Hypolipidemic Combination for Diabetic Dyslipidemia

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ABSTRACT

One of the necessary drugs for the treatment of diabetic dyslipidemia affecting lipid metabolism is hydroxycis-methylglutaryl-coenzyme A-reductase inhibitors (statins) [2] and ezetimibe, which blocks the absorption of cholesterol in the epithelium of the small intestine, thereby preventing erythematic enterohepatic circulation of cholesterol [2,4]. Their effectiveness in correcting atherogenic dyslipidemia (DLP) and preventing macroangiopathies has been studied in patients with diabetes mellitus (DM). The aim of this study was to study the lipid-lowering efficacy of the combination therapy of rosuvastatin with ezithymibe in patients with type 2 diabetes mellitus

Keywords: diabetes mellitus (DM) , lipid-lowering therapy, rosuvastatin, ezetimibe, total cholesterol (TC), low dencity lipoproteins (LDL), high dencity lipoproteins (HDL).

Diabetes mellitus (DM) is a chronic progressive disease that has taken over in 21st century a truly pandemic spread. According to the latest data, the number of patients with diabetes in the world has more than doubled over the past 10 years, and by the end of 2017 exceeded 425 million people. According to the forecasts of the International Diabetes Federation , 629 million people will suffer from diabetes by 2045 [1] . The prevalence of cardiovascular diseases (CVD) among patients with type 2 diabetes is 2–4 times higher than people without diabetes, they are the cause of death in more than 65% of patients [2,3,5,6]. The most dangerous consequences of diabetes are its systemic vascular complications - nephropathy, retinopathy , damage to the main vessels of the heart, brain, 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 are 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 hyperglycemia has a decisive importance in the development of atherosclerosis in patients with type 2 diabetes [2,9]. The British prospective diabetes study (UKPDS) showed that the compensation of carbohydrate metabolism reduces the risk of microvascular complications without significant affecting the macrovascular complications in patients with type 2 diabetes. At the same time, this and other studies clearly demonstrated the relationship between the level of total cholesterol (TC) and low dencity lipoproteins (LDL) cholesterol and the risk of developing macrovascular complications both in the general population and in patients with type 2 diabetes [10,12,13,14]. Analysis of results of a multicenter randomized , placebo-controlled studies enrolled patients with type 2 diabetes, suggests a positive effect of the application of lipid-lowering therapy using the

of inhibitors GMG CoA - reductase both as primary and secondary prevention of cardiovascular disease in these patients [14]. At the moment there is evidence that anti-atherogenic properties of GMG inhibitors CoA – reductase caused not only by their effect on the lipid profile. The pleiotropic antiatherogenic effects of some representatives of this class of drugs are described that do not depend on the main mechanism of their action, in particular, the effect on atherosclerotic inflammation [4,5,6]. However assignment of GMG CoA - reductase inhibitors in clinical practice for correction of the lipid metabolism in patients with diabetes type 2 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 efficacy of rosuvastatin monotherapy with rosuvastatin and ezetimibe combination therapy.

The aim of this work was to assess the efficacy and safety of Rosulip plus 10/10 mg in patients with diabetic dyslipidemia .

Materials and methods. We screened 35 patients with type 2 diabetes with confirmed dyslipidemia (LDL ≥ 2,6 mmol/l and triglyceride≥1,7 mmol/ l) II A type (by Fredrickson), treated in the department of endocrinology clinic 3-TMA . Among them, 12 are men and 23 are women. The duration of the disease ranged from 1 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. Also, apparently 10 healthy individuals were examined, 53.5% of this group suffered from ischemic heart disease, 88.4% - arterial hypertension.

Most of the patients received aspirin, B-blockers and angiotensin –converting enzyme inhibitors. All patients were overweight - their body mass index (BMI) exceeded 25 kg / m^2 . Overweight was diagnosed in 11 (31.4%) patients, obesity in 24 (68.6%) patients (BMI ≥30 kg / m^2). The average waist circumference was 105.1 ±2.0 cm for men, 108.3 ±3.0 cm for women. The majority of patients 19 (48.5%) received sulfonylurea and metformin as hypoglycemic agents, 12 (34.2%) - iDPP4, 7 (20.0%) received insulin in combination with metformin. Considering that all patients were diagnosed with decompensation of the disease, the hypoglycemic therapy was corrected, so 60% of patients were transferred to insulin therapy.

All patients underwent general clinical examination. Fasting and postprandial glycemia was studied using the glucose-oxidase method. The study of glycated hemoglobin (HbA1c) was carried out according to the Fluckiger method. Lipid metabolism indices were determined by the enzymatic method using a set of reagents from the company "Human" (Germany) on the analyzer "Randox" (Great Britain). The data obtained were processed on a computer using the statistical software package "Statistika-6".

