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ASSESSMENT OF THE RELATIONSHIP OF LIPID METABOLISM INDICATORS AND PULMONARY HYPERTENSION IN THE INITIAL PERIODS OF MYOCARDIAL INFARCTION IN MEN UNDER 60 YEARS OLD

DOI 10.25789/YMJ.2024.85.02

UDC 616.24:616.12-008.341: 616.127-005.8: 616.153.915

Pulmonary hypertension (PH) is an understudied but significant complication of myocardial infarction (MI). Currently, there are no diagnostic algorithms that can predict the development of PH in the setting of myocardial infarction, which requires the development of prediction models based on the results of routine examination, for example, lipid profile. The purpose of the research was to study the parameters of lipid metabolism in men with PH that developed against the background of MI and their impact on the risk of developing PH. The results of examination of men aged 32-60 years with verified MI were studied. According to the level of mean pulmonary artery pressure (MPAP) determined by echocardiography, patients were divided into two groups: the study group (with a MPAP level of more than 20 mm Hg at the end of the third week of MI) and the comparison group (with a normal MPAP level at the end of the third week of MI). The studied indicators were compared based on the Mann-Whitney, Wilcoxon, and Chi-square tests; correlations were performed using the Spearman method. It was found that patients in the study group had lower levels of the atherogenic coefficient (AC) and the total cholesterol/high-density lipoprotein (TC/HDL) index at the end of the third week of MI. Levels of triglycerides (TG) < 1.3 mmol/l and very low density lipoprotein (VLDL) ≥ 1.2 mmol/l, TC/HDL indices < 6.0 and LDL/HDL < 3.2 in the first 48 hours, LDL <2.4 mmol/l, AC value <5.0, TC/HDL indices <6.0 and LDL/HDL <3.2 at the end of the third week of MI influence the risk of developing PH in the subacute period of MI. Correlations have also been established between the level of MPAP and lipid profile parameters. It is advisable to use the obtained results when developing a model for predicting the development of PH against the background of MI.

Keywords: pulmonary hypertension, myocardial infarction, lipid metabolism, mean pulmonary artery pressure, heart failure, men, young and middle age.

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Introduction. Diseases of the cardiovascular system currently dominate the structure of causes of mortality throughout the world, and myocardial infarction (MI) remains one of the most significant among them [12]. The prognosis of a patient with MI largely depends on the presence and severity of complications, among which it is worth highlighting pulmonary hypertension (PH) [1]. This syndrome is characterized by a predominantly asymptomatic course, which leads to its detection only at the stage of development of irreversible changes in pulmonary hemodynamics, aggravating the course of MI and contributing to an increase in mortality [17]. Timely diagnosis of PH in MI will allow identifying patients at high risk of its development for dynamic monitoring and timely implementation of preventive and therapeutic measures. It is advisable to base forecasting models on routine diagnostic methods that do not require additional time and economic

costs. It is assumed that one of them may be the determination of the lipid profile, and therefore it is advisable to study the influence of its parameters on the course of PH in MI. The importance of lipids and lipoproteins for the development and course of lung pathology, including PH, is currently being actively studied. The influence of apoliproteins E and A I on the pathogenesis of bronchial asthma, cancer, fibrosis and emphysema, as well as PH [4,16]. It is believed that the development of PH in the setting of MI is caused mainly by left ventricular (LV) systolic dysfunction, which, in turn, is associated with apolipoprotein levels [9].

Aim. To consider patterns of changes in lipid metabolism in men under 60 years of age with MI complicated by the development of PH in its subacute period, from the point of view of their role in the formation of this complication and use as its predictors.

Material and methods. The study involved men aged 32-60 years with type I MI according to the IV universal definition (2018). It excluded cases of decreased glomerular filtration rate of 29 or less ml/min/1,73 m2 (CKD-EPI, 2011), congenital anomalies of the development of coronary arteries and their consequences, coronaritis, infectious endocarditis, thrombophilia and true polycythemia, hemorrhagic diathesis, viral hepatitis B and C, HIV infection, liver cirrhosis, diseases connective tissue against the background of continuous immunosuppressive therapy, endocrine diseases (except diabetes mellitus), malignant neoplasms, with hemoglobin levels less than 130 g/l, the number of leukocytes less than $3.0*10^9$/l and platelets – less than $100*10^9$/l. The study was approved by the Independent Ethics Committee at the Military Medical Academy named after S.M. Kirov (Protocol No. 258 dated December 21, 2021).

Patients received examination and treatment within the framework of approved clinical guidelines. Transthoracic echocardiography (ECHO-KG) performed according to protocols for patients in the acute period of MI [6,8], including noninvasive assessment of mean pulmonary artery pressure (MPAP) (A. Kitabatake, 1983 - calculation of the ratio of acceleration time (time to reach maximum flow velocity) to the time of ejection of the right ventricle (right ventricular ejection time – RVET)) [15] and lipidogram assessment [3] were performed twice: in the first 48 hours of MI and at the end of the third week of this disease.

