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Rosuvastatin and ezetimibe in the treatment of diabetic dyslipidemia in patients with type 2 diabetes mellitus

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ANNOTATION
This article studied lipid metabolism in patients with type 2 diabetes. Against the background of decompensation, diabetic dyslipidemia was detected in the examined patients, with an increase in total cholesterol, triglycerides, and atherogenic fractions of low-density lipoproteins, as well as a decrease in high-density lipoproteins. At the same time, a relationship was revealed between the content of lipoproteins of various classes with duration and BMI of patients. An analysis was conducted between monotherapy and monotherapy for diabetic dyslipidemia. Rosuvastatin 10 mg/ day and the fixed drug rosuvastatin + ezetimibe at a dose of 10/10 mg/ day. A combination therapy of rosuvastatin and ezetimibe 10/10 mg is an effective drug for the treatment of diabetic dyslipidemia.
Keywords: diabetic dyslipidemia, statins, rosuvastatin, ezetimibe.

Diabetes mellitus (DM) is a chronic progressive disease that has become widespread in the 21st century, truly pandemic nature of the spread. According to the latest data, the number of patients with diabetes in the world has more than doubled over the past 10 years. According to the International Diabetes Federation, by 2045, 629 million people will suffer from diabetes [1]. Cardiovascular disease remains the leading cause of morbidity and mortality in patients with type 2 diabetes, despite the recent introduction of multifactorial interventions to control cardiovascular risk factors [3].

The prevalence of cardiovascular diseases (CVD) among patients with type 2 diabetes is 2–4 times higher than that among persons without diabetes; they are the cause of death in more than 65% of patients [2,3,5,6]. The most dangerous consequences of the global epidemic of diabetes are its systemic vascular complications - nephropathy, retinopathy, and damage to the great vessels of the heart, brain, and arteries of the lower extremities. These complications are the main cause of disability and mortality in patients with diabetes. The high prevalence of CVD among patients with type 2 diabetes is due to a cluster of risk factors for atherosclerosis, which is based on insulin resistance, dyslipidemia, arterial hypertension, increased activity of the blood coagulation system, visceral obesity, and hyperglycemia [7,8]. However, at present, not everyone agrees that it is hyperglycemia that is crucial in the development of atherosclerosis in patients with type 2 diabetes [2,9]. The UK Prospective Diabetes Study (UKPDS) showed that carbohydrate compensation reduced the risk of microvascular complications without significantly affecting macrovascular complications in patients with type 2 diabetes. At the same time, this and other studies

demonstrated the relationship between the level of total cholesterol (TC) and cholesterol LDL and the risk of developing macrovascular accidents both in the general population and in patients with diabetes 2 types [10,12,13,14]. Analysis of the results of multicenter randomized placebo-controlled studies that included groups of patients with type 2 diabetes allows us to conclude that lipid-lowering therapy with HMG- CoA reductase inhibitors have a positive effect both as primary and secondary prevention of CVD in this group of patients [14]. Currently, there is evidence that the antiatherogenic properties of HMG- CoA reductase inhibitors are due not only to their effect on the lipid spectrum. Pleiotropic antiatherogenic effects of some representatives of this class of drugs have been described, independent of the main mechanism of their action, in particular, the effect on atherosclerotic inflammation [4,5,6]. However, the prescription of HMG- CoA reductase inhibitors in clinical practice to correct lipid metabolism disorders in patients with type 2 diabetes remains extremely rare [4]. Rosuvastatin is the most effective statin currently available. However, patients with coronary artery disease may not achieve targets on monotherapy [10,14]. The study compares the effectiveness of monotherapy rosuvastatin and combination therapy with rosuvastatin and ezetimibe.

