ATO (40 mg/day)/12-week washout — background therapy/12-week placebo (sequence 1) or 12-week placebo/12-week washout — background therapy/12-week ATO (40 mg/day) (sequence 2) (Fig. 1). Allocation was performed by a

person that was independent of the research team according to a computer generated randomized list. The patients received 40 mg of ATO as tablets (Sortis 40, Pfizer) once a day. The target BP during the whole study was an office visit BP of 130/80 mm Hg or less. The dosages of ACEI, ARB and diuretics, once established in the run-in period, were left unchanged throughout the study and in the washout period. At the randomization point and after the end of each treatment periods, office trough BP, serum creatinine, potassium, proteinuria measured as 24-h urine protein excretion (DPE), sodium excretion (Na ex), urea excretion, and surrogate markers of tubular injury (urine excretion of *N*-acetyl- β -D-glucosaminidase (NAG), α_1 -microglobulin (α_1m)) were determined. The study was approved by the local ethical committee (NKE-BN/749/2003) and all the patients gave informed consent. The study was registered at www.clinicaltrials.gov and received a positive opinion (NCT00572312).

Procedures and laboratory analyses. The office trough BP was measured with Speidel+Keller sphyngomanometer in a sitting position after 10 min of rest and expressed as a mean value of two consecutive measurements taken 2 min apart. DPE, Na ex and urea excretion were evaluated on the basis of 24-h urine collection. All patients were equipped with a sealed container and were strictly informed how to collect 24-h urine. They collected two 24-h urines — of those the mean value of DPE was calculated for data evaluation. Patients were asked not to perform heavy physical activity on the urine collection days and were recommended not to change their usual daily protein and sodium intake during the study period. The excretion of urea was used to calculate the protein intake according to Maroni equation: protein intake normalized to weight (g/kg per day) = $6.25 \times (\text{urea-N-excretion urine 24 h (g/day)} + [0.0031 \times \text{body weight (kg)}]) / \text{body weight (kg)}$ (Maroni *et al.*, 1985). eGFR was calculated according to Cockcroft-Gault formula (Cockcroft & Gault, 1976). NAG and α_1m were analyzed in the second morning spot urine sample. NAG was determined by the spectrophotometric method according to Maruhn (1976). Incubation medium contained in a final volume of 0.4 ml, 5 nmol/l *P*-nitrophenyl-2-acetamido- β -D-glucopyranoside as a substrate in 50 mmol/l citrate buffer (pH 4.14). The reaction was started by the addition of 0.2 ml of undialysed urine, carried out for 15 min. at 37°C, and then terminated with 1 ml of glycine buffer, pH 10.5. Absorbance was measured at 405 nm against a sample terminated at time zero. The calculation of the NAG level was made from the molar absorbance coefficient of the product of the reaction, *P*-nitrophenol, equal to 18.5 cm²/ μ mol. From preliminary experiments it was clear that the dialysis of urine did not affect NAG level in urine. Immunoturbidimetric test (Tina-quant α_1 -microglobulin, Roche, Basel, Switzerland) was used for quantification of

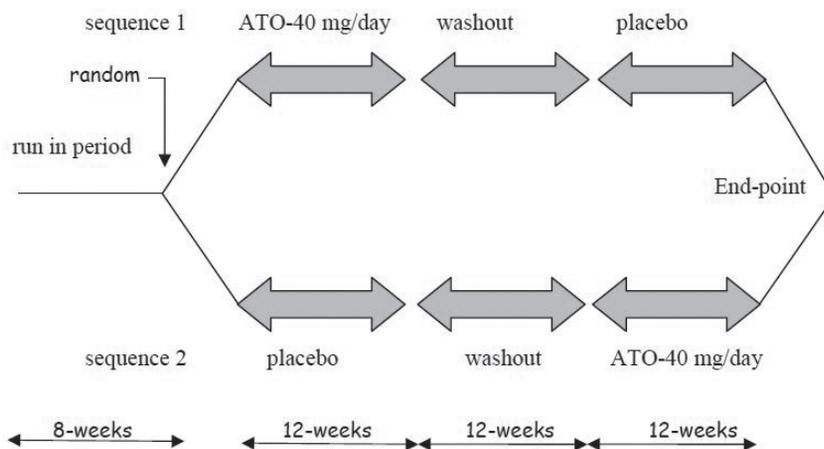


Figure 1.

