

PRO-ATHEROGENIC METABOLIC DISORDERS IN PATIENTS WITH CHRONIC KIDNEY DISEASE OF NONDIABETIC ORIGIN: POSSIBILITY OF STATIN THERAPY

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ABSTRACT

In order to trace the dynamics of lipid profile, levels of glycosylated hemoglobin, uricemia and the functional ability of kidneys during atorvastatin administration combined with the standard cardioprotective treatment, we examined 54 patients with chronic kidney disease of nondiabetic origin. All patients were divided into 2 groups. Group I involved 31 patients with glomerular filtration rate below 60 ml/min; these patients were additionally administered atorvastatin 20 mg/day. Group II made 23 patients with glomerular filtration rate equal to or greater than 60 ml/min. On the first day of hospitalization and after 6 months of treatment we determined the levels of blood pressure (systolic, diastolic, pulse pressure), lipid profile, levels of uric acid, glycosylated hemoglobin, and the glomerular filtration rate. Administration of atorvastatin alongside with combination of standard treatment of chronic kidney disease in nondiabetic patients allowed to achieve the significant reduction in levels of atherogenic lipid fractions, glycosylated hemoglobin, uricemia, lipid peroxidation indices, as well as systolic and pulse pressure by 4-5 mm Hg. Six-month statin therapy was accompanied by increased levels of glomerular filtration rate in patients with initial levels of this parameter below 60 ml/min.

Thus, statin therapy not only improves lipid metabolism in patients with chronic kidney disease of nondiabetic origin, but also helps to reduce the levels of glycosylated hemoglobin and uricemia, improves the control of blood pressure and the functional ability of kidneys.

Keywords: *chronic kidney disease, lipid, carbohydrate and purine metabolism, coronary atherosclerosis, glomerular filtration rate.*

INTRODUCTION

The presence of a continuous (more than three months) renal disease, with or without proteinuria and/or renal dysfunction leading to a decrease in glomerular filtration rate (GFR), is a sign of chronic kidney disease (CKD) [Weir M. *et al.*, 2011]. Mostly it develops due to *diabetes mellitus* and hypertension, and more rarely because of primary glomerular pathology. It is known that CKD is associated with an extremely high risk of cardiovascular diseases (CVD) development and, first of all, it is associated with coronary heart disease (CHD) [Bartnicki P. *et al.*, 2009]. At all stages of CKD high risk

of cardiovascular events, several times greater than the probability of end-stage renal failure or dialysis, are recorded in patients. According to modern views, patients with CKD (GFR below 60 ml/min) are a group of people with a high or very high cardiovascular risk [Perk J. *et al.*, 2012].

The central role in the formation of a high risk of CHD at patients with CKD belongs to pro-atherogenic metabolic disorders that accelerate the progression of not only cardio-, but the renal continuum as well. Dyslipidemia and related prooxidant activity and pro-inflammatory processes not only increase the probability of serious cardiovascular events in CKD, but also exacerbate renal dysfunction [Sheng X. *et al.*, 2012]. The most active pro-atherogenic, pro-inflammatory and pro-fibrogenic effects on both the arterial blood ves-

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sels, and the structure of the kidney tissues are provided by low-density lipoproteins (LDL) and very low density lipoproteins (VLDL) subjected to peroxidation, the intensity of which always substantially increases in CKD [Siems W. et al., 2002; Hyre A. et al., 2007]. An independent risk factor for CHD correlated with the severity of nephrosclerosis is hyperuricemia, which is often detected in patients with hypertension and CKD. The elevated level of glycosylated hemoglobin (HbA1c) is another marker of high risk for cardiovascular morbidity and mortality in the general population, including also patients with CKD of nondiabetic origin [Moraes T. et al., 2011]. Signs of lipid, carbohydrate and purine metabolism disturbance in their interrelation quite often show up at early stages of the CKD, and their expression significantly increases at GFR depression.

In recent years the results of several prospective studies showing the beneficial effects of statin therapy on the prognosis for CKD progression and cardiorenal continuum have been extensively discussed. Statin therapy carried out against the background of basic treatment with inhibitors of renin-angiotensin system not only leads to a better prognosis of patients, but also to a significant reduction of proteinuria and the rate of CKD progression [Bianchi S. et al., 2003].

