Treatment Optimization of the Dyslipidemia in Type 2 Diabetes

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ABSTRACT

This article studies the data on evaluation of the efficacy and safety of the drug Rozulip plus 10/10 mg in patients with type 2 diabetes mellitus with diabetic dyslipidemia. In addition, the research and basic results are given with numbers. The safety of examination was assessed by the number and type of registered adverse side effects, as well as by the detection of clinically significant changes in blood biochemical parameters.

Keywords: dyslipidemia, diabetes, lipid-lowering therapy, Rosuvastatin, ezetimibe, carbohydrate metabolism, lipid-lowering drugs.

The prevalence of cardiovascular diseases (CVD) among patients with type 2 diabetes is 2-4 times higher than that among people without diabetes, they are the cause of death for more than 65% of patients [2,3,5,6]. According to the latest data, the number of patients with diabetes in the world over the past 10 years has more than doubled, and by the end of 2017 it exceeded 425 million people. According to the forecasts of the International Diabetes Federation, 629 million people will suffer from diabetes by 2045 [1]. The most dangerous consequences of the global epidemic of diabetes are its systemic vascular complications - nephropathy, retinopathy , damage to the main vessels of the heart, brain, arteries of the lower extremities. It is these complications that 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 are based on insulin resistance , dyslipidemia , arterial hypertension, increased activity of the blood coagulation system, visceral obesity and hyperglycemia [7,8]. Analysis of the results of multicenter randomized placebo-controlled studies, which included groups of patients with type 2 diabetes, allows us to conclude that lipid-lowering therapy with HMG-CoA reductase inhibitors has a positive effect both as primary and secondary prevention of CVD in this group of patients [14]. However, the appointment of HMG-CoA reductase inhibitors in clinical practice for the correction of 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]. Study compares effectiveness of monotherapy rosuvastatin and combination therapy with rosuvastatin and ezetimibe .

The aim of this work was to evaluate the efficacy 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 42 patients with moderate type 2 diabetes with confirmed dyslipidemia (LDL ≥ 2.6 mmol /l and

triglycerides ≥1.7 mmol /l) II A type (according to Fredrickson), treated in the department of endocrinology of the 3-clinic of TMA. Among them, 18 men and 24 women. The duration of the disease ranged from 1 to 10 years, the mean age was 56.6±9.8 years. Patients with severe comorbidities and micro- and macrovascular complications were not included in the study. 10 non-diabetic patients were also studied , 53.5% of this group suffered from coronary artery disease, 88.4% from arterial hypertension.

All patients were overweight - their body mass index (BMI) exceeded 25 kg/m ^{2} . Overweight was diagnosed in 13 (31.4%) patients, obesity (BMI ≥30 kg/m ^{2}) was diagnosed in 29 (68.6%) patients. The average waist circumference was 105.1± 2,0 смin men and 108.3± 3,0 смin women. Most of the patients 20 (48.5%) received sulfonylurea and metformin as hypoglycemic agents , 14 (34.2%) received iDPP4, 8 (20.0%) received insulin in combination with metformin. Given 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 was studied by the glucose oxidase method. The study of glycated hemoglobin (HbA 1 c) was carried out according to the Fluchiger method . Lipid metabolism parameters 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 Statistics-6 statistical software package.

Patients of both groups did not differ in age and duration of the disease. Patients complained of increased blood pressure, dry mouth, thirst, frequent urination, recurrent pain in the heart, headaches, overweight.

Results of own researches .

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

Tab. 1

Biochemical parameters of blood 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 1c , %	4.5±0.5	7.9±1.0*
OH, mg \ dl	3.7±1.0	6.6±1.2*
LDL, mg \ dl	1.85±0.04	3.15±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	0.30±0.02	0.30±0.02
AST	0.18±0.01	0.18±0.01

Note : n is the number of examined patients;
*--the presence of reliability (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 compared with the control group.

At the same time, the content of TC in the blood is 34.0% (P< 0.05) higher than in the control group, LDL increased by 37.5%, TG by 40.6% (P<0.01). The content of HDL by 60.2% (P < 0.05) was lower in the main group compared to the control (Table 1). The obtained results of an increase in atherogenic lipoproteins such as LDL, 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 according to the duration of the disease showed that LDL-C, 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 disease group 6-10 were increased by 28.2% (P < 0.05) compared with the under 3 years group and by 22.5% (P < 0.05) compared with the 3-6 years group. This is also confirmed by the literature data, which describes the deterioration of 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-C was 36.0% (P < 0.05) lower in the group of patients aged 6-10 years compared to 3 years of the disease. This is reflected in the atherogenicity 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, in relation to the control (Table 2).

