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FEATURES OF THE MANAGEMENT OF CORONARY HEART DISEASE IN PATIENTS WITH METABOLICALLY ASSOCIATED FATTY LIVER DISEASE

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Abstract

Among chronic non-communicable diseases, which make a significant contribution to mortality rates in the developed countries of the world, the leading positions are occupied by diseases of the circulatory system. According to statistics, one million people a year die from cardiovascular diseases in Russia. In an extensive nosological group of diseases of the circulatory system, coronary heart disease is the main cause of death and disability in the adult population. The annual mortality from coronary heart disease among the population of Russia is 27 %. To date, the number of patients with coronary heart disease with comorbid pathology, especially with diseases of the hepatobiliary system, metabolic syndrome, is increasing. The prevalence of metabolically associated fatty liver disease is 20 to 30 % in the population and tends to increase. The combined course of metabolically associated fatty liver disease and coronary heart disease occurs in 14-18 % of cases.

Objective: to determine the impact of metabolically associated fatty liver disease on the course of coronary heart disease and the possibility of correcting metabolic disorders to prevent the development of cardiovascular complications.

Materials and methods. 35 patients with coronary heart disease and metabolically associated fatty liver disease were examined; they were noted to have more severe clinical course of stenocardia and higher risk of cardiovascular complications, then those patients without liver diseases.

Results and its discussion. It was estimated, that using thiotriazoline and ursodeoxycholic acid in addition to standard medicamentous therapy improves clinical course of stenocardia as well as overall quality of life due to high antianginal and antioxidant effects.

Conclusions. Hepatoprotective therapy increases possibility of correction of metabolic defects, dyslipidemia, decreases the risk of oxidative stress, prevents development of life threatening cardiovascular conditions and can be used to optimize treatment of comorbid patients.

Keywords: *heart disease, non-alcoholic fatty liver disease, thiotriazoline, ursodeoxycholic, metabolic defects.*

Introduction

Among chronic non-communicable diseases, which make a significant contribution to mortality rates in the developed countries of the world, the leading positions are occupied by diseases of the circulatory system [*Gheorghe A. et al., 2018*]. So, both in Russia and around the world, despite ongo-

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ing therapeutic and preventive measures, cardiovascular pathology still ranks first in the structure of morbidity and mortality. The statistics of cardiovascular diseases in the world is disappointing – more than 17 million deaths, which is one third of the total number of deaths [*Gheorghe A. et al., 2018*; *Drożdż, K. et al., 2022*].

According to statistics, one million people a year die from cardiovascular diseases in Russia. In an extensive nosological group of diseases of the circulatory system, coronary heart disease (CHD) is the main cause of death and disability in the adult population. The annual mortality from coronary heart disease among the population of Russia is 27 % [*Tsutsumi T. et al., 2021*]. It is important that 42 % of all deaths as a result of coronary heart disease die at working age. At the same time, even in relatively "prosperous" countries, an epidemic of diseases of the circulatory system is expected – thus, an increase in the prevalence of coronary artery disease in the world by 2030 by 9.3 % is predicted, and an increase in direct medical costs by 98 % compared with the indicators 2010 [*Zhou X.D. et al., 2022*]. Of particular concern is the fact that about 40 % of deaths from coronary heart disease occur in the active working age (up to 50 years), and the disease has pronounced gender characteristics – men suffer from coronary heart disease about three times more often than women .

To date, the number of patients with coronary heart disease with comorbid pathology, especially with diseases of the hepatobiliary system, metabolic syndrome, is increasing [*Tsutsumi T. et al., 2021*]. Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease and considered a liver manifestation of metabolic syndrome [*Lonardo A. et al., 2015; Estes C. et al., 2018*]. It is in close relationship with insulin resistance, obesity, diabetes mellitus, all of which increased risk of cardiovascular disease [*Ugur Arslan, Mustafa Yenerçağ, 2020; Klyarytskaya I. L. et al., 2015*]. In 2020, metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed as a more appropriate term than NAFLD, because this nomenclature better defines the pathophysiology of this liver disease and its associated metabolic abnormalities [*Méndez-Sánchez N., 2022; Eslam M. et al., 2022*]. The term "non-alcoholic" may also confuse patients in terms of the real cause of their disease, which is not conducive to a good therapeutic relationship [*Fouad Y. et al., 2020*]. Significantly different from NAFLD, MAFLD is defined as a condition characterized by liver fat accumulation in the presence of at least one of the following three metabolic conditions: overweight/obesity, T2DM, or at least two of seven metabolic risk abnormalities in those subjects who do not have T2DM and are lean by ethnic-specific body mass index (BMI) criteria [*Zhou et al., 2022*]