The study group (I) included 102 patients (51.0 ± 7.0 years) with PH (MPAP less than 20 mm Hg at the first measurement and exceeding this value at the second measurement). The comparison group (II) was formed from 468 patients (51.4 ± 6.0 years, p = 0.9) without PH (MPAP less than 20 mmHg at the second measurement point). The value of total pulmonary resistance (TPR) was obtained by calculation using the formula: TPR = ((MPAP – 5) × 80) /CO, where TPR is the total pulmonary resistance (din×s×cm-5), MPAP is the average pressure in the pulmonary artery (mmHg), CO is the cardiac output (l/min) [7].

The studied groups of patients did not differ significantly in the characteristics of MI (localization, sequence, presence of a Q wave), the presence of concomitant pathology (obstructive pulmonary diseases, diabetes mellitus, metabolic syndrome), as well as coronary angiography parameters (number of affected vessels, length of stenoses, myocardial revascularization). When assessing disturbances in local myocardial contractility, no differences were found in the lesion segments in the studied groups. All patients received drug therapy in accordance with approved clinical guidelines [5]. Patients included in the study did not take lipid-lowering drugs before the development of MI.

Among the lipid parameters in the blood serum of the examined patients, we determined the concentration of total cholesterol (TC), very low density lipoproteins (VLDL), high density lipoprotein (HDL) and low density lipoprotein (LDL), and triglycerides (TG). We also calculated the coefficient (CA = (TC- LDL)/HDL) and indices (TC/ HDL, LDL/ HDL) of atherogenicity [3].

Comparisons between groups of quantitative variables were performed using the Mann-Whitney method. The dynamics of quantitative parameters between measurement points were assessed using the Wilcoxon test. To calculate the absolute (AR) and relative (RR) risk of the occurrence of PH at the end of the subacute period of MI, taking into account the values of lipid metabolism parameters, the Pearson Chi-square test was used. Analysis of correlations between indicators of lipid metabolism and levels of MPAP and TPR was performed according to Ch. Spearman (r). A p value less than 0.05 was considered statistically significant.

Results. When comparing the parameters of lipid metabolism in the first hours, they drew attention to the fact that in patients of the control group (II), in contrast to the studied group (I), higher values of TC (I: 5,6 ± 1,3 (1,92-8,46); II: 5,7 ± 1,3 (1,90-10,32) (mmol/l), p = 0,7), TG (I: 2,3 ± 1,5 (0,57-6,80); II: 2,6 ± 2,0 (0,35-13,80) (mmol/l), p = 0,4), LDL (I: 3,8 ± 1,2 (0,30-6,00); II: 3,9 ± 1,3 (0,92-8,62) (mmol/l), p = 0,6), and also CA (I: 4,9 ± 2,3 (0,70-11,40); II: 5,1 ± 2,0 (0,38-12,60), p = 0,3) and LDL/HDL index (I: 4,3 ± 2,1 (0,27-11,38); II: 4,4 ± 2,0 (0,75-12,68), p = 0,7). However, they did not reach a reliable level.

When studying lipid metabolism parameters in the subacute period of MI (end of the third week of MI), lower values of CA (Fig. 1a) and TC/HDL (Fig. 1b) were revealed in the study group compared to the control group. These changes are probably associated with the initiation or intensification of lipid-lowering therapy, as well as with the involvement of lipids in the processes of peroxidation in the inflamed zone, which are more pronounced against the background of the development of PH [19].

It is worth noting that the low content of atherogenic fractions of OH is recognized, among other things, as a marker of an unfavorable prognosis of MI. [2].

It has been established that the risk of developing PH at the end of the subacute period of MI is influenced by the following indicators determined in the first 48 hours of MI: levels of TG < 1,3 mmol/l (RR: 1,75; p=0,02) и VLDL ≥ 1,2 mmol/l (RR: 2,01; p=0,03), values of indices TC/HDL < 6,2 (RR: 1,72; p=0,03) and LDL/HDL < 2,4 (RR: 0,35; p=0,04). The influence of these factors on the AR value is presented in Figure 2a.

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At the end of the third week of MI, the following parameters turned out to be significant for the risk of developing PH in the subacute period: level of LDL < 2,4 mmol/l (RR: 2,78; p=0,02), values of CA < 5,0 (RR: 4,57; p=0,0002), as well as the values of TC/HDL indices < 6,0 (RR: 4,57; p=0,0002) and LDL/HDL indices < 3,2 (RR: 2,61; p=0,03). The influence of these factors on the AR value is presented in Figure 2b.

