Atorvastatin in the regulation of dyslipidemia in patients with stage II and III chronic kidney disease caused by type 2 diabetes mellitus in combination with coronary heart disease

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Introduction

Currently, a clear trend in the world to increase the number of people with chronic kidney disease (CKD) is reported. One of the most urgent tasks of modern nephrology is the prevention and/or maximum delay of the onset of the terminal stage of CKD. According to the results of many population and epidemiological studies, even early subclinical disorders of kidney function are independent risk factors for the cardiovascular complications and significantly increase the risk of coronary heart disease (CHD), heart failure, arterial hypertension (AH) in this category of patients (Sarnak M.J. et al. ., 2003). Thus, in the initial stages of renal failure, the risk of cardiovascular diseases (CVD) is higher than in the general population (30.1% vs. 13.2%), and in patients on hemodialysis, the risk of CVD and CVD mortality 10-30 times higher than in the population (Weiner D. et al., 2004). It should be noted that CKD and CVD share a number of potentially modifying risk factors, the most important of which are diabetes mellitus (DM), dyslipidemia, smoking and hypertension.

DM is a significant social and economic and medical problem in Ukraine and the world. The annual increase in the prevalence of DM in Ukraine is about 4.4% (A.Y. Dyadyk et al., 2010). In connection with the steady increase in the number of patients with type 2 diabetes mellitus, there is a progressive increase in the prevalence of diabetic nephropathy (DN) – a severe complication of diabetes mellitus, one of the leading causes of the development of chronic renal failure (CKD). Today, among patients receiving renal replacement therapy, people with diabetic nephropathy make up about 40-50% (A.I. Dyadyk et al., 2010). It should be noted that the development of DN in patients with diabetes mellitus significantly worsens the cardiovascular prognosis (American Diabetes Association, 2007; Ryden L. et al., 2007).

Previously, it was believed that CKD develops in response to changes that occur in blood vessels in diabetes and hypertension (Sarnak M.J. et al., 2003). However, dyslipidemia and an increase in the level of low-density lipoprotein (LDL) cholesterol are currently considered to be one of the main factors in the development of CVD in CKD. The presence of dyslipidemia is a key point in the development and progression of CVD in CKD and other pathologies, so the effect on lipid profile indicators is the goal of pharmacotherapy. The prevalence of dyslipidemia in patients with CKD and/or DM significantly exceeds similar indicators in the general population, while the degree of lipid metabolism disorder is associated with the glomerular filtration rate (GFR) and indicators of daily proteinuria (Berezyn A.E., 2010).

In the early stages of CKD, the following blood lipid changes are observed: the level of cholesterol bound to high-density lipoproteins (HDL) decreases, the concentration of triglycerides (TG) increases, the level of LDL and very low-density lipoprotein (VLDL) increases (A.V. Smirnov et al., 2005). Similar blood lipid changes are also characteristic of patients with metabolic syndrome.

In recent years, many reports have accumulated about the positive effect of statin therapy on the rate of progression and course of CKD. Statins (inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A-reductase) are recognized as one of the most effective drugs that not only reduce the level of total cholesterol (cholesterol), LDL cholesterol, but also increase the level of HDL cholesterol and have a pronounced anti-atherogenic effect. Since the presence of DM and/or CKD is a significant risk factor for the development of CVD (European Association for Cardiovascular Prevention & Rehabilitation et al., 2011), prescribing statins to this category of patients is considered as a drug of slowing the development and progression of CKD (recommendation class IIa, level of evidence C) . According to data from a meta-analysis of 13 clinical studies (n>170 thousand people), in which the effect of hypolipidemic therapy on the functional state of the kidneys was evaluated, the use of statins in patients with CKD was accompanied by the preservation of GFR and a decrease in the level of proteinuria (Bays H., 2006).