Despite the close relationship between the renal dysfunction and CHD development, to date there is insufficient data on the effects of traditional and specific metabolic cardiovascular risk factors in patients with nondiabetic CKD. The most studies on both mentioned factors and the effectiveness of statin therapy were conducted in patients with CKD developed primarily on the basis of *diabetes mellitus*.

Hence, the research objective was to study the dynamics of lipid metabolism indices, the levels of HbA1c, uricemia, indices of lipid peroxidation (LPO) and GFR on the background of atorvastatin application in a complex of standard angioprotective treatment of patients with CKD of nondiabetic origin.

MATERIAL AND METHODS

The study involved 54 patients with CKD (41 men and 13 women; mean age – 60.19 ± 1.50 years). Among them, there were 31 (57.4%) patients with a chronic glomerulonephritis and 23 (42.6%) hypertensive nephropathy patients. The condition of

renal function was evaluated by blood serum creatinine and GFR. The latter was determined by the direct method of endogenous creatinine clearance and calculated in ml/min [Cocroft D., Gault M., 1976]. The diagnosis of CKD was set according to the criteria accepted by the II National Congress of Nephrologists of Ukraine (Kharkiv, 2005) [Ivanov D., 2010], those established by the Order of the Health Ministry of Ukraine № 593 dated 12.12.2004 [Order, 2004], as well as the international clinical guidelines [Levey A. et al., 2005; 2010].

To assess the metabolic status of patients with CKD, we measured levels of total cholesterol, LDL cholesterol, VLDL cholesterol, high-density lipoproteins (HDL) cholesterol, triglycerides, uric acid, fasting glucose and glucose during exercise, as well as HbA1c. The blood serum concentrations of total cholesterol and triglycerides were determined by the enzymatic method [Rifai N. et al., 1999]. The content of LDL cholesterol was calculated by Friedewald formula and expressed in $mmol/L$ [Friedewald W. et al., 1972; Horyachkovskiy A., 1998]:

$$LDLchol. = total\ chol. - HDLchol. - triglycerides/2.2.$$

The state of carbohydrate metabolism was assessed by the blood glucose level and HbA1c (%) according to method of V. Cromy and co-workers [Cromy V. et al., 1986] in the modification of “Erba Lachema” Co. (Czech Republic). The condition of purine metabolism was assessed by blood plasma concentration of uric acid, which was determined colorimetrically using the Mueller-Zeifert method [Kolb V., Kamishnikov V., 1982]. The state of LPO was estimated by the level of malondialdehyde (MDA), which was determined by the V.B. Gavrilova’s method in the modification of E.N. Korobeynikova [Korobeynikova E., 1989], and by the activity of ceruloplasmin (CP) determined according to method of N. Revin in modification of S.V. Bestuzhev and V.G. Kolb [Horyachkovskiy A., 1998].

All patients received standard therapy by antiplatelets, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Patients with $GFR < 60\ ml/min$ (group I; $n = 31$; mean age of 60.19 ± 2.19 years) additionally took 20 mg atorvastatin per day. Group II was composed of 23 patients with $GFR \geq 60\ ml/min$ (mean age: 60.17 ± 1.98 years), who did not take statins for

various reasons. In both groups men prevailed: 87.1% in group I and 60.9% in group II. Patients distribution according to renal pathology was as follows: patients with hypertensive nephropathy made 25.8% and 56.5%, those with chronic glomerulonephritis –74.2% and 43.5%, appropriately.

On the first day of hospitalization and in 6 months after treatment we determined the levels of blood pressure (BP): systolic (SBP), diastolic (DBP) and pulse pressure (PBP), GFR, as well as the above listed indices of lipid, carbohydrate and purine metabolism and LPO. The research data were processed on the personal computer using “Microsoft Office Excel 2007” and “StatSoft Statistica 6.0” programs.

RESULTS AND DISCUSSION

In patients with CKD pro-atherogenic lipid disorders are observed: high cholesterol, high triglyceride, increased concentration of triglyceride remnant and lipoprotein (a), reduced HDL cholesterol [Vaziri N. et al., 2011]. With the progression of CKD atherogenic dyslipidemia increases: the LDL metabolic rate decreases, the levels of total cholesterol, LDL cholesterol and triglyceride significantly increase leading to a significant increase in cardiovascular risk [Perk J. et al., 2012].