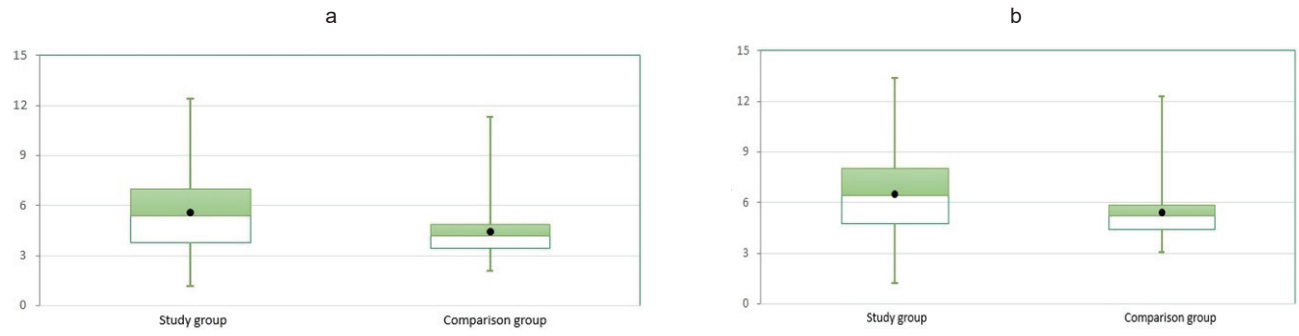

Fig. 1. Significant differences (p=0.006) in the values of CA (a) and the TC/HDL index (b) in the studied groups, determined at the end of the third week of MI. Designations used in the figure: dot – arithmetic mean, horizontal segment – median, rectangle – intraquartile range, vertical segments – minimum and maximum values

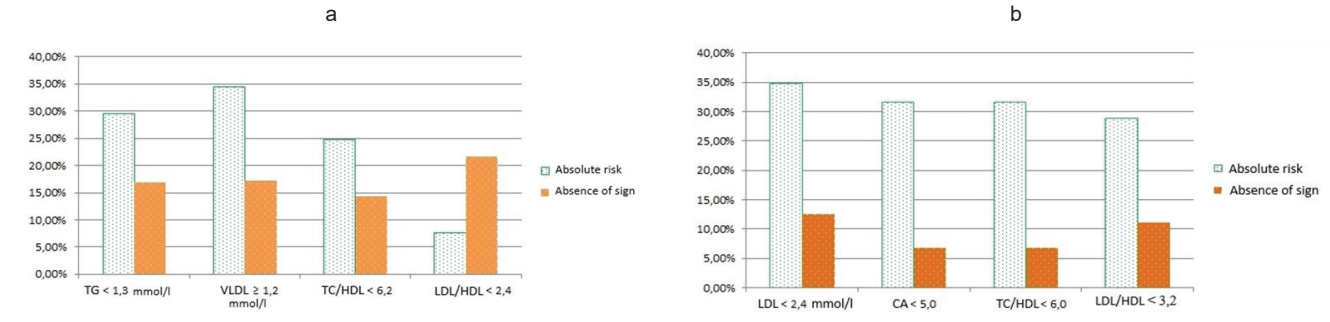

Fig. 2. Significant influence of lipid metabolism parameters obtained at the first (a) and second (b) measurement points on the absolute risk (AR, %) of developing PH in those examined

When analyzing the dynamics of lipid profile parameters in the studied groups, multidirectional changes in the concentrations of TC, CA, TG, HDL, as well as the TC/HDL index were noted between the measurement points (Fig. 3). Similar dynamics in both studied groups were revealed in relation to the LDL/HDL index, LDL and VLDL levels (Fig. 3). The most pronounced increase was noted for the level of VLDL both in the study group and in the comparison group (Fig. 3).

As can be seen from Figure 3, patients in the comparison group are characterized by less pronounced dynamics of lipid profile indicators, as well as lower levels of atherogenic fractions, which may be explained by the involvement of lipids in oxidation processes involved in the pathogenesis of PH [19].

Table 1 presents data on the presence of significant correlations between indicators of lipid metabolism and the value of MPAP during the first 48 hours (a) and the end of the third week of MI (b) in the group of patients with PH.

In addition, in the patients of the study group, a direct correlation of medium strength ($r = 0.39$, $p < 0.001$) was established between the level of HDL in the acute period of MI and the value of TPR in the first hours of MI, as well as a direct correlation of medium strength ($r = 0.39$, $p < 0.05$) between the concentration of VLDL in the first hours of MI and the value of TPR in the subacute period of MI. The presence of these correlations further indicates the contribution of lipid metabolism to the formation of PH. An increase in TC, mainly due to atherogenic fractions, in parallel with an increase in pressure in the pulmonary artery, is most likely due to the depletion of the HDL pool, involved as an anti-inflammatory agent under conditions of oxidative stress in PH [19].