Most clinical guidelines initially recommend the use of statins in patients with dyslipidemia and diabetes. In cases where target low-density lipoprotein cholesterol (LDL-C) levels are not achieved with statin treatment alone, combination therapy with ezetimibe is recommended [11,13,14]. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, reducing cholesterol production in the liver. Meanwhile, ezetimibe is a cholesterol absorption inhibitor that acts in the small intestine through direct binding to Niemann-Pka C1-like 1, avoiding the reabsorption of intrinsic cholesterol, which is released into the intestine as bile acid, resulting in its excretion. Combination therapy with statins and ezetimibe reduces LDL cholesterol levels by 15–20% more than monotherapy statins; in addition, it demonstrates additional cardiovascular benefits.

The study compares the effectiveness of monotherapy rosuvastatin and combination therapy with rosuvastatin and ezetimibe.

The purpose of this work was to evaluate the effectiveness and safety of the drug Rozulip plus 10/10 mg in patients with type 2 diabetes mellitus with diabetic dyslipidemia.

Materials and methods. We examined 35 patients with moderate type 2 diabetes with confirmed dyslipidemia (LDL level ≥ 2.6 mmol /l and triglycerides ≥1.7 mmol/l) type II b (according to Fredrickson), treated in the endocrinology department of the 3-clinic TMA. Among them are 12 men and 23 women. The disease duration ranged from 1 year to 10 years, the average age was 56.6±9.8 years. Patients with severe concomitant diseases and micro- and macrovascular complications were not included in the study. 10 practically healthy individuals were also studied. 53.5% of this group suffered from coronary artery disease, 88.4% from arterial hypertension.

Most patients received aspirin, B- blockers, and angiotensin-converting enzyme inhibitors. All patients were overweight - their body mass index (BMI) exceeded 25 kg/ m^2 . 11 (31.4%) patients were diagnosed with overweight, and 24 (68.6%) patients were obese (BMI ≥30 kg/m2). The average waist circumference was 105.1± 2,0 in men, and 108.3± 3,0 in women. The majority of patients 19 (48.5%) received sulfonylureas and metformin as hypoglycemic agents, 12 (34.2%) received DPP4, and 7 (20.0%) received insulin in combination with metformin. Considering that all patients were diagnosed with decompensation of the disease, hypoglycemic therapy was corrected, so 60% of patients were transferred to insulin therapy.

All patients underwent a general clinical examination. Fasting and postprandial glycemia were studied using the glucose oxidase method. The study of glycated hemoglobin (HbA 1c) was carried out using a biochemical method using a Respons -920 apparatus (Germany). Lipid metabolism indicators were determined by the enzymatic method using a set of reagents from Human (Germany) on a Randox analyzer (Great Britain). The obtained data were processed on a computer using the statistical software package "Statistika-6".

Patients in both groups did not differ from each other in age and duration of the disease. Patients complained of increased blood pressure, dry mouth, thirst, frequent urination, periodic pain in the heart, headaches, and excess weight.

Results of our research.

Thus, according to carbohydrate metabolism data, all patients show an increase in fasting and postprandial glycemia and HbA 1 c, which were increased by 41.0, 43.2, and 43.5%, indicating decompensation of diabetes.

Table 1

Biochemical blood parameters in patients with type 2 diabetes before treatment

Index	Control n - 10	Before treatment n- 35
Fasting glycemia, mmol /l	4.2±0.48	7.1±0.37*
Postprandial glycemia, mmol\l	5.8±0.67	10.2±0.33*
HbA 1 s , %	4.5±0.5	7.9±1.0*
TC, mg\dl	3.7±1.0	6.6±1.2*
LDL, mg\dl	1.85±0.04	3.85±0.09*
HDL, mg\dl	1.53±0.03	1.21±0.05
TG, mg\dl	1.11±0.03	3.93±0.09*
Atherogenic coefficient	2.02+0.09	4.71±0.25**
ALT, U\l	18.8±3,7	24.8±4,0
AST, U\l	23.1±2.9	25.8±3,3

Note: n is the number of examined patients;

*-- presence of significance (P< 0.05), **(P<0.01)

When analyzing the lipid spectrum in patients with type 2 diabetes, hyperlipoproteinemia was observed - a significant increase in lipid metabolism parameters compared to the control group. At the same time, the content of TC in the blood was 34.0% (P< 0.05) higher than in the control group, LDL increased by 37.5%, and TG by 40.6% (P<0.01). The HDL content was 60.2% (P< 0.05) lower in the main group compared to the control group (Table 1). The obtained results of an increase in atherogenic lipoproteins such as LDL, and TG and a decrease in the level of the

antiatherogenic fraction - HDL in patients with type 2 diabetes coincided with the data described in the literature [12].