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Table 1. Patient characteristics at baseline

Parameter	
Gender: female/male (n)	7/7
Mean age (years)	34.2±6.94
Mean systolic blood pressure (mm Hg)	111.5±7.8
Mean diastolic blood pressure (mm Hg)	71.2 (66.4–75.7)
Urinary protein excretion (g/24 h)	0.85 (0.35–1.8)
Serum creatinine (mg/dl)	1.05±0.27
eGFR (ml/min)	104.7±33.3
Total cholesterol (mg/dl)	191.9±21
hsCRP (mg/l)	0.91 (0.33–2.22)
BMI (kg/m ²)	25.97 (23.3–29.3)
Histopathological diagnosis: (n)	8
Mesangial glomerulonephritis	1
Mesangiocapillary glomerulonephritis	3
Membranous glomerulonephritis	1
IgA nephropathy	3
Unknown non-diabetic proteinuric chronic kidney diseases	6
Background hypotensive therapy: (n)	
ACEI and ARB	10
ACEI	3
ARB	1

Note: To convert serum creatinine in mg/dl to $\mu\text{mol/l}$, multiply by 88.4; eGFR in ml/min/1.73 m² to ml/s/1.73 m², multiply by 0.01667; Abbreviations: BMI, Body mass index; hsCRP, high sensitive C-reactive protein; eGFR, estimated glomerular filtration rate

α1m in urine. The detection limit of the method was 2 mg/l. Urinary NAG and α1m were reported per mg or g of urine creatinine to correct for the variation in urine concentration. We measured high sensitive C-reactive protein (hsCRP) with a commercial ELISA Kit (DRG, EIA-3954) and reported it in mg/l. Total cholesterol, LDL cholesterol, HDL cholesterol, serum triglyceride, ASAT, ALAT, creatine phosphokinase (CK), potassium, sodium, urea, protein and creatinine levels were measured in fresh blood samples drawn after fasting overnight for at least 12 h. These parameters were measured by standard laboratory techniques. Body mass index (BMI) was calculated as mass (kilograms) divided by height (meters) squared. Adverse effects were recorded at each visit in response to questionnaires or as observed by the investigators.

Table 2. Changes of parameters after ATO and placebo

	Baseline — ATO Δ	Baseline — Placebo Δ	P
DPE (g/24 h)	-0.23±0.08	-0.001±0.13	0.98
α1m excretion (mg/g creat.)	-8.18±3.39	-0.17±0.68	0.033
NAG excretion (IU/creatinine)	-0.92±0.29	-0.16±0.18	0.038
Total cholesterol (mg/dl)	-68.88±7.52	-0.11±8.44	0.001
LDL-C (mg/dl)	-49.0±4.25	-3.22±6.02	0.001
HDL-C (mg/dl)	-5.88±2.85	-1.22±1.21	0.14
Triglycerides (mg/dl)	-21.88±14.2	15.4±16.16	0.12

Note: To convert total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) in mg/dl to mmol/l multiply by 0.02586. To convert triglycerides in mg/dl to mmol/l multiply by 0.01129. Abbreviations: DPE, urinary protein excretion; α1m , $\alpha\text{1-microglobulin}$; NAG, N-acetyl- β -D-glucosaminidase

Statistics. The primary end point of this study was a change in DPE in measurements available for each patient. A sample size of 12 patients adequately allowed a power of 80% to detect a difference in variables equal to within patient standard deviation, that is a standardized effect size of 1.0 at a significance level of 0.05 (two-tailed). Secondary end points included urine NAG and α1m excretion. Normality and homogeneity of the variances were verified by means of the Shapiro-Wilk test and Levene test, respectively. Because of their skewed distribution, diastolic BP, DPE, NAG excretion, hsCRP, serum creatinine and daily protein intake were logarithmically transformed before statistical analysis and expressed as geometric means and 95% confidence intervals. Other results are presented as means \pm S.E.M. Differences in variable changes between treatment with ATO and placebo were assessed using Student's *t*-test (Table 2). Differences in variables measured more than twice (Table 3) were assessed using ANOVA. *P* values less than 0.05 (2-tailed) were considered statistically significant. Data were evaluated using Statistica (version 7.1; StatSoft Inc., Tulsa, OK) software package.