One of the most active and researched agents of the statin class is atorvastatin, a synthetic statin which efficacy and safety have been studied in numerous randomized controlled clinical trials: IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering), REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering), CARDS (Collaborative Atorvastatin Diabetes Study), ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes — Trial Lipid Lowering Arm), TNT (Treating to New Targets), PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy), MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) etc.

The National Kidney Foundation (2003) guidelines indicate statin doses based on GFR. Thus, for patients with severe renal insufficiency (GFR<15 ml/min), the preference is given to atorvastatin due to its predominantly non-renal elimination from the body (only <2% is excreted in the urine). This drug does not require dose adjustment. Prescribing simvastatin, lovastatin, and especially rosuvastatin requires a reduction of the average daily dose of the drug by 50% in patients with CKD at GFR of 30-59 ml/min (Bakris G. et al., 2010).

The results of a randomized open prospective study wherein the patients with CKD were given atorvastatin in addition to angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (sartans) demonstrate that the addition of this drug contributes to a more significant reduction in the level of proteinuria and the progression of CKD (Bianchi S. et al., 2003). Atorvastatin has demonstrated high efficacy in a wide range of daily doses (10-80 mg) with a low incidence of side effects.

The purpose of our work is to evaluate the effectiveness of using atorvastatin for the regulation of dyslipidemia in patients with CKD stage II and III (GFR 30-89 ml/min), caused by type 2 diabetes mellitus in combination with CHD, and to determine the effect of this therapy on the level of C-reactive protein (CRP) and daily proteinuria.

Scope and method of research

Dynamic monitoring and treatment of 32 patients (12 men, 20 women) aged 38-65 years (50.7 (8.7)±2.3 years on average) with II and III stage CKD caused by type 2 diabetes mellitus were carried out in combination with CHD in the stage of compensation or subcompensation of carbohydrate metabolism. All patients gave voluntary consent to participate in the study and were under dynamic monitoring in the nephrology department of the Regional Clinical Hospital named after I.I. Mechnikova (Dnipropetrovsk). The diagnosis of CKD and the stage of the disease were established in accordance with the classification approved by the II National Congress of Nephrologists of Ukraine (Kharkiv, 2005) and the Order of the Ministry of Health of Ukraine No. 593 dated 12.12.2004 "On approval of protocols for providing medical care in the specialty "Nephrology".

Among the patients with type 2 diabetes mellitus, 22 (68.8%) had a compensation state of carbohydrate metabolism, and 10 (31.3%) had a subcompensation state according to the known diagnostic criteria of the WHO (World Health Organization, 1999). The diagnosis of CHD was established in accordance with the Order of the Ministry of Health of Ukraine No. 436 dated 03.07.2006 "On the approval of protocols for providing medical care in the specialty "Cardiology". GFR in the examined patients averaged 45.61 (10.2)±2.14 ml/min/1.73 m^2; duration of CKD — 11.78 (8.75)±2.23 years, Type 2 diabetes mellitus — 15.76 (10.34)±2.87 years. All patients had elevated blood pressure (BP) and dyslipidemia of mixed type. During observation, all study participants followed a hypolipidemic diet, continued to take individual hypoglycemic therapy, which did not change during the entire observation period: 10 (31.3%) patients – gliclazide, 5 (15.6%) – glimepiride, 17 (53.1 %) of patients received insulin. Patients are prescribed concomitant therapy aimed at normalizing BP (iACE inhibitors, sartans, calcium antagonists, β-adrenoceptor blockers, diuretics, imidazoline receptor agonists), correction of anemia (iron preparations, cyanocobalamin, folic acid), water and electrolyte imbalance, as well as acetylsalicylic acid as a disaggregatant.

When carrying out clinical diagnostic and treatment measures, we relied on the diagnostic and treatment protocols approved by the Order of the Ministry of Health of Ukraine No. 593 dated 02.12.2004, the Order of the Ministry of Health of Ukraine No. 436 dated 03.07.2006, on the Recommendations of the European Society of Nephrologists on the diagnosis and treatment of CKD.