The distribution of patients with type 2 diabetes depending on BMI revealed that the level of LDL cholesterol was 16.8% higher in the group of patients with BMI>30 compared with overweight. The level of HDL cholesterol in the same group was 26% higher (P < 0.05) compared to the study group (Table 2). The TG level was higher by 29.0% (P < 0.05), which was reflected in the atherogenic coefficient, which was higher by 24% (P < 0.05). Thus, the results showed that as the patient's body weight increases, the lipid profile worsens, which affects the development of micro- and macrovascular complications of diabetes [9].

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Table 2

Clinical characteristics of patients and biochemical parameters in patients with type 2 diabetes depending on BMI

Indicators	control n-10	BMI< 30, n- 11	BMI>30, n- 24
Age, years	54.9±8.9	55.9 ± 7.6	54.7±8.3
Duration of disease, years	-	6.9±4.8	7.5±3.9
Fasting glycemia, mmol /l	4.2±0.48	7.7±1.9*	7.5±2.0*
Postprandial glycemia, mmol/l	5.8±0.67	11.2±3.9*	12.9±4.1*
HbA1c ,%	4.5±0.5	7.8±2.1*	8.3±2.4*
TC, mmol/l	3.7±1.0	6.1±1.2*	6.3±1.7*
LDL, mmol/l	1.85±0.04	3.48±0.09*	3.49±0.07*
HDL, mmol/l	1.53±0.03	1.2±0.05	0.81±0.08 *,* *
TG, mmol/l	1.11±0.03	3.2±0.4*	4.5±0.9 *,* *
Atherogenic coefficient	2.02+0.09	4.0±0.7	4.68±0.79 *,* *

Note: n – number of examined patients;

*- the presence of significance about control (P < 0.05)

**-availability of significance concerning the group with BMI <30 (P < 0.05)

The distribution of patients with type 2 diabetes according to the duration of the disease showed that LDL cholesterol, depending on the duration of the disease, was increased relative to the control group, but these indicators did not differ from each other. Triglycerides in the 6-10 disease group were increased by 28.2% (P < 0.05) compared with the <3 year group and by 22.5% (P < 0.05) compared with the 3-6 year group. This is confirmed by literature data, which describes a deterioration in the lipid spectrum with a predominant increase in triglycerides in the blood lipid spectrum compared to total cholesterol in diabetic dyslipidemia [5]. The level of HDL cholesterol was 36.0% (P < 0.05) lower in the group of patients 6-10 years old compared to those up to 3 years of illness. This is reflected in the atherogenic index, while AI in the first group was increased by 60.0%, in the second by 65.4%, and in the third by 65.3%, respectively, relative to the control (Table 3).

Table 3

Clinical characteristics of patients and biochemical parameters in patients with type 2 diabetes depend on the duration of the disease.

Indicators	control n-10	Up to 3 years old n-10	36 years, n-14	6-10 years n-11
Age	54.9±8.9	52.9 ± 4.1	56.4±5.9	54.7±8.2
Duration of the disease	-	1.9±1.5	4.9±1.8	8.4±2.8
Fasting glycemia, mmol/l	4.2±0.48	6.9±1.33	7.1±1.37	6.8±1.27
Postprandial glycemia, mmol/l	5.8±0.67	11.8±3.3	9.9±3.7	13.0±3.1*
HbA1c , %	4.5±0.5	8.5±2.4*	7.9±1.9*	8.3±2.7*
TC, mmol/l	3.7±1.0	6.3±1.7*	6.0±1.5*	6.6±1.1 *,* *
LDL cholesterol, mmol/l	1.85±0.04	3.0±0.3*	3.49±0.3*	3.51±0.5*
HDL cholesterol, mmol/l	1.53±0.03	1.4±0.06	1.2±0.05	0.90±0.07 *,* *
TG, mmol/l	1.11±0.03	3.4±0.9*	3.7±0.4*	4.7±0.9*
Atherogenic coefficient	2.02+0.09	3.5±0.9	4.0±0.5	4.0±0.6