Tab. 2

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

Indicators	control n-10	Up to 3 years n-16	3-6 years old _ n-14	6-10 years old n-12
Age	54.9±8.9	52.9 ± 4.1	56.4±5.9	54.7±8.2
Disease duration	-	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*
HbA 1c , %	4.5±0.5	8.5±2.4*	7.9±1.9*	8.3±2.7*
OX, 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*	3.4±0.3*	3.2±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 is the number of examined patients;

*- presence of significance (P < 0.05)

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

With insufficient effectiveness of statins in achieving the target level of LDL-C 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. In connection with a decrease in the intake of bile acids and dietary cholesterol from the intestine to the liver, the uptake of cholesterol from blood serum by hepatic cells

increases, due to which its content in the blood decreases [11].

Rosuvastatin was added to the treatment complex at a dose of 10 mg / day, group 2, these are 23 patients , they added a combination drug rosuvastatin with ezetimibe (Rozucard plus 10/10). Patients took lipid-lowering drug 1 tablet per day in the evening for 3 months. Correction of the dose of drugs was carried out after a month and 3 months to achieve the target level of blood lipids.

The safety of therapy was assessed by the number and type of registered adverse side effects, as well as by the detection of clinically significant changes in blood biochemical parameters: an increase in the level of hepatic transaminases by 3 times or more. A month and 3 months later, 38 (91.6%) patients were re-examined, the remaining 4 (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, rise in blood pressure, changes in heart rate, a significant decrease in body weight and BMI.

On the background of treatment, there are positive changes in carbohydrate metabolism in both groups. Thus, HbA 1 c in groups 1 and 2 decreased by 21 and 22%, respectively.

The results showed that in groups 1 and 2 there were 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 trend towards its increase by 15.2% 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%, triglycerides by 49% compared with admission and by 32% compared to group 1 (P <0.05). It is known that the target values of LDL 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% relative to the values at admission and by 23% relative to group 1 (P < 0.05). The atherogenic index decreased by 60% and 44%, respectively, and by 32% in relation to group 1 (P < 0.05), which indicates a decrease in total cholesterol and an increase in the amount of "good" HDL-C lipids..

Table 3
Biochemical parameters of blood in patients with type 2 diabetes on the background of complex therapy with the inclusion of lipid-lowering therapy

Index	Before treatment n -42	1 group n -19	2 group n -23
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*
HbA 1c , %	7.9±1.0	6.3±0.54*	6.2±0.8*
OH, mg/ dl	6.6±1.2	5.8±1.2	5.2±0.9*
LDL, mg / dl	3.15±0.09	2.98±0.09*	2.48±0.04*,**
HDL, mg/ dL	1.21±0.05	1.47±0.09*	1.84±0.07*
TG, mg/ dl	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	0.30±0.02	0.31±0.0 7	0.30±0.02
AST	0.18±0.01	0.26±0.0 6	0.22±0.01

Note: n is the number of examined patients;

*- the presence of significance (P < 0.05) in relation to the group at admission

**- presence of significance (P < 0.05) in relation to group 1

Biochemical parameters of blood - AST, ALT did not change statistically significantly.

In group 2 , where patients took rosuvostatin with ezetimibe , a decrease in LDL

levels was found during the observation period ($p < 0.05$). The average level of LDL 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 Rozucard plus, out of 23 examined patients, 14 (62.5%) reached the target LDL level by the end of the period, the rest of the patients were recommended to increase the dose of the drug to 20/10 mg/ day . During the period of treatment with Rosuvastatin , out of 19 examined patients, 8 (43.7%) reached the target level of LDL by the end of the period, the rest of the patients were also recommended to increase the dose of the drug to 20 mg/ day .

Thus, the ability to achieve the target level of LDL in a short time in the treatment with the combination drug Rozucard plus, 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. In the study of lipid metabolism in patients with type 2 diabetes, a significant increase in total cholesterol, triglycerides and atherogenic fractions of lipoproteins - LDL by 34.0, 40.6 and 37.5% was revealed, and the content of antiatherogenic fractions of lipoproteins - HDL by 60.2 % was lower compared to the control group.
2. The relationship between the content of lipoproteins of various classes with duration and BMI of patients was revealed.
3. The combination therapy of rosuvostatin and ezetimibe 10/10 mg is an effective drug for the treatment of diabetic dyslipidemia , while there was a decrease in TC by 22%, T by 32%, LDL by 49% and an increase in HDL by 23% compared with the monotherapy group rosuvastatin , where the lipid spectrum also improved, but not significantly.
4. The good tolerability of the combined drug, the favorable cost / effectiveness ratio allows us to recommend Rosulip plus 10/10 mg as one of the drugs of choice in the treatment of diabetic dyslipidemia .

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