The inclusion criteria were the presence of CKD II and III stage caused by type 2 diabetes mellitus in combination with CHD, the presence of dyslipidemia according to the classification of ATP (Adult Treatment Panel) III, and the patient's consent. Exclusion criteria from the study were acute or exacerbation of chronic liver diseases (viral hepatitis, increased levels of hepatic transaminases — alanine aminotransferase (ALT), aspartate aminotransferase (AST) > 3 times); oncological diseases; type 1 diabetes mellitus; acute disorder of cerebral circulation; vascular thrombosis; pathology of the thyroid gland; arrhythmia requiring correction with antiarrhythmic drugs (ventricular extrasystole, atrial fibrillation and flutter, paroxysmal tachycardia, bradysystole syndrome); nephrotic syndrome; use of cyclosporine, tacrolimus, macrolide antibiotics, fibrates, nicotinic acid; period of pregnancy and breastfeeding; patient refusal.

Patients were divided into two groups: 1st group (n=17) — patients whose nephroprotective therapy included atorvastatin (Limistin 10 or Limistin 20 by Ananta Medicare, UK) at a dose of 10-20 mg/day (the average dose per group — 15.9 (4.9)±0.88 mg/day); The 2nd group (n=15) — patients who were not treated with atorvastatin. At baseline, the patients of the 1st and 2nd groups were comparable in terms of blood lipid profile. The duration of observation was 8 weeks. Before the start of the study, the patients had not received statins or other lipid-lowering drugs for 3 months.

Table 1. Characteristics of patients at baseline

Parameter	Group 1 group (n=17)	2 group (n=15)	Control group (n=10) M (Sd)±m
Age, years	45,17 (9,34) ± 2,15	46,48 (9,71) ± 2,04	43,21 (7,15) ± 1,84
Gender, male/female.	7/10	5/10	4/6
Total cholesterol, mmol	6,77(2,35)±1,64*	6,68(2,72) ±1,59*	4,02 (1,37)±0,62
HDL cholesterol, mmol/l	1,03(0,68)±0,03*	1,06(0,74)±0,11*	1,40 (0,70)±0,28
LDL cholesterol, mmol/l	4,96(2,05)±1,37*	4,52(2,73)±1,19*	2,04 (1,2)±0,52
Triglycerides, mmol/l	1,93(1,03)±0,37*	1,98(1,09)±0,21*	1,20 (0,66)±0,55
CRP, mg/l	6,89(2,24)±0,66*	6,27(2,16)±0,59*	1,47 (1,16)±0,37
Daily proteinuria, g/day	1,67 (0,69)±0,45*	1,51 (0,65) ±0,24*	0,032 (0,02)±0,005

* Significant difference compared to the control group (p<0,05).

The control group included 10 practically healthy individuals, similar in gender and age to representatives of the main groups (Table 1).

Objective and subjective signs of CKD were determined for all patients, anamnestic data were collected, physical examination and laboratory-instrumental methods were performed at the beginning and at the end of the study: electrocardiography (ECG), clinical examination of blood and urine; determination of daily proteinuria; biochemical blood test — the level of creatinine, urea, sugar, total protein and albumin of the blood, the level of glycosylated hemoglobin; Cockcroft-Hault formula to determine the level of GFR; blood pressure level and heart rate (HR) were assessed as well. The concentrations of total cholesterol and TG in blood serum was determined by immunoenzymatic methods by using a colorimetric test from the sets of the company "HUMAN" (Germany) on the biochemical analyzer "Chemistry Analyzer RT-1904C" (Rayto Electronics, USA/China). The levels of LDL-C and LDL-C were calculated according to O.M. Klimov formulas. HDL-C was determined by the immunoenzymatic method when added to LDL-C and LDL-C followed by centrifugation of the precipitating reagent based on phosphorous-tungstic acid "Cholesterol liquicolor Test kit" ("HUMAN", Germany). The level of CRP in blood serum was measured by semiquantitative determination in undiluted serum by the method of agglutination of latex particles by using HUMATEX kits (HUMAN, Germany) on a semi-automatic analyzer "Chemistry Analyzer RT-1904C".