Note: n – number of examined patients;
*- presence of significance ($P < 0.05$)

Thus, a relationship was identified between the content of lipid metabolism indicators with carbohydrate metabolism indicators, duration of the disease, and BMI. This probably indicates a connection between the process of atherogenesis and the patient's body weight. The results obtained coincided with the data described in the literature [7].

Assessing the category of cardiovascular risk (CVR) is extremely important for developing optimal patient management and prescribing adequate therapy that can maintain optimal LDL cholesterol levels. Following the provisions of the ESC/EASD consensus recommendations on diabetes, prediabetes, and cardiovascular diseases (CVD), adopted in 2019, patients with diabetes should be considered as a group of high and very high risk of CC complications: patients with diabetes and at least one risk factor for CV disease or target organ damage should be considered a very high-risk group, and all other patients with DM should be considered a high-risk group [9].

Achieving a target LDL cholesterol level below 2.5 mmol/l (for patients with high cardiovascular risk), and even more so below 1.8 mmol/ l, is quite a difficult task, which dictates the need to use the most effective statins in high doses. According to some authors, the use of rosuvastatin at a dose of 10 mg led to a decrease in LDL cholesterol levels by 34%, while the risk of CV events decreased by 23%, and the difference with the group of patients receiving placebo was statistically significant [9].

Statins are insufficiently effective in achieving the target level of LDL cholesterol in patients with type 2 diabetes, it is possible to use combination therapy: adding ezetimibe to statin therapy. The latter belongs to the class of cholesterol absorption inhibitors. The mechanism of action of ezetimibe is that it prevents the absorption of cholesterol at the level of the villous epithelium of the small intestine. Due to a decrease in the supply of bile acids and dietary cholesterol from the intestine to the liver, the uptake of cholesterol from the blood serum by liver cells increases, due to which its content in the blood decreases [11].

In this regard, for the treatment of patients with type 2 diabetes, along with hypoglycemic and complex therapy, patients were divided into 2 groups: group 1 - 17 patients, rosuvastatin was added to the treatment complex at a dose of 10 mg/day, group 2 - 18 patients, they added a combination drug rosuvastatin with ezetimibe (Rozulip plus 10/10 mg). Patients took a lipid-lowering drug, 1 tablet per day in the evening for 3 months. Drug dosage adjustments were carried out after a month and 3 months until the target blood lipid level was achieved.

The safety of therapy was assessed by the number and type of registered undesirable side effects, as well as by identifying clinically significant changes in biochemical blood parameters: an increase in the level of liver transaminases by 3 times or more. After a month and 3 months, 32 (91.6%) patients were re-examined; the remaining 3 (8.4%) did not appear for re-examination due to various personal reasons.

During the study, there were no cases of exacerbation of angina attacks, increases in blood pressure, changes in heart rate, or significant decreases in body weight and BMI.

During therapy with Rosuvastatin and Rosuvastatin with ezetimibe, no significant changes in the lipid spectrum were detected after a month. Also, there were no changes in liver blood enzymes. In this regard, patients were recommended to continue lipid-lowering therapy.

During treatment, positive changes in carbohydrate metabolism were observed in both groups. Thus, HbA 1c in groups 1 and 2 decreased by 21 and 22% ($P < 0.05$), respectively.

The results showed that after 3 months of treatment, groups 1 and 2 showed positive changes in carbohydrate and lipid metabolism. In group 1, there was a decrease in TC by 19.8%, LDL by – 16.0%, and TG by – 23.1% ($P <0.05$) (Table 4). The concentration of HDL in the blood did not undergo significant changes. However, a tendency towards its increase by 1–5.2 % was revealed. This is all reflected in the atherogenic index, which was reduced by 32% ($P < 0.05$).