According to the Guidelines of the European Society of Cardiologists for the treatment of dyslipidemia [Perk J. et al., 2012] and CVD prevention [Reiner Z. et al., 2011], the target level of LDL cholesterol for patients with moderate and profound CKD severity: stages 2-4, GFR of 15-89 ml/min, i.e. for those at high or very high cardiovascular risk should not exceed 2.5 mmol/L, though the preferable level is 1.8 mmol/L (level of evidence IIa, C) [Perk J. et al., 2012]. In our study, the average increase in LDL cholesterol levels above 2.5 mmol/L was recorded in all (100%) patients, triglyceride above 1.7 mmol/L was observed in 2/3 of the patients in both groups. Significantly higher levels of total cholesterol, LDL cholesterol and VLDL cholesterol were significantly higher in patients with initially lower GFR (<60 ml/min), i.e. in patients of group I compared with the group II (Table).

At the beginning of the study patients with GFR <60 ml/min (group I) had significantly higher mean levels of HbA1c, – despite the absence of diabetes or impaired glucose tolerance compared with group

II patients. Elevated levels of HbA1c $\geq 7\%$ was recorded in 41.9% patients of group I and 26.1% in group II. Mean levels of mentioned indicator were $7.13 \pm 0.13\%$ (group I) and $6.41 \pm 0.22\%$ (group II). The data obtained are consistent with the results of the study, according to which even the CKD of non-diabetic origin is accompanied by the increase in HbA1c levels and is associated with an increased risk of cardiovascular events [Selvin E. et al., 2011].

Hyperuricemia is an independent marker of high cardiovascular risk and a significant stimulus in progression of atherosclerosis [Weiner D. et al., 2004]. Elevated uricemia (over 0.24 mmol/L) was recorded at 2/3 of patients with CKD, and its average value in group I patients was higher than in group II: 0.32 ± 0.02 mmol/L and 0.29 ± 0.02 mmol/L, respectively ($p > 0.05$).

At the start of the study, in patients with lower GFR (group I) we recorded significantly higher activity of pro-oxidant processes: the levels of LPO in group I significantly exceeded those in group II; the level of MDA made 0.59 ± 0.01 nmol/mg (group I) and 0.49 ± 0.01 nmol/mg (group II); CP amounted 325.51 ± 6.68 mg/L (group I) and 315.51 ± 8.57 mg/L (group II) (Table). The excessive formation of lipid peroxides and free radicals characteristic for patients with progressive loss of renal function leads to deterioration of endothelial dysfunction, atherosclerosis progression [Kao M. et al., 2010] and, accordingly, – to development of coronary artery disease and its complications.

Significant pro-atherogenic metabolic abnormalities in patients with CKD progressing to deterioration of renal function necessitated the inclusion of statin therapy. Its main goal in CKD (stages 2-4, GFR of 15-89 ml/min) is the reduction in LDL cholesterol levels (level of evidence I, A) [Hyre A. et al., 2007]. The preference is given to statins primarily metabolized in the liver (atorvastatin, fluvastatin, pitavastatin). Lowering LDL cholesterol reduces the risk of cardiovascular diseases in patients with CKD (IIa, B) [Sandhu S. et al., 2006; SHARP, 2010], as well as slows down the progression of renal dysfunction. They prevent the onset of end-stage CKD requiring dialysis (IIa, C) and have a positive effect on proteinuria [Douglas K. et al., 2006; Perk J. et al., 2012].

Within the study we stated a significant decrease in levels of atherogenic lipid fractions in

patients receiving statin therapy for 6 months (group I): total cholesterol decreased from 6.49 ± 0.15 mmol/L to 5.05 ± 0.07 mmol/L ($p < 0.001$); LDL cholesterol – from 4.22 ± 0.15 mmol/L to 3.23 ± 0.15 mmol/L ($p < 0.001$); VLDL cholesterol – from 0.87 ± 0.03 mmol/L to 0.80 ± 0.03 mmol/L and triglyceride – from 1.94 ± 0.06 mmol/L to 1.87 ± 0.07 mmol/L ($p < 0.05$). The significant positive dynamics of the mentioned parameters was not identified in patients of group II (Table).

