

The acute effect of atorvastatin on proteinuria in patients with chronic glomerulonephritis

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Key words

atorvastatin – chronic kidney failure – cholesterol – creatinine – HDL cholesterol – hydroxymethylglutaryl – COA reductase inhibitors – hyperlipidemia – LDL cholesterol – lipoproteins – plasma albumin – proteinuria – triglycerides

Abstract. Background: Hyperlipidemia may develop early in the course of renal disease, and statin treatment to lower lipid levels in these patients is effective. In addition, it has been suggested that proteinuria may decrease after prolonged periods of statin treatment. In the present study, we set out to evaluate the short-term effect of atorvastatin after only six weeks of therapy. Material and methods: Plasma albumin, creatinine, creatinine clearance, proteinuria and lipid profiles were assessed in 31 consecutive patients with glomerulonephritis and proteinuria > 0.3 g/24 h. All patients were treated with ACE inhibition for more than three months. Twenty patients consented to receive additional treatment with atorvastatin 10 mg daily in conjunction with a cholesterol-reducing diet, while 11 patients received standard care. Analyses were performed at baseline and after six weeks. Results: After six weeks of treatment with atorvastatin urinary protein excretion was reduced from 1.80 g/24 h to 1.42 g/24 h (22%, $p = 0.005$), while no change was observed in this parameter in the untreated patients over the same period. Plasma albumin did not change in treated or in untreated patients. Lipid and lipoprotein parameters improved in all treated patients (all $p < 0.001$). No correlation was observed between the percentual changes in lipids and proteinuria. Plasma creatinine and creatinine clearance did not change ($p > 0.05$). Conclusions: Six weeks of therapy with low-dose atorvastatin, added to ACE inhibition, resulted in a 22% decrease of proteinuria compared to untreated patients.

lated both to the degree of renal impairment and to the rate of urinary protein excretion. A low dose of atorvastatin combined with a cholesterol-lowering diet was effective in reducing both cholesterol and triglycerides in these patients, and was well-tolerated.

In two recent studies in patients with moderate renal failure, it has been shown that lipid-lowering treatment was associated with a decrease in glomerular proteinuria. In the first [Bucmi et al. 2000], 13 patients with IgA nephropathy were studied who were treated with fluvastatin during a period of six months. Urinary protein excretion decreased from 0.8 g/24 h to 0.5 g/24 h. In the second [Bianchi et al. 2003], 28 patients with chronic glomerulonephritis were treated with atorvastatin for 12 months. Proteinuria decreased from 2.5 g/24 h to 1.5 g/24 h in these patients, whereas creatinine clearance remained unchanged in treated patients and decreased in controls.

Information on the acute effects (less than six months of therapy) of lipid-lowering therapy in the earlier stages of renal disease is lacking. Therefore, the present study was conducted to prospectively explore the effects of a short course of atorvastatin on proteinuria.

Methods

Subjects

A cohort of 210 consecutive, non-diabetic patients of the outpatient nephrology clinic at the Academic Medical Center of the University of Amsterdam, was screened from 1999 – 2001 for proteinuria, chronic glomerulonephritis as underlying disease (biopsy-proven), the use of ACE inhibition and other medications, and hyperlipidemia [Ozsoy et al. 2003].

Introduction

In an earlier study [Ozsoy et al. 2003], we found a high prevalence of hyperlipidemia combined with increased levels of other cardiovascular risk factors in 150 patients with chronic renal disease and mild to moderate renal impairment. Hypercholesterolemia and hypertriglyceridemia were found to be re-

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Table 1. The baseline characteristics of 31 patients.

	Atorvastatin group (n = 20)	Untreated group (n = 11)	p
Age (years, range)	50 (35 – 70)	35 (25 – 50)	< 0.001
Gender (No. male, %)	17 (85)	8 (73)	0.4
BMI (kg/m ²)	27 (1)	23 (1)	0.001
Systolic blood pressure (mmHg)	125 (4)	120 (6)	0.4
Diastolic blood pressure (mmHg)	77 (1)	77 (5)	0.9
Urinary protein excretion (g/24 h)	1.8 (0.3)	1.4 (0.3)	0.4
Plasma albumin (g/l)	40 (1)	39 (1)	0.1
Plasma creatinine (µmol/l)	174 (27)	201 (39)	0.6
Total cholesterol (mmol/l)	6.6 (0.3)	5.0 (0.2)	< 0.001
HDL cholesterol (mmol/l)	1.4 (0.1)	1.3 (0.1)	0.4
LDL cholesterol (mmol/l)	4.3 (0.2)	3.1 (0.2)	0.001
Triglycerides (mmol/l)	2.4 (0.6)	1.5 (0.2)	0.3
Total cholesterol to HDL cholesterol ratio	5.3 (0.4)	4.2 (0.3)	0.08
LDL cholesterol to HDL cholesterol ratio	3.3 (0.2)	2.6 (0.3)	0.05

All values are mean (SEM).