The effectiveness of Limistin therapy was assessed by the decrease in the level of LDL cholesterol <1.8 mmol/l in accordance with the recommendations of the European Association for Cardiovascular Prevention & Rehabilitation (2011) and LDL cholesterol <4.6 mmol/l (according to ATP-III) in patients with high and very high cardiovascular risk (European Association for Cardiovascular Prevention & Rehabilitation et al., 2011). The specified parameters of lipid metabolism were determined in the initial state of patients before the prescription of Limistin and after 8 weeks of drug use.

In order to assess the safety of Limistin in the dynamics of monitoring patients, biochemical blood tests were carried out with the determination of the content of urea, creatinine, and the activity of hepatic transaminases (AST, ALAT) by standard methods (F.I. Komarov and co-authors, 1999). The incidence of adverse reactions based on the subjective feelings of patients was assessed.

Statistical processing of the obtained data was carried out by using the licensed program STATISTICA 6.1 ("StatSoft", USA). Mean values (M), standard deviation (Sd), standard error of the mean value (m) were determined. The Mann-Whitney U-test was used to compare the parameters in two independent groups and the Wilcoxon test (W) was used to compare two dependent groups. The degree of relationship between pairs of independent features expressed on a quantitative scale was assessed by using Spearman's rank correlation coefficient — r. Statistically significant differences in research results were determined at the level of p<0.05.

Results and discussion

During the initial examination of the patients, a probable increase in the levels of CSC was found in 30 patients (93.8%), TG – in 23 patients (71.9%), LDL-C – in 27 patients (84.4%), and a decrease in the level of HDL-C – in 15 patients (46.9%) according to ATP III classification. The average level of total cholesterol in patients with II and III stage CKD caused by type 2 diabetes mellitus in combination with CHD was 6.14 (2.02)±1.26 mmol/l, LDL-C was 4.51 (2.39)±1.54 mmol/l, HDL cholesterol — 1.10 (0.48)±0.59 mmol/l, TG — 1.13 (0.99)±0.56 mmol/l. Moderate correlations were established between the levels of CSC, LDL-C and GFR in the examined patients (r=-0.3996, p=0.0087 and r=-0.3599, p=0.0192, respectively).

In the group of patients who additionally received Limistin (10 or 20 mg/day, respectively) for 8 weeks, there was a significant decrease in the concentration of total cholesterol in the blood serum by 34.12% (p<0.05), LDL-C by 48, 79% (p<0.05) and TG — by 25.9% (p<0.05).

An increase in HDL cholesterol by 13.6% turned out to be statistically improbable. This indicates the need for longer use of Limistin to achieve probable changes in this parameter. At the end of observation in the 1st group, 7 (41.3%) patients reached the recommended target level of TG (<1.7 mmol/l), 6 (35.3%) — the recommended target level of HDL-C (women >1.2 mmol/l), 15 (88.2%) patients — the recommended target level of total cholesterol (<4.6 mmol/l) and 9 (52.9%) patients — the target level of LDL cholesterol (<1.8 mmol/l)

It should be noted that among patients of the 1st group who did not reach the target level of LDL-C, the level of LDL-C <2.6 mmol/l was observed in 3 (37.5%) patients (Table 2).

It was found that the normalization of the blood lipid profile was slower in patients who did not include Limistin in the complex therapy compare to those of the 1st group. Thus, at the end of the observation period, patients in the 2nd group showed a tendency to decrease CHD, LDL-C, TG by 9.6% (p>0.05), 9.9% (p>0.05) and 17.2 % (p>0.05), respectively, as well as an increase in the level of HDL cholesterol in blood serum by 3.8% (p>0.05).