RESULTS

Of the 14 patients who entered the study, 12 (86%) completed the protocol. Two of them were dropped out because of withdrawal of informed consent. This decision was not due a side effect of therapy. Clinical characteristics of patients are listed in Table 1.

Twenty-four-hour urine protein excretion (DPE)

There was no significant change in DPE after ATO as compared to placebo (Table 2).

Table 3. Changes of parameters during the study

Parameter	Randomization point	After ATO	After Placebo	P
Sodium urine excretion (mmol/24 h)	223.9±28.8	208.8±27.3	215.1±28.4	0.68
Daily protein intake (g/24 h)	1.1 (0.93–1.14)	1.0 (0.94–1.12)	1.12 (0.83–1.39)	0.64
Serum creatinine (mg/dl)	1.05±0.1	1.07±0.1	1.12±0.1	0.08
hsCRP (mg/l)	0.91 (0.3–2.21)	0.47 (0.29–0.77)	0.77 (0.4–1.49)	0.47
ALAT (IU/l)	22.3 (18.6–27.8)	29.6 (19.3–48.2)	22.2 (17.1–30.5)	0.049
ASAT (IU/l)	20.4 (17.8–23.8)	25.2 (16.8–38.6)	19.9 (17.4–23.0)	0.089
Creatine phosphokinase (IU/l)	97 (18–252)	111.8 (85.7–153)	93.5 (18–240.6)	0.14
Systolic blood pressure (mmHg)	111.5±2.5	114.4±2.12	115.0±1.97	0.27
Diastolic blood pressure (mmHg)	71.2 (66.4–76.6)	72.1 (68.8–75.6)	69.5 (67.5–71.5)	0.67

Note: To convert serum creatinine in mg/dl to $\mu\text{mol/l}$, multiply by 88.4. **Abbreviations:** hsCRP, high sensitive C-reactive protein; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase

Urinary NAG and α1m excretion

Urinary NAG ($P=0.038$) and α1m excretion ($P=0.033$) decreased significantly after adding of ATO as compared to placebo (Table 2).

Serum lipid levels

Total cholesterol ($P=0.001$) and LDL cholesterol ($P=0.001$) decreased significantly after ATO as compared to placebo. There were no significant changes in triglyceride and HDL cholesterol during the study (Table 2).

Blood pressure, renal function, hsCRP, sodium and protein intake

The control of BP was adequate in all study periods; all patients reached the target office trough BP below 130/80 mm Hg. There were no differences in office trough systolic and diastolic BP between the treatment periods. Renal function assessed by means of serum creatinine and eGFR remained stable throughout the study. hsCRP levels had a tendency to decrease in ATO treatment but it was not statistically significant ($P=0.47$). There were no differences in sodium and protein intake between treatment periods (Table 3).

Safety

ATO therapy was well tolerated by all patients. Adverse effects were not reported. ASAT and CK were unchanged during the study period. ALAT statistically increased after ATO ($P=0.049$) but it was still in the normal range.

DISCUSSION

To the best of our knowledge, the present study was the first to evaluate the influence of atorvastatin, an HMG-CoA reductase inhibitor, on the markers of renal outcome in proteinuric CKD patients without dyslipidemia and CVD. We analysed the effects of ATO (40 mg/day) on proteinuria, the fundamental marker of glomerular injury and impaired glomerular permselectivity. Proteinuria is also a marker of long-term renal outcome. In the present study, the administration of ATO provided no change in proteinuria level ($P=0.98$) in non-diabetic CKD patients. Only a few randomized

controlled trials directly addressing the effect of statins on renal function and proteinuria have been reported. Most of those studies were of small size or short duration, used a variety of statins, and many did not include a placebo arm. Some of them suggest that statins reduce proteinuria and the rate of decline of GFR (Bianchi *et al.*, 2003; Tonelli, 2006). These positive effects have been summarized in published meta-analyses (Fried *et al.*, 2001; Sandhu *et al.*, 2006; Strippoli *et al.*, 2008). Interestingly, there are also studies suggesting that statins, particularly at high doses, may increase proteinuria (Deslypere *et al.*, 1990; Verhulst *et al.*, 2004). Finally, the National Lipid Association Statin Safety Task Force recently reported that statin-induced proteinuria is not associated with renal impairment or renal failure (McKenney *et al.*, 2006).