Patients who had a nephrotic syndrome were excluded, as well as those patients who were in a pre-dialysis phase with a plasma creatinine > 500 µmol/l. Of the 210 patients, 121 had proteinuria > 0.3 g/24 h. When patients with nephrotic syndrome were excluded, 91 patients remained in our cohort. Of these 91 patients, 78 had a plasma creatinine < 500 µmol/l. Of these, 48 patients had glomerulonephritis as primary renal disease. Only 36 of the 48 patients used angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II antagonists at a stable dose for more than three months; 31 of the 36 patients consented to participate in this study. The dose of ACE inhibition was left unchanged during the study, as well as the use of other medications.

Twenty of these 31 patients were then prescribed cholesterol-lowering treatment with 10 mg atorvastatin, because they were considered at risk for cardiovascular disease according to criteria formulated by the International Task Force for the Prevention of Coronary Heart Disease [Assmann et al. 1999]: the atorvastatin group included 19 patients with LDL cholesterol values > 2.6 mmol/l who had either one or more cardiovascular risk factors, and one patient who had a history of cardiovascular disease. The cardiovascular risk factors consisted mainly of hypertension, n = 16 (80%) and smoking, n = 9 (45%). The second group included 11 patients with proteinuria

who did not receive treatment with atorvastatin. These were either the patients, who according to previously defined criteria [Assmann et al. 1999] had no indication for statin treatment (n = 6), or patients who refused statin treatment notwithstanding the presence of one or more cardiovascular risk factors (n = 5). The other baseline characteristics of the patients are presented in Table 1.

Informed consent was given by each participant, and the study was approved by the Institutional Review Board of the Academic Medical Center of the University of Amsterdam.

All data of the two groups were analyzed at baseline and after a study period of six weeks.

Laboratory methods

Blood samples were taken after an overnight fast. Plasma albumin (spectrophotometric reagents) and plasma creatinine (enzymatic method) were measured, and concentrations of plasma total cholesterol (TC), HDL cholesterol, triglycerides (TG) were determined (enzymatic techniques); LDL cholesterol concentrations were calculated by the Friedewald formula only if triglyceride concentrations were below 4.5 mmol/l [Defesche et al. 1993]; 24-hour urine samples were collected at baseline and after six weeks. In this sample protein and creatinine were determined. Kidney function was estimated by use of the Cockcroft-Gault formula and by calculating creatinine clearance (CCl) from the 24-h urine collections.

Statistical analyses

Statistical analyses were carried out using the SPSS statistical software package version 12. Values were presented as mean (SD) or mean (SEM). Statistical analyses of triglycerides were performed after logarithmic transformation because of their skewed distribution. Changes in plasma albumin, plasma creatinine, plasma lipids, proteinuria and creatinine clearance were assessed by Wilcoxon paired samples and with Kruskal-Wallis tests. Trends were analyzed with a multiple linear regression method. To search for violations of necessary assumptions in multiple regression, normal plots of the resid-

Table 2. Clinical characteristics during the study.

	Atorvastatin group (n = 20)			Untreated group (n = 11)		
	Baseline	Follow-up	p	Baseline	Follow-up	p
Plasma albumin (g/l)	40 (1)	39 (1)	0.06	39 (1)	38 (1)	0.2
Plasma creatinine ($\mu\text{mol/l}$)	174 (27)	173 (28)	0.1	201 (39)	206 (42)	0.3
CCI (ml/min)	74 (11)	76 (12)	0.3	57 (10)	60 (11)	0.3
CCI* (ml/min)	81 (13)	75 (11)	0.3	63 (12)	72 (15)	0.08

All values are mean (SEM), CCI = creatinine clearance calculated by the Cockcroft-Gault formula, CCI* = creatinine clearance calculated from urine.