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

Results of own research.

So, according to the data of carbohydrate metabolism, all patients have an increase in fasting and postprandial glycemia and HbA1c, which are increased by 41.0, 43.2 and 43.5%, which indicates diabetes decompensation.

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	7, 1 ± 0 , 37	7, 1 ± 0 , 37 *

Postprandial glycemia, mmol / l	11, 2 ± 3.33	10 2 ± 0 33 *
HbA 1 c ,%	4.9 ± 1.0	7.9 ± 1.0 *
TC, mg / dl	6.6 ± 1.2	6.6 ± 1.2 *
LDL, mg / dl	3.15 ± 0.09	3.15 ± 0.09 *
HDL, mg / dl	1.21 ± 0.05	1.21 ± 0.05
TG, mg / dl	3.93 ± 0.09	3.93 ± 0.09 *
Atherogenic coefficient	4 , 71 ± 0 , 25	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;
* - presence of reliability (P < 0.05) , ** (P <0.0 1)

By analyzing the lipid spectrum in patients with type 2 diabetes, was observed hyperlipoproteinemia - a significant increase in lipid metabolism as compared with 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%, TG by 40.6% (P <0.01). The content of HDL cholesterol was 60.2% (P < 0.05) lower in the main group than in the control group (Table 1). The obtained results of an increase in atherogenic lipoproteins such as LDL, TG and a decrease in the level of 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 a BMI> 30 in comparison with overweight, and the level of HDL cholesterol in the same group was 26% (P < 0.05) lower than in the studied group (table l . 2). The TG level was 29.0% higher (P < 0.05) , it was reflected on the atherogenic coefficient which was 24% higher (P <0.05). Thus, the results showed that with an increase in the patient's body weight, the lipid profile worsens, which is reflected in the development of micro- and macrovascular complications of diabetes [9].

Table l . 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 the disease, years	-	6.9 ± 4.8	7.5 ± 3.9
Fasting glycemia, mmol / l	7, 1 ± 0 , 37	7.7 ± 1.9 *	7.5 ± 2.0 *
Postprandial glycemia, mmol / l	11, 2 ± 3.33	11.2 ± 3.9 *	12.9 ± 4.1 *
HbA1c ,%	4.9 ± 1.0	7.8 ± 2.1 *	8.3 ± 2.4 *
TC, mmol / l	6.6 ± 1.2	6.1 ± 1.2 *	6.3 ± 1.7 *
LDL, mmol / l	3.15 ± 0.09	3.18 ± 0.09 *	3.45 ± 0.07 *
HDL, mmol / l	1.21 ± 0.05	1.2 ± 0.05	0.81 ± 0.08 *, **
TG, mmol / l	3.93 ± 0.09	3.2 ± 0.4 *	4.5 ± 0.9 *, **
Atherogenic coefficient	1.4 6 +0.09	4.0 ± 0.7	4.68 ± 0.79 *, **

Note: n is the number of examined patients;
- the presence of reliability in relation to control (P < 0.05)
** - the presence of reliability in relation to the group with BMI <30 (P < 0.05)

The distribution of patients with type 2 diabetes by the duration of the disease showed that LDL cholesterol, depending on the duration of the disease, was increased in relation to the control group, but these indicators did not differ among themselves. Triglycerides in the group with duration of the disease from 6 to10 years were increased by 28.2% (P <0.05) compared with the group under 3 years o and by 22.5% (P <0.05) compared with the group 3-6 years. This is confirmed by the literature data, which describes the deterioration of the lipid spectrum with a predominant increase in triglycerides in the lipid spectrum of blood 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 aged 6-10 years compared to 3 years of illness. This is reflected in the atherogenic index , while the AI in the first group was increased by 60.0%, in the second by 65.4% and in the third - 65.3%, respectively (Table 3).

Tab. 3

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

Indicators	control n-10	Up to 3 years old, n-10	3- 6 years , n-14	6-10 years old 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	7.1 ± 0.37	6.9 ± 1.33	7.1 ± 1.37	6.8 ± 1.27
Postprandial glycemia, mmol / l	11.2 ± 3.33	11.8 ± 3.3	9.9 ± 3.7	13.0 ± 3.1 *
HbA 1 c ,%	4.9 ± 1.0	8.5 ± 2.4 *	7.9 ± 1.9 *	8.3 ± 2.7 *
TC, mmol / l	6.6 ± 1.2	6.3 ± 1.7 *	6.0 ± 1.5 *	6.6 ± 1.1 *, **
LDL cholesterol, mmol / l	3.15 ± 0.09	3.0 ± 0.3 *	3.4 ± 0.3 *	3.2 ± 0.5 *
HDL cholesterol, mmol / l	1.21 ± 0.05	1.4 ± 0.06	1.2 ± 0.05	0.90 ± 0.07 *, **
TG, mmol / l	3.93 ± 0.09	3.4 ± 0.9 *	3.7 ± 0.4 *	4.7 ± 0.9 *
Atherogenic coefficient	4.71 ± 0.25	3.5 ± 0.9	4.0 ± 0.5	4.0 ± 0.6