Currently, metabolically associated fatty liver disease occupies a firm position in the list of the most common liver diseases all over the world [*Chalasani N. et al., 2018*]. According to the latest systematic review, the prevalence of MAFLD in most regions of the world is well over 20 % and tends to increase [*Maksimova et al., 2022*]

Global trends are typical for the Russian Federation as well. In the Russian Federation, the frequency of MAFLD was 27 % in 2007 (according to the epidemiological study DIREG_L_01903), and in 2014 it was 37.1 % (an increase of more than 10 %), which puts it in first place among liver diseases – 71.6 % [*Klyarytskaya I. L. et al., 2015*]. Back in 2007, in Russia, according to a screening program among 30,754 people, MAFLD was detected only in 27 % of participants, among them about 80 % had steatosis, about 17 % had steatohepatitis, and 3 % had liver cirrhosis [*Klyarytskaya I. L. et al., 2015*]. Thus, we can say that there is a progressive increase in the number of patients with this nosology. The combined course of MAFLD and coronary heart disease occurs in 14-18 % of cases [*Alharthi J. et al., 2022*].

The development of coronary heart disease and MAFLD has common risk factors, pathogenetic links and mutually aggravating influence. On the one hand, in patients with coronary heart disease, blood circulation in the liver is disturbed and its metabolic functions are disturbed. On the other hand, the liver is directly involved in the development of atherogenic dyslipidemia: it initiates the development of lipid metabolism disorders, and then becomes its target itself [*Buzzetti E. et al., 2016*]. At the same time, the presence of concomitant chronic liver diseases in patients with coronary heart disease deepens the violation of intracardiac work. MAFLD is associated with a higher rate of cardiovascular disease [*Cai J. et*

al., 2020]. Detection of signs of MAFLD, according to ultrasound, is associated with a 10-year risk of developing coronary heart disease [*Chalasani N. et al., 2018*].

Factors that determine liver dysfunction in MAFLD can also negatively affect the state of ischemic myocardium. According to foreign meta-analyses, patients with MAFLD are more prone to cardiovascular diseases. In addition, it has been shown that the frequency and severity of cardiovascular events are higher in patients with more severe metabolically associated fatty liver disease [*Patil R, Sood G.K., 2017*]. This is explained by the fact that the accumulation of fat in the liver and oxidative stress initiate an increase in the fraction of low and very low density lipoproteins, trigger hyperglycemia and the release of inflammatory markers such as interleukin-6, C-reactive protein, fibrinogen, tumor necrosis factor-alpha, which induce dysfunction endothelium, the development of atherosclerosis, ischemic stroke and myocardial infarction [*Chan K.E. et al., 2022*]. A relationship was also noted between the presence of MAFLD in a patients and an elevated level of calcium in the coronary arteries, regardless of traditional risk factors [*Younossi Z. et al., 2018*].

In a study of young men without diabetes, obesity, with normal blood pressure and newly diagnosed metabolically associated fatty liver disease, it was shown that FAFLD provokes a change in myocardial metabolism in the form of a decrease in glucose uptake, and also accompanies left ventricular dysfunction and changes in myocardial perfusion [*Drożdż, K. et al., 2022*]. These factors are potentially associated with an increased risk of congestive heart failure. In addition, it was found that elevated levels of transaminases were closely associated with the risk of developing atrial fibrillation within 10 years [*Zhang X.L. et al., 2022*].

Objective: to determine the effect of MAFLD on the nature of the course of coronary heart disease and the possibility of correcting metabolic disorders to prevent the development of cardiovascular complications.

Materials and methods.