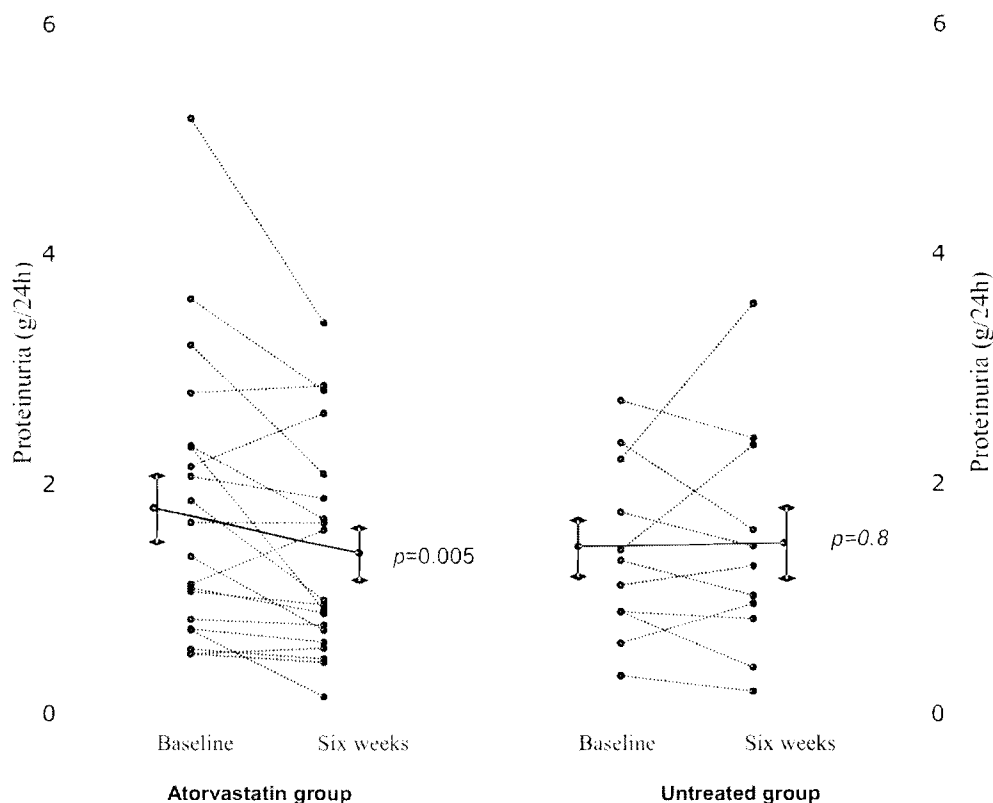


Figure 1. The change in proteinuria (g/24 h) with mean \pm (SEM) in patients treated for a period of six weeks with 10 mg atorvastatin (n = 20) and in patients who were not treated with atorvastatin (n = 11).

uals of the regression models were produced. Because of the normal plots, regression models of proteinuria were formed after logarithmic transformation of these factors. Analyses were adjusted for age, sex, creatinine clearance and proteinuria. Statistical significance was assessed at the 5% level of probability.

Results

The changes in proteinuria in the two groups are shown in Figure 1. The mean chan-

ges in other factors are given in Table 2, while the changes in the lipid profile in the atorvastatin group are given in Table 3. In the atorvastatin group, mean proteinuria decreased from 1.82 g/24 h at baseline to 1.42 g/24 h after six weeks (22% decrease, $p = 0.005$, Figure 1). This was in contrast to the 11 untreated patients, in whom mean proteinuria did not decrease ($p = 0.8$, Figure 1). There was no decrease in mean blood pressure in the patients treated with atorvastatin. The blood pressure of the patients in the untreated group was similar to those of the treated patients and there

Table 3. Changes in lipids during treatment with atorvastatin.

	Atorvastatin group (n = 20)			
	Baseline	Follow-up	% change	p
TC (mmol/l)	6.6 (0.3)	4.7 (0.2)	-30	< 0.001
HDL-C (mmol/l)	1.4 (0.1)	1.4 (0.1)	3	0.3
LDL-C (mmol/l)	4.3 (0.2)	2.5 (0.1)	-40	< 0.001
TG (mmol/l)	2.4 (0.6)	1.5 (0.3)	-35	0.001
TC/HDL ratio	5.3 (0.4)	3.6 (0.3)	-32	< 0.001
LDL/HDL ratio	3.3 (0.2)	2.0 (0.1)	-40	< 0.001

TC = total cholesterol, LDL-C, low-density lipoproteins cholesterol, HDL-C = high-density lipoproteins cholesterol, TG = triglycerides.

was no change during follow-up. There were no changes in plasma albumin or creatinine clearance in the treated and untreated group. This held true for creatinine clearance estimated by the Cockcroft-Gault formula and for creatinine clearance calculated from 24-h urine. Plasma creatinine did not change either. In linear regression analysis, there was no association between the changes in proteinuria and changes in plasma albumin ($p = 0.8$).