Note: n is the number of examined patients;

- availability of reliability (P < 0.05)

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

Assessment of the cardiovascular risk category (CVR) is extremely important for the development of optimal patient management and the appointment of adequate therapy that can maintain an optimal level of LDL cholesterol. In accordance with the provision of agreed recommendations ESC / EASD diabetes, pre-diabetes and cardiovascular disease (CVD) , adopted in 201 9 , it should be considered that the patients with diabetes allow to a group of high and very high risk of CV-complications, the patients with diabetes and whether one risk factor of CV disease or damage to target organs should be considered as a very high risk group, and all other patients with diabetes - as a high risk group [9]. Achieving the target level of LDL cholesterol below 2.5 mmol / L (for patients with high CV R), and even more so below 1.8 mmol / L, is a rather difficult task, which dictates the need to use the most effective statins in high doses. The use of rosuvastatin at a dose of 20 mg led to a 34% decrease in LDL cholesterol levels, while the risk of CV events decreased by 23%, and the difference with the group of patients receiving placebo was statistically reliable [9].

With insufficient effectiveness of statins in achieving the target level of LDL cholesterol in patients with type 2 diabetes, it is possible to use combination therapy: adding to statin therapy the ezetimibe . The latest 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 food cholesterol from the intestine into the liver, the uptake of cholesterol by hepatic cells from the blood serum 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, these are 18 patients , they added a combination of rosuvastatin and ezetimibe (Rosucard plus 10/10). The patients took a lipid - lowering drug, 1 tablet per day in the evening for 3 months. Dose adjustments were made in a month and 3 months until the target blood lipid level was reached .

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 blood biochemical parameters: an increase in the level of hepatic transaminases by 3 times or more. After a month and 3 months, 32 (91.6 %) patients were re-examined , the remaining 3 (8.4 %), due to various personal reasons, did not appear for a second examination.

During the study, there were no cases of exacerbation of angina attacks, an increase in blood pressure, changes in heart rate, a significant decrease in body weight and BMI.

On the background of the therapy with Rosuvastatin and Rosuvastatin with ezeti mibe, after a month, were not revealed significant changes in the lipid spectrum were revealed. Also, there were no changes in the liver enzymes in the blood. In connection with this, the patients were encouraged to continue Lipidlowering therapy.

During treatment, positive changes in carbohydrate metabolism were observed in both groups. Thus, HbA 1 c in groups 1 and 2 decreased by 17 and 19%, 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 show significant changes. However, there was a tendency to its increase by 15.2%. This all reflects on 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 to the indicators on admission and by 32% in relation 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 cardiovascular diseases developing reduces by 2 times [9].

HDL cholesterol increased by 15% in relation to the indicators at admission and by 23% in relation 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" lipids of HDL cholesterol.

Table 4

Blood biochemical parameters in patients with type 2 diabetes on the background of complex therapy with the inclusion of lipid-lowering therapy

Index	Before treatment n- 35	1st 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	11.2 ± 3.33	9.3 ± 2.5 *	8.09 ± 0.1 *
HbA 1 c ,%	9.9 ± 1.0	7 , 3 ± 0.54 *	7.2 ± 0.8 *
TC, 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 reliability (P < 0.05) in relation to the group upon admission

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

Blood biochemical parameters - AST, ALT did not change 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 Rosucard plus, out of 16 examined patients, 10 (62.5%) reached the target LDL level by the end of the term, 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 16 examined patients, 7 (43.7%) reached the target LDL level 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 reach the target level of LDL in the short term for the treatment of combined drug P ozukard plus , its safety and tolerability, as well as a favorable ratio of "cost / benefit" can be recommended as one of the drugs of choice among lipid lowering drugs.

Conclusions: 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 anti-atherogenic lipoprotein fractions - HDL by 60 , 2% was lower compared to the control group.

The combination therapy of rosuvastatin and ezetimibe 10/10 mg is an effective drug for the treatment of diabetic dyslipidemia , with a decrease in TC by 22%, T - by 32%, LDL by 49% and an increase in HDL by 23% compared to the group with rosuvastatin monotherapy . where the lipid spectrum indicators also improved, but not significantly. Good tolerance of the combined drug, favorable cost / effectiveness ratio allows Rosulip plus 10/10 mg to be recommended as one of the drugs of choice in the treatment of diabetic dyslipidemia .

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