Statin therapy also contributed to reduced levels of HbA1c (from $7.13 \pm 0.13\%$ to $6.44 \pm 0.15\%$, $p < 0.001$), concentration of uric acid in the blood (from 0.32 ± 0.02 mmol/L to 0.23 ± 0.01 mmol/L, $p < 0.001$) and prooxidant activity processes (MDA level decreased from 0.59 ± 0.01 nmol/mg to 0.51 ± 0.01 nmol/mg, $p < 0.05$) [Heymann E. et al., 2012]. At the same time, in group II these indices had only a tendency to decrease, i.e. remained virtually unchanged (respectively, HbA1c decreased from $6.41 \pm 0.22\%$ to $6.29 \pm 0.31\%$, lithemia – from 0.29 ± 0.02 mmol/L to 0.28 ± 0.02 mmol/L; MDA –

from 0.49 ± 0.01 nmol/mg to 0.49 ± 0.01 nmol/mg) (Table). The obtained data testified to the complex beneficial effect of atorvastatin on the metabolic status of the patients in group I and the reduction of its pro-atherogenic potential.

The study of lipid profile in 3303 non-dialysis patients with stage 3-5 CKD (GFR < 60 ml/min), of which 44.5% were patients with chronic glomerular and tubulointerstitial lesions, 38.1% with diabetic and 11.1% – with hypertensive nephropathy, showed that high levels of atherogenic lipid fractions (total cholesterol, LDL cholesterol, cholesterol none-HDL) were associated with deterioration of the renal function and are independent predictors of progressive renal damage [Chen S. et al., 2013]. Disorders of lipid metabolism were especially expressed in the presence of diabetes or the nephrotic syndrome [Perk J. et al., 2012]. Hyperlipidemia and activation of prooxidant processes in CKD contribute to the deterioration of renal microcirculation due to deposition of oxidized lipoproteins in the glomerular structures, expression of

TABLE.

Studied indices in patients: dynamics of the follow-up

Indices	Group I (n=31)		Group II (n=23)	
	start of therapy	after 6 months of treatment	start of therapy	after 6 months of treatment
total cholesterol (mmol/L)	$6.49 \pm 0.15^{\dagger\dagger}$	$5.05 \pm 0.07^{***}$	5.34 ± 0.15	5.21 ± 0.16
low density cholesterol (mmol/L)	$4.22 \pm 0.15^{\dagger\dagger}$	$3.23 \pm 0.15^{***}$	3.46 ± 0.19	3.17 ± 0.21
very low density cholesterol (mmol/L)	$0.87 \pm 0.03^{\dagger\dagger}$	$0.80 \pm 0.03^*$	1.04 ± 0.07	0.98 ± 0.08
high density cholesterol (mmol/L)	$1.08 \pm 0.06^{\dagger\dagger}$	1.15 ± 0.02	1.26 ± 0.02	1.25 ± 0.02
triglycerides (mmol/L)	1.94 ± 0.06	$1.87 \pm 0.07^*$	2.01 ± 0.17	2.05 ± 0.17
glucose (mmol/L)	5.17 ± 0.17	5.21 ± 0.11	5.18 ± 0.18	5.12 ± 0.15
glycated hemoglobin (%)	$7.13 \pm 0.13^{\dagger\dagger}$	$6.44 \pm 0.15^{***}$	6.41 ± 0.22	6.29 ± 0.31
uric acid (mmol/L)	0.32 ± 0.02	$0.23 \pm 0.01^{***}$	0.29 ± 0.02	0.28 ± 0.02
creatinine (mcmol/L)	$179.61 \pm 18.26^{\dagger\dagger\dagger}$	$129.04 \pm 18.30^{**}$	98.61 ± 7.06	$122.83 \pm 11.36^{**}$
ceruloplasmin (mg/L)	$325.51 \pm 6.68^{\dagger}$	$337.79 \pm 9.32^*$	315.38 ± 8.57	317.09 ± 6.45
malondialdehyde (nmol/mg)	$0.59 \pm 0.01^{\dagger}$	$0.51 \pm 0.01^*$	0.49 ± 0.01	0.48 ± 0.02
glomerular filtration rate (ml/min)	$54.09 \pm 2.50^{\dagger\dagger}$	$61.13 \pm 4.61^*$	78.14 ± 3.41	71.42 ± 5.28
systolic pressure (mm Hg)	162.90 ± 4.21	$128.52 \pm 1.22^{***}$	162.26 ± 3.16	$133.00 \pm 1.14^{***}$
diastolic pressure (mm Hg)	97.42 ± 1.57	$85.74 \pm 0.96^{***}$	96.17 ± 1.11	$85.22 \pm 0.76^{***}$
pulse pressure (mm Hg)	65.48 ± 3.20	$42.77 \pm 1.34^{***}$	66.09 ± 2.51	$47.78 \pm 1.14^{***}$