All plasma lipids and lipoproteins improved in the treated patients (all $p < 0.001$). In multiple linear regression analyses, no direct correlation was observed between the percentual decrease in proteinuria and the percentual changes in total cholesterol, LDL cholesterol, triglycerides, the ratios of total cholesterol to HDL cholesterol or LDL to HDL cholesterol (all $p > 0.05$). Nine of the 20 treated patients did not reach their target LDL cholesterol level within six weeks of treatment. In three of these patients the target LDL levels were subsequently reached by increasing the dosage up to 40 mg without a change in ACE inhibition dosage. This increase of atorvastatin dosage was accompanied by an additional 43% decrease in proteinuria in all three patients: mean proteinuria at baseline was 1.2 g/24 h; at six weeks mean proteinuria was 0.7 g/24 h and at the time of reaching the target value of LDL cholesterol (around 13 months) the proteinuria was decreased to 0.4 g/24 h.

Discussion

In this study, we observed a 22% reduction in proteinuria in 20 patients with chronic

glomerulonephritis treated with the lowest dose of atorvastatin for only a period of six weeks. This decrease in proteinuria appears to be additive to that derived from treatment with ACE inhibition. Using regression analyses, it was found that the decrease in proteinuria was not related to the various changes in the lipids. There was a tendency for the mean plasma albumin levels to decrease as well, but this did not reach statistical significance. This borderline significant decrease cannot explain the decrease in proteinuria; because in linear regression analyses the decrease in proteinuria did not correlate with the change in plasma albumin.

Obviously, in an uncontrolled, unblinded observational study, the possibility must be considered that a decrease in urinary protein excretion is the consequence of other causes. For instance, a change in glomerular filtration rate, diet or physical activity might cause a change in proteinuria. However, no changes in creatinine clearance were seen and careful assessments during follow-up did not support the possibility of other causes. For comparison, we included a group of untreated patients. This group was younger and had lower risk factor prevalence. During the six-week period, no change in proteinuria was observed in this group, making it more likely that the change in proteinuria in the treated group was the consequence of atorvastatin therapy.

It is unlikely that the observed change in proteinuria is the result of the continuing effect of ACE inhibition. First, the patients in the untreated group had a similar proteinuria at baseline as the treated patients and they had also used ACE inhibition for more than three months, but they did not have a decrease in proteinuria within six weeks. Second, our findings are supported by the results of a long-term study in patients with glomerular proteinuria [Bianchi et al. 2003]. These authors found a decrease in proteinuria of 20 – 30% after one year of statin therapy on top of the effect of ACE inhibition.

It should be pointed out that a 22% reduction of proteinuria after a short period as six-week treatment is mainly interesting from a pathophysiological point of view, but that the clinical impact is limited. It has to be proven, that the effect is persistent in the long term. If so, we know from other studies that

patients with less proteinuria do better in the preservation of renal function than patients with higher urinary protein loss [Ruggenenti et al. 2001].

The rather rapid decrease of proteinuria in the present study might be due to the direct and non-cholesterol-dependent anti-inflammatory and antioxidant effects of statins on the glomerular mesangial cells as described in animal studies [Asberg et al. 2001, Buemi et al. 1999, Grandaliano et al. 1993, Usui et al. 2003, Vazquez-Perez et al. 2001, Werner et al. 2002]. Statins may also have a beneficial effect on the glomerular barrier, because some of the proteins in the glomerular barrier are produced by endothelial cells [Haraldsson and Sorensson 2004].

The decrease in proteinuria after atorvastatin occurred, despite the fact that all patients already used a stable dose of ACE inhibitors or AII antagonists. So, it is conceivable that the observed decrease in proteinuria by statins is associated with mechanisms which are adjuvant to ACE inhibition, for instance inhibition of ACE upregulation by VEGF as described in an experimental study [Saijonmaa et al. 2004].

In the present study only a low dose of atorvastatin was used. nevertheless, half of the patients reached their target LDL levels and the majority of the treated patients had a decrease of proteinuria already at this dose.

In patients with glomerular disease, several studies have suggested a reduction in proteinuria after long term treatment with statins, both in Caucasian as well as in Asian populations. Based on the present study it is likely that this effect is already present after six weeks. Further studies, especially randomized controlled trials, are needed to assess the possible effects of statins on proteinuria and renal function in these patients.

In conclusion, low-dose atorvastatin, in addition to chronic ACE inhibition, induced a 22% decrease of proteinuria within six weeks in patients with glomerular disease, while there was no change in the patients who continued ACE inhibition only.

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