To achieve this goal, 52 patients (25 men and 27 women) aged 45 to 77 years (average 61.0 ± 4.5 years) with coronary artery disease, stable angina II-III FC (according to the WHO classification in modification of the All-Russian Scientific Center of the Russian Academy of Medical Sciences), postinfarction cardiosclerosis, arterial hypertension I-II degree were examined. Heart failure did not exceed stage IIA, functional class (FC) was from I to III according to the NYHA classification. The average duration of the disease was 10.9±3 years. The study did not include patients with acute coronary syndrome, grade III arterial hypertension, congestive heart failure, respiratory failure II-III, life-threatening arrhythmias and conduction disorders, impaired renal and hepatic functions, and decompensated diabetes mellitus.

Among patients with coronary heart disease, 35 patients had MAFLD (20 women and 15 men), and 17 patients (9 men and 8 women) had no MAFLD (control group). The diagnosis of MAFLD according to the 2020 international expert consensus statement, in which 32 experts representing 22 countries took part, was exhibited on the basis of proven liver steatosis (according to abdominal ultrasound, abdominal CT) in combination with one of the following criteria: overweight/obesity, type 2 diabetes/insulin resistance syndrome, signs of metabolic dysregulation. For diagnosis of MAFLD is no longer a prerequisite for the exclusion of the fact of abuse of hepatotoxic doses of alcohol, as well as other etiological variants of chronic liver disease. In patients suffering from MAFLD, it was noted: obesity I-III degree in 33 patients (94.3 %), dyslipidemia in 30 patients (85.7 %), type II diabetes mellitus in 20 patients (57.1%), impaired glucose tolerance in 12 patients (34.3%).

All patients at the initial examination, as well as after treatment (after 4 weeks and 12 weeks), were questioned, physical examination, biochemical tests (ALT, AST, troponins, bilirubin and its fractions, glycosylated hemoglobin), ECG, echocardiography were prescribed. The blood lipid spectrum was studied by determining total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (HLDL). The state of lipid peroxidation (LPO) and antioxidant protection (AOP) was determined. All patients underwent abdominal ultrasound. All patients were comparable in terms of gender, age, severity of the condition, hemodynamic parameters, as well as the

doses of basic therapy medications used. All patients received standard basic therapy in accordance with the recommendations of the ESC and the Russian Society of Cardiology: taking β-blockers, calcium antagonists, nitrates, antiplatelet agents, ACE inhibitors, statins.

Patients with coronary heart disease and MAFLD were blindly randomized into two groups: the first study group included patients (18 people) receiving only basic therapy (beta-blockers, calcium antagonists, nitrates, antiplatelet agents, angiotensin-converting enzyme inhibitors, statins); the second study group consisted of 17 patients who additionally received thiotriazoline 2.5 % - 4 ml intravenously in a saline NaCl solution 0.9 % 200 ml for 10 days and ursodeoxycholic acid at the rate of 15 mg/kg/day for a month, divided into 3 doses for 12 weeks.

The control group consisted of 17 patients without signs of MAFLD who received only basic standard therapy. The results of the studies were processed by the method of variation statistics on a personal computer using the Excel application and the statistical program Statistics 12 (StatSoftInc.), the data were considered reliable at $p < 0.05$.

Results and Discussion.

An analysis of the clinical, laboratory and instrumental examination and treatment showed an improvement in the well-being and condition of patients, a decrease in the number of angina attacks and their duration in all clinical groups, probably due to the use of a standard complex for the treatment of stable angina pectoris. However, during the follow-up, the dynamics of clinical efficacy, laboratory parameters and instrumental methods of research differed depending on the therapy and the presence of concomitant NAFLD. The patients participating in the study had a high frequency of angina attacks during the week before the start of treatment, and there were no significant differences between the groups (Table 1) in the number of attacks, their duration, and also in the amount of nitroglycerin used. After the treatment, patients of the 1st group showed a decrease in the number of angina attacks by 24.5 % ($p<0.05$), a decrease in the duration of attacks by 26.1 % ($p<0.05$) and a decrease in the number of nitroglycerin tablets used per week by 27.7 % ($p<0.05$). However, 5 patients (27.7 %) of the 1st group had paroxysms of supraventricular tachycardia and atrial fibrillation, as well as polytopic ventricular extrasystoles. In 4 patients of this number (22.2 %), progression of angina pectoris was observed, followed by the formation of acute myocardial infarction (AMI), and in 2 (11.1 %), hypertensive crises developed. In 12 patients of the 1st group (66.6 %), after the treatment, pain in the right hypochondrium, nausea, discomfort, dryness and bitterness in the mouth, and symptoms of dyspepsia still persisted.