NOTES: Significant differences in the groups before and after treatment: * - $p < 0.05$; ** - $p < 0.01$; *** - $p < 0.001$; significant differences between groups I and II at the start of therapy: † - $p < 0.05$; †† - $p < 0.01$; ††† - $p < 0.001$.

cytokines and growth factors involved in inflammation, fibrogenesis and sclerosis of *glomeruli* [Abrass C., 2004; Perk J. et al., 2012]. The occlusion of glomerular capillaries by lipid complexes and foam cells decreases glomerular filtration, leads to an increase in systemic blood pressure and intraglomerular intact nephrons also contributing to the progression of glomerulosclerosis [Abrass C., 2004; Perk J. et al., 2012]. Therefore, the use of statins is a key element of the nephroprotective strategy to inhibit the progression of CKD, preventing or permanently postponing the renal failure development.

In the current study, we observed an improvement of renal function on the background of atorvastatin, as evidenced by the significant increase in the average level of GFR in patients of group I, i.e. in individuals with low baseline levels of GFR (<60 ml/min): from 54.09±2.50 ml/min to 61.13±4.61 ml/min (Table). On the contrary, in patients with the preserved renal function (GFR >60 ml/min) without taking statins the level of GFR tended to decrease (from 78.14±3.41 ml/min to 71.42±5.28 ml/min).

Nowadays, the effectiveness of statin therapy in patients with CKD is sufficiently evidence-based. Most research works focused on the study of cardiovascular outcomes risk. For example, according to the results of meta-analysis of 50 studies involving 30,144 patients with CKD (GFR <60 ml/min), statin therapy resulted in a significant reduction in total cholesterol, LDL cholesterol, daily proteinuria and was accompanied by a decrease in the frequency of fatal and non-fatal cardiovascular events by 19% and 22% [Strippoli G. et al., 2008]. Similar results were obtained in a meta-analysis of 31 studies, embracing data of 48,429 patients with CKD [Hou W. et al., 2013]. The researchers concluded that statin therapy in patients with CKD reduced the risk of cardiovascular events by 23%, coronary – by 22%, cardiovascular and all-cause mortality – by 8-9%. The generalized results of monitoring study on 9,438 patients at high risk of CKD demonstrated that in patients receiving ezetimibe in combination with simvastatin, as compared with those, who received placebo, the incidence of major cardiovascular events decreased by 17% [SHARP, 2010]. Importantly, these results were similar in patients receiving and not receiving hemodialysis.

At the same time, data concerning the effect of statins on renal function are insufficient and contradictory. No conclusive evidence of an explicit nephroprotective effects of statins in the above-mentioned meta-analyzes [Strippoli G. et al., 2008; Hou W. et al., 2013] was received, even though there was a clear tendency to reduce the risk of chronic renal failure by 5% as measured by 25% decline in GFR or doubling of serum creatinine. This can be explained by the inclusion in the mentioned studies of patients with different stages, as well as different etiologies of CKD (including on the background of *diabetes mellitus*) [Hou W. et al., 2013].