Table 2. **Dynamics of blood lipid profile, blood biochemical parameters in patients with II and III stage CKD caused by type 2 diabetes mellitus in combination with CHD, against the background of treatment**

Parameters	Group			
	1 group (n=17) M (Sd)±m		2 group (n=15) M (Sd)±m	
	Before treatment	After treatment	Before treatment	After treatment
Total cholesterol, mmol	6,77 (2,35) ± 1,64*	4,46 (1,97) ± 1,03*,#	6,68 (2,72) ± 1,59	6,04 (2,0) ± 1,27
HDL cholesterol, mmol/l	1,03 (0,68) ± 0,03	1,17 (0,94) ± 0,34	1,06 (0,74) ± 0,11	1,10 (0,59) ± 0,15
LDL cholesterol, mmol/l	4,96 (2,05) ± 1,37*	2,54 (2,27) ± 0,73*,#	4,52 (2,73) ± 1,19	4,07 (2,29) ± 1, 70
Triglycerides, mmol/l	1,93 (1,03) ± 0,37*	1,43 (0,74) ± 0,13*,#	1,98 (1,09) ± 0,21	1,64 (0,89) ± 0,17
CRP, mg/l	6,89 (2,24) ± 0,66*	4,73 (1,79) ± 0,59*,#	6,27 (2,16) ± 0,59	6,04 (2,34) ± 0,61
Daily proteinuria, g/day	1,67 (0,69) ± 0,45*	0,82 (0,31) ± 0,27*	1,51 (0,65) ± 0,24	1,02 (0,49) ± 0,15*

* Significant difference before and after treatment (p<0.05); # significant difference compared to the 2nd group at the end of treatment (p<0.05).

Table 3. **Safety parameters of treatment in patients with stage II and III CKD caused by type 2 diabetes mellitus in combination with CHD**

Parameters	1 group (n=17) M (Sd)±m		2 group (n=15) M (Sd)±m	
	Before treatment	After treatment	Before treatment	After treatment
Systolic blood pressure, mm Hg	160,6(11,8)± 2,09	138,4(9,6)±1,88*	157,7(10,9)± 2,11	135,8 (9,4) ±1,74*
Diastolic blood pressure, mm Hg	92,5(8,8) ±1,56	84,1(7,6)±1,42*	92,7(9,0)±1,54	84,5 (8,7) ±1,47*
Heart rate	80,4(10,0)±1,77	78,1(9,6)±1,65	82,1(10,1)±1,79	77,2 (9,2) ±1,56
Blood sugar, mmol/l	6,44(1,0)± 0,18	6,01(0,89)±0,18	6,36(0,9)± 0,22	6,25 (0,98) ± 0,21
Creatinine, μmol/l	206,6(57,3)±10,13	189,3(45,9)±9,27	204,3(49,3)± 9,74	196,5 (47,8) ± 9,34
Urea, mmol/l	15,8(2,15)± 0,38	12,6(1,56)±0,22	15,7(2,18)± 0,42	12,8 (1,89) ± 0,34
ALT, units/liter	18,5(4,8)± 0,85	20,0(5,1)±0,87	18,7(4,8)± 0,81	19,7 (4,9) ± 0,78
AST, units/liter	21,7(5,0)± 0,87	23(5,2)±0,98	22,0(5,1) ±0,90	22 (5,0) ± 0,85
GFR, ml/min	54,94(17,6)± 3,11	60,23(20,1)±4,76	55,12(18,1)± 3,56	58,41(19,83) ±4,78

* Significant difference before and after treatment

These parameters were significantly different from similar ones of patients of the 1st group (Table 2). Among the 2nd group, no patient had the target levels of CSC, LDL-C, TG at the end of the observation. Only 2 (13.3%) patients reached the target level of HDL-C against the background of treatment.

The obtained data indicate a reliable effect of Limistin therapy (10–20 mg/day) on lipid metabolism parameters in patients with II and III stage CKD caused by type 2 diabetes mellitus in combination with CHD, and demonstrate that dietary restrictions alone cannot significantly affect lipid metabolism in this category of patients.