Significant positive clinical dynamics was observed in patients of the 2nd group who received hepatoprotective therapy. Thus, a decrease in the number of angina attacks was noted by 48.4% ($p<0.001$), a decrease in the duration of attacks by 34.5% ($p<0.01$) and a decrease in the number of used nitroglycerin tablets per week by 44.7%

Table 1

Clinical characteristics of patients with coronary artery disease and NAFLD

Parameters	1st group CHD + MAFLD (n=18)		2st group CHD + MAFLD (n=17)		Control group (n=17)	
	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
Number of angina attacks per week	15.5±2.4	11.7±2.3*	15.1±2.5	7.8±1.5**	14.8±2.3	7.3±1.4***
Duration of angina attacks (min) for 1 week	107.3±9.2	79.4±7.3*	104.9±8.9	68.7±6.8***	106.7±8.3	65.7±6.4***
Number of nitroglycerin tablets in 1 week	11.9±2.5	8.6±2.1*	12.3±2.8	6.8±1.9**	11.7±2.3	5.9±1.8***
Number of pills for stopping an attack	0.89±0.08	0.84±0.07	0.81±0.06	0.79±0.07	0.85±0.05	0.84±0.03

Notes: * - $p<0.05$, ** - $p<0.01$, *** - $p<0.001$

(p<0.01). .01). In all patients of this group, angina attacks disappeared at rest. In 4 patients of the 2nd group (23.5%), supraventricular extrasystolic arrhythmia was recorded. In 5 patients (29.4%), aching pains in the right hypochondrium, bitterness in the mouth persisted, but the severity of these symptoms decreased.

In the control group, in patients without concomitant NAFLD and receiving only standard basic therapy, clinical parameters changed more significantly than in patients of the 1st group. The number of angina attacks per week decreased by 50.7% (p<0.001), no angina attacks were observed at rest; the duration of attacks and the number of nitroglycerin tablets consumed per week were reduced by 38.4% (p<0.001) and 49.6% (p<0.001), respectively. The results obtained in the control group are comparable with those in patients of the 2nd group. No cardiovascular complications were observed in the control group. There were no significant differences between the groups before and after treatment in terms of the number of nitroglycerin tablets needed to stop one attack.

Positive clinical dynamics in all groups after treatment was due to the use of a standard complex of anti-ischemic drugs, however, a significant difference between the 1st and 2nd groups 12 weeks after treatment, expressed after the use of thiotriazoline and ursodeoxycholic acid and characterized by a more significant decrease in patients group 2: the number of anginal attacks by 23.9 % (p<0.001), the duration of attacks by 8.4 % (p<0.05) and the decrease in the number of nitroglycerin tablets taken by 17 % (p<0.01) compared with the 1st group indicates the antianginal effect of thiotriazoline in combination with ursodeoxycholic acid and a positive effect on the course of angina with concomitant MAFLD.

Determination of the blood lipid spectrum made it possible to identify hypercholesterolemia and dyslipidemia in patients of all studied groups, which was more pronounced in MAFLD (Table 2). However, if in patients of the 1st group, after the treatment, there were no significant changes in indicators, then in patients of the 2nd group, there was a decrease in total cholesterol by 27.8% (p<0.01), triglycerides by 14.7% (p< 0.05), low-density lipoprotein cholesterol by 50.1% (p<0.001). In the control group, there was a less significant decrease in indicators, so the level of total cholesterol decreased by 20.3% (p<0.01), triglycerides by 14.7% (p<0.05), and low-density lipoprotein cholesterol by 41.5 % (p<0.001). The content of high-density lipoprotein cholesterol did not change during treatment. Despite the fact that the target level of total cholesterol and low-density lipoprotein cholesterol was not achieved in any of the groups, a more significant decrease in these indicators was recorded in patients receiving antioxidant and hepatoprotective therapy.