In group 2, TC was reduced by 22% ($P < 0.05$), LDL by 23%, and triglycerides by 49% ($P < 0.05$) compared to the values at admission and by 32% compared to group 1 ($P < 0.05$). It is known that target LDL levels should be below 2.5 mmol/l, at which the risk of developing cardiovascular diseases is reduced by 2 times [9].

HDL increased by 15% compared to the values at admission and by 23% compared to group 1 ($P < 0.05$). The atherogenicity coefficient decreased by 32 and 62%, respectively, and by 44% compared to group 1 ($P < 0.05$), indicating a decrease in total cholesterol and an increase in the amount of “good” lipids HDL cholesterol.

Table 4

Biochemical blood parameters in patients with type 2 diabetes during complex therapy including lipid-lowering therapy

Index	Before treatment n- 35	1 group n- 16	2nd group n-1 6
Fasting glycemia, mmol/l	7.1±0.37	6.4±0.73	6.2±0.23
Postprandial glycemia, mmol/l	10.2±0.33	9.3±2.5*	8.09±0.1*
HbA1c, %	7.9±1.0	6.3±0.54*	6.2±0.8*
TC, mmol/l	6.6±1.2	5.8±1.2	5.2±0.9*
LDL, mmol/l	3.15±0.09	2.98±0.09*	2.41±0.04 *,* *

HDL, mmol/l	1.21±0.05	1.47±0.09*	1.84±0.07*
TG, mmol/l	3.93±0.09	2.9±0.23	2.05±0.04 *,* *
Atherogenic coefficient	4.71±0.25	3.2±0.19*	1.89±0.11 *,* *
ALT	24.8±4,0	22.4±3,4	24.1±3,9
AST	25.8±3,3	23.1±4,0	23.8±3,1

Note: n – number of examined patients;
*- presence of significance (P < 0.05) about the group at admission
**- presence of significance (P < 0.05) in relation to group 1

Biochemical blood parameters - AST, and ALT did not change statistically significantly.
In group 2, where patients took rosuvastatin with ezetimibe, a decrease in LDL levels was found during observation (p <0.05). The average LDL level at the beginning of the study was 3.15±0.09 mmol/l, at the end – 2.48±0.04 (p < 0.05). During the period of treatment with Rozulip plus 10/10 mg, out of 16 patients examined, 10 (62.5%) achieved the target LDL level by the end of the period; the remaining patients were recommended to increase the dose of the drug to 20/10 mg/ day. During the period of treatment with Rosuvastatin, out of 16 patients examined, 7 (43.7%) reached the target LDL level by the end of the period; the remaining patients were also recommended to increase the dose of the drug to 20 mg/ day.
Thus, the ability to achieve the target LDL level in a short time when treated with the combined drug Rozulip plus 10/10 mg, its safety and good tolerability, as well as the favorable cost/effectiveness ratio allows us to recommend it as one of the drugs of choice among lipid-lowering drugs.

Conclusions:

1. A study of lipid metabolism in patients with type 2 diabetes revealed a significant increase in total cholesterol, triglycerides, and atherogenic fractions of lipoproteins - LDL by 34.0, 40.6 and 37.5%, and the content of antiatherogenic fractions of lipoproteins - HDL was 60.2% lower compared to the control group.
2. A relationship was revealed between the content of lipoproteins of various classes with duration and BMI of patients.
3. Combination therapy of rosuvastatin and ezetimibe 10/10 mg is an effective drug for the treatment of diabetic dyslipidemia, with a decrease in TCh by 22% (p <0.05), TR - by 32% (p <0.05), LDL by 49 % (p <0.05) and a 23% increase in HDL compared to the monotherapy group rosuvastatin, where the lipid profile also improved, but not significantly.
4. The good tolerability of the combined drug and favorable cost/effectiveness ratio allows us to recommend Rozulip plus 10/10 mg as one of the drugs of choice in the treatment of diabetic dyslipidemia.

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