We also evaluated the pleiotropic effect of atorvastatin based on the analysis of the dynamics of CRP levels and daily proteinuria. CRP is an independent factor of high risk of CVD (including the development of myocardial infarction, cerebral circulation disorders) and CVD mortality, which is correlated with the prevalence of subclinical atherosclerosis. According to some authors, even a single determined CRP concentration is a more significant predictor of coronary events than LDL-C. This parameter helps to identify patients with a high cardiovascular risk but with a normal level of LDL-C and can significantly supplement the prognostic significance of the information obtained using the Framingham algorithm, which requires further study (Prichard S., 2003). Among the examined patients, the increase in CRP levels in blood serum was recorded in 21 (65.7%) patients, and the level of CRP ranged from 4 to 18 mg/l. The average level of CRP was 7.98 (2.11)±0.78 mg/l and was significantly different from the level of CRP in the control group (see Table 1). Against the background of treatment in the 1st group, at the end of the observation, the CRP level decreased by 31.4% (p<0.05) that was 88.29% (p<0.001) higher than the parameter in the 2nd group (see Table 2). The level of CRP in the dynamics of observation completely normalized in 13 patients (76.5%) of the 1st group and in 5 patients (33.3%) of the 2nd group.

Thus, the use of Limistin (10–20 mg/day) led to a pronounced and reliable decrease in the level of CRP in blood serum in patients with II and III stage CKD, caused by type 2 diabetes mellitus in combination with CHD, which indicates a significant anti-inflammatory effect of the drug.

Among the examined patients, daily proteinuria was observed in 30 (93.8%) patients and significantly differed from the parameters of the control group (see Table 1). Proteinuria <0.5 g/day occurred in 9 patients (28.1%), 0.5-3.49 g/day – in 21 patients (65.6%). We registered a moderate correlation between the levels of total cholesterol, LDL cholesterol, CRP and daily proteinuria (r=0.3854; p=0.0052; r=0.4462; p=0.0044 and r=0.3350; p=0.0243, respectively) in patients with stage II and III CKD caused by type 2 diabetes mellitus in combination with CHD. The level of daily proteinuria in the patients of the 1st and 2nd groups in the initial state did not differ significantly (see Table 1).

The analysis of the decrease in the level of daily proteinuria at the end of the study showed the decrease by 50.9% p<0.05) among patients of the 1st group and by 31.1% (p<0.05) among patients of the 2nd group. Thus, the addition of Limistin (10-20 mg/day) to basic therapy led to a more significant (by 38.8% p<0.05) decrease in daily proteinuria.

The positive dynamics of blood pressure and heart rate levels were observed in all groups of patients at the end of the study. In the course of the study, there were no negative changes in laboratory parameters, including the activity of AST, ALT, levels of creatinine, urea, and GFR.

Limistin has a positive effect on GFR and carbohydrate metabolism, as evidenced by a tendency to lower fasting blood glucose in the absence of correction of daily doses of hypoglycemic agents (Table 3). In general, the patients took the drug satisfactorily. Side effects were registered in 5 patients. In 2 cases, phenomena of flatulence were reported, in 1 case — a feeling of discomfort in the stomach, in 1 case — a decrease in appetite, and in 1 case — a headache. In all registered cases, the described phenomena were temporary in nature and did not require discontinuation of the drug.

Conclusions

1. The use of Limistin for 8 weeks in order to regulate dyslipidemia in patients with II and III stage CKD, caused by type 2 diabetes mellitus in combination with CHD, allows to reduce the level of total cholesterol in the blood by 34.12% (p<0.05), LDL C — by 48.79% (p<0.05) and TG — by 25.9% (p<0.05).
2. Limistin helps to reduce the level of CRP by 31.4% (p<0.05) and daily proteinuria by 50.9% (p<0.05).
3. Limistin is safe to use in patients with stage II and III CKD, caused by type 2 diabetes mellitus in combination with CHD. It does not cause significant side effects that require changes in the daily dose or discontinuation of treatment.

References: *www.umj.com.ua*