Considering that tubular epithelial cell injury may initiate the fibrosis process in kidneys and the fact that the extent of tubulointerstitial damage is a crucial predictor of renal outcome, tubular cells have become a renal site of particular interest. To evaluate tubulointerstitial effects of our interventions, the tubular involvement markers NAG and α1m were analysed (Bazzi *et al.*, 2002).

An increased excretion of NAG is thought to be a specific marker of tubular injury in many renal pathologies including non-diabetic CKD (Bazzi *et al.*, 2002). Increased urinary excretion of α1m , a low-weight protein physiologically filtered and reabsorbed by tubular cells, might indicate a reduced capacity of its reabsorption by such cells and it might be a marker of established tubular damage, with greater urinary concentrations pointing to greater severity of damage (Holdt-Lehmann *et al.*, 2000). Our results show that treatment with ATO reduces markers of tubular injury. Similar results (although in experimental models) were described by Tsujihata and co-workers (2008). That group reported that ATO had inhibitory effects on renal tubular cell injury. In human subjects Nakamura and co-workers (2006) presented data suggesting that pitavastatin ameliorated tubulointerstitial damage in CKD patients. That effect was independent of the lipid-lowering effect (Nakamura *et al.*, 2006).

The pleiotropic effects of statins have important clinical implications, independent of their lipid-lowering effects (Fathi *et al.*, 2004; Tonelli *et al.*, 2004; Epstein and Campese, 2005; Nissen *et al.*, 2005; Ridker *et al.*, 2005; Goicoechea *et al.*, 2006; Panichi *et al.*, 2006; Renke *et al.*, 2010). In our previous pilot study we confirmed that ATO therapy attenuated oxidative stress in patients with CKD (Renke *et al.*, 2010). They are at an increased risk

for CVD, and recent reviews suggested that inflammation and oxidative stress could be the primary mediators explaining the burden of CVD in CKD patients (Arici & Walls, 2001). Moreover, inflammation plays a central role in the progression of CKD (Tonelli *et al.*, 2005; Zoja *et al.*, 2006). Our study used hsCRP, a protein found in the blood, as a marker of inflammation. Interestingly, patients with elevated basal levels of CRP are at an increased risk of diabetes, hypertension and cardiovascular disease (Pradhan *et al.*, 2001; Dehghan *et al.*, 2007). In our study this parameter had a tendency to decrease with ATO treatment, but the result was not statistically significant ($P=0.47$). The fact that most of the patients had serum hsCRP levels in the normal range at the beginning of the study is probably the main reason why our results are different from those of some other authors (Chang *et al.*, 2002; Ichihara *et al.*, 2002; Vernagione *et al.*, 2004). Our study confirms the findings of others (Newman *et al.*, 2006; Shurraw & Tonelli 2006; Newman *et al.*, 2008) that ATO therapy is well tolerated by CKD patients. Adverse effects were not reported during the study period. It is unlikely that confounding factors might have influenced the outcome of the present study. The treatment periods did not differ with respect to blood pressure, patients' sodium and protein intake as well as renal function. We believe that the nephroprotective properties of ATO need to be addressed further in future controlled long term studies.

A potential limitation of the study is the relatively small sample size, although it was sufficiently powered to detect a significant difference equal to the S.D. value between treatment periods. A further limitation would be the fact that the participants were selected on the basis of their stability. The 24-h urine collections used to assess proteinuria may be associated with significant collection errors, largely because of improper timing and missed samples, leading to over- and under-collection. In addition, one should realize that the potential benefits for tubules and interstitium were extrapolated from presumptive early surrogates. Such evidence should be confirmed by histological examination.

In conclusion, the study results suggest that treatment with ATO (40 mg/day) for 12 weeks in nondialysis patients with CKD induced, in addition to its lipid-lowering effect, a significant decrease in biomarkers of tubular injury and damage without change in proteinuria. The treatment was safe and well tolerated by patients.

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