However, there is evidence of direct nephroprotective effects of statins [Heymann E. et al., 2012]. Primarily, it was demonstrated in a large-scale study involving 4,444 CHD patients, among which in 409 CKD was diagnosed. During the period of 5.5 years simvastatin taking showed a significant reduction in the frequency and probability of reducing the filtration function of the kidneys. In the active treatment group slowing of decline in GFR was observed [Huskey J. et al., 2009]. In a meta-analysis that included 27 trials, involving 39,704 patients, statins also slowed the progression of decline in GFR, particularly in groups of patients with underlying cardiovascular diseases [Sandhu S. et al., 2006]. The study among simvastatin patients showed a significant reduction in the rate of decline in GFR compared with the placebo group [Collins R. et al., 2003]. In another study statin compared with placebo in patients with GFR <50 ml/min and proteinuria was helpful in reducing the rate of renal dysfunction progression and allowed to slow down the loss of kidney function in patients with moderate to severe CKD [Tonelli M. et al., 2003]. The effect of statins on GFR was also assessed in patients with chronic ischemic heart disease, dyslipidemia, and preserved renal function; statin therapy led to 4.9% increase in GFR as opposed to those, who were not taking statins and had a decrease of this index by 5.2%. The use of atorvastatin was accompanied by a nearly 12% increase in GFR. The risk of cardiovascular events was reduced by 16% for every 5% increase in GFR [Athiros V. et al., 2004]. In our study, there was an increase in GFR over 11% on the background of six-month therapy with atorvastatin in subjects with baseline GFR <60 ml/min (Table).

The application of pitavastatin in 958 patients with hypercholesterolemia and baseline GFR <60 ml/min resulted in GFR significant increase (by 5.4 ml/min, $p<0.001$) during 104 weeks of observation [Kimura K. et al., 2010]. In a subanalysis of another study, pitavastatin demonstrated the potential to increase GFR in patients with subclinical carotid atherosclerosis. This anti-atherosclerotic effect was more pronounced in patients with lower GFR compared to patients with high levels of GFR [Shimoda Y. et al., 2012].

We also analyzed the dynamics of BP in CKD patients. The baseline average BP levels were similar in both groups. Increased BP was observed in 31 (100%) patients of group I (SBP – 162.90±4.21 mm Hg; DBP – 97.42±1.57 mm Hg; PBP – 65.48±3.20 mm Hg) and in 22 (95.7%) patients of group II (SBP – 162.26±3.16 mm Hg; DBP – 96.17±1.11 mm Hg; PBP – 66.09±2.51 mm Hg). After the treatment, which included ACE inhibitors or ARBs (prescriptions or correction of their doses), a significant reduction in the average levels of BP was recorded in patients of both groups. In patients additionally treated with atorvastatin the levels of SBP and PBP were lower than in those, who did not take the specified medicine ($p<0.01$): SBP made 128.52±1.22 mm Hg (group I) and 133.00±1.14 mm Hg (group II); PBP – 42.77±1.34 mm Hg (group I) and 47.78±1.14 mm Hg (group II). In patients of group I we managed to achieve further significant reduction in SBP by 5 mm Hg and PBP by 4 mm Hg ($p<0.01$). This is consistent with the results of meta-

analysis, which demonstrated the possibility of statin therapy to more effectively control BP and to achieve a further reduction in BP [Strazzullo P. et al., 2007] (Table).

Thus, in patients with CKD of nondiabetic origin with GFR <60 ml/min statin therapy not only improves lipid metabolism, but also helps to reduce levels of HbA1c and uricemia, as well as ensures better control of BP and the renal function.

CONCLUSION

In CKD the mean levels of atherogenic lipid fractions, HbA1c, uricemia and prooxidant activity processes were increased. The most expressed metabolic changes of pro-atherogenic character were recorded in patients with initially lower GFR (<60 ml/min).

Taking 20 mg atorvastatin as a part of complex therapy of CKD allowed to improve the metabolic status of patients: to reduce not only levels of atherogenous lipid fractions, but also glycated hemoglobin (HbA1c) and uricemia.

Against the background of atorvastatin a significant additional reduction in mean levels of SBP by 5 mm Hg and PBP by 4 mm Hg was reached, in comparison with patients with CKD, who did not take it.

The six-months therapy with atorvastatin contributed to renal filtration improvement in CKD patients with GFR <60 ml/min, while patients with GFR >60 ml/min, who did not receive statin therapy, showed a trend towards the reduction.

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