Malonic dialdehyde (MDA) activity was assessed as the main marker of oxidative stress in the body and a prognostic marker of severe coronary heart disease (Table 3). To determine the state of antioxidant protection (AOP), patients were examined for the activity of superoxide dismutase (SOD) and catalase. So, if in patients of the 1st group after the treatment there were no significant changes in lipid peroxidation and AOD, then in patients of the 2nd group there was a decrease in MDA by 20.0 % (p<0.01) and an increase in SOD by 11 % (p<0.05). In the control

Table 2

Blood lipid profile in patients with IHD and NAFLD

Index	1st group CHD + MAFLD (n=18)		2nd group CHD + MAFLD (n=17)		Control group (n=17)	
	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
Cholesterol, mmol/l	7.3±0.31	6.2±0.27	7.2±0.41	5.2±0.21**	6.9±0.35	5.5±0.27**
Triglycerides, mmol/l	1.99±0.08	1.81±0.07	1.98±0.09	1.69±0.06*	1.97±0.09	1.68±0.04*
LDL, mmol/l	3.62±0.11	3.35±0.12	3.71±0.12	1.85±0.09***	3.57±0.10	2.09±0.08***
HDL, mmol/l	1.10±0.02	1.11±0.03	1.12±0.03	1.19±0.02	1.11±0.02	1.10±0.02

Note: * - p <0.05, ** - p<0.01, *** - p<0.001

Table 3

Indicators of lipid peroxidation (LPO) and antioxidant protection (AOP) in patients with coronary artery disease and MAFLD

Indicator	1st group CHD+MAFLD (n=18)		2nd group CHD+MAFLD (n=17)		Control group (n=17)	
	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
Malondialdehyde (MDA), μmol/l Catalase, %	4.99±0.10	4.78±0.13	5.01±0.12	4.01±0.12**	4.98±0.11	4.29±0.10*
Superoxide dismutase (SOD), c.u.	47.3±3.10	50.1±3.12	47.4±3.14	52.4±3.18*	46.3±3.13	52.1±3.15*
Catalase, %	37.8±3.18	39.7±3.12	36.4±3.16	40.1±3.13	37.5±3.17	43.1±3.15*

Note:CHD - coronary heart disease, * - p<0.05, ** - p<0.01, *** - p<0.001

group, there was also a positive dynamics of the studied parameters: the MDA level decreased by 13.9 % (p<0.05), and the SOD content increased by 12.5 % (p<0.05). Catalase activity increased by 14.9 % (p<0.05) only in patients of the control group, and did not undergo significant changes in patients of other groups.

The adverse effect of ursodeoxycholic acid was noted in 4 patients of the 2nd group in the form of unformed stools, short-term diarrhea. These side effects required a reduction in the dose of the drug by 500 mg, after which the stool returned to normal, and treatment continued. Side effects of thiotriazoline were not observed.

Conclusions

Our data indicate that the addition of hepatoprotective drugs (thiotriazoline and ursodeoxycholic acid) to the basic therapy in patients with coronary heart disease and MAFLD improves the clinical course of angina pectoris and the quality of life of patients by reducing the frequency and duration of anginal attacks, the number of nitroglycerin tablets. In addition to improving the clinical condition, combination therapy using thiotriazoline and ursodeoxycholic acid makes it possible to correct metabolic disorders to prevent the development of life-threatening cardiovascular events and optimize the treatment of comorbid patients.

Patients with coronary artery disease and MAFLD have a more severe course of the disease than patients without liver pathology. With this combination, the development of acute coronary syndrome (22.2 %, p<0.01) and life-threatening arrhythmias (27.7 %, p<0.01) is more often noted. This is probably due to more pronounced dyslipidemia, oxidative stress, and lower activity of antioxidant defense as the main predictors of possible cardiovascular complications.

The use of thiotriazoline and ursodeoxycholic acid as part of complex therapy in patients with stable coronary artery disease and NAFLD leads to a decrease in the number of angina attacks by 48.4% (p<0.001), a decrease in the duration of attacks by 34.5 % (p<0.01) and reduction in the number of nitroglycerin tablets used by 44.7 % (p<0.01), indicating an anti-ischemic effect.

The use of thiotriazoline and ursodeoxycholic acid as part of complex therapy in patients with IHD and MAFLD leads to a decrease in total cholesterol by 27.8 % (p<0.01), triglycerides by 14.7% (p<0.05) and lipoprotein cholesterol low density by 50.1 % (p<0.001), which indicates the lipid-lowering effect of the drugs.

A decrease in the content of malondialdehyde by 20 % (p<0.01) and an increase in the activity of superoxide dismutase by 11 % (p<0.05) indicates the antioxidant effect of thiotriazoline and ursodeoxycholic acid.

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