Discussion. Systolic and diastolic dysfunction as early manifestations of heart failure are considered to be the main causes of clinical PH associated with diseases of the left heart [13]. It is assumed that mechanical resistance due to high pressure in the pulmonary veins is one of the main causes of PH in cases of ischemic cardiomyopathy with systolic dysfunction of the left ventricle [13]. When cardiac function declines, vascular remodeling of the pulmonary vessels in response to prolonged high pressure stimulation is thought to lead to PH [13]. However, the main pathological mechanisms and specific processes remain unclear [13]. It is believed that elucidating the relationship between MI and the development of PH may lead to a better understanding of potential risk factors and improved treatment of this complication [13]. The results of the present study confirm the influence of lipid profile parameters on pulmonary hemodynamics. The literature describes mechanisms for the implementation of the relationship between lipids and MPAP using exosomes [22], filled with regulatory microRNAs [14], which realize their action through a number of pathways (inflammatory reactions, cell migration, proliferation, apoptosis, autophagy, including mitochondrial [20], and epithelial-mesenchymal transition) [20]. They also involve transforming growth factor beta [10], oxidized variants of lipoproteins and enzymes of this oxidation [22], as well as apolipoproteins A1 and E [3,15]. Most of them have proven importance not only in the pathogenesis of PH, MI, but also diabetes mellitus and other types of cardiovascular pathology (atherosclerosis, heart failure, ischemia-reperfusion injury of the myocardium) [11,20]. In metabolomic studies of plasma during treatment of patients with PH with metformin, lipid derivatives are the most altered [18]. It is also known about the contribution of atherogenic lipid fractions to the formation of idiopathic venous thromboembolism and PH [21]. The results of the study also prove the influence of lipid metabolites on the development of PH in MI, which requires further detailed study of them as markers for predicting the development of this complication.

Table 1

Changes in lipid metabolism parameters in the compared groups between observation points (p – significance level)

Indicator	Study group		Comparison group	
	Dynamics, %	p	Dynamics, %	p
TC	- 4.8	<0.0001	+ 1.2	<0.0001
TG	+ 0.7	0.0002	- 7.7	<0.0001
LDL	+ 21.9	0.0003	+ 48.1	<0.0001
VLDL	+ 176.5	<0.0001	+ 260.4	<0.0001
HDL	+ 1.1	0.0004	- 6.8	<0.0001
CA	- 10.8	0.0002	+ 8.9	<0.0001
TC/HDL index	- 13.7	0.0004	+ 3.3	<0.0001
LDL/HDL index	+ 11.4	0.0003	+ 51.1	<0.0001

Table 2

Reliable correlations between the parameters of lipid metabolism and MPAP of the first (a) and repeated (b) measurement points in the study group

а		б	
Indicator	r	Indicator	R
TG (1), p<0.05	-0.29	TC (2), p<0.05	0.33
VLDL (1), p<0.05	-0.33	LDL (2), p<0.001	0.73
TG (2), p<0.05	0.6	LDL/HDL (2), p<0.001	0.74

Note. 1 - indicators obtained in the first 48 hours of MI, 2 - indicators at the end of the third week of the disease; r - correlation coefficient; p – significance level

Conclusion. In PH that develops after MI in men under 60 years of age, lower CA and TC/HDL are recorded during the period of its first manifestations. The risk of developing PH after MI increases with levels of TG < 1,3 mmol/l, VLDL ≥ 1,2 mmol/l, TC/HDL < 6,2 и LDL/HDL < 2,4 during the first 48 hours of MI, LDL < 2,4 mmol/l, CA < 5,0, TC/HDL < 6,0 и LDL/HDL < 3,2 at the end of the third week of MI. Reliable relationships have been established between indicators of lipid metabolism and pulmonary hemodynamics. The data obtained are promising for modeling the risk of PH after MI in young and middle-aged men.

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ASSOCIATION OF POLYMORPHISM rs1495741 *NAT2* GENE WITH INFLAMMATORY LIVER DISEASE DEVELOPMENT UNDER EXPOSURE TO EXTERNAL FACTORS

DOI 10.25789/YMJ.2024.85.03

UDC 575.167[616.36-04+616.36-003.826]

Slow acetylation of substrate is associated with drug-induced liver damage and transformation of viral and alcohol hepatitis in cirrhosis. Increasing xenobiotic load is a significant factor in development of metabolic associated liver diseases. This interaction between genotype and environment should be studied to reveal disease pathogenesis. We analysed polymorphism rs1495741 genotypes in control group and in patients with cryptogenic liver cirrhosis and non-alcohol fatty liver disease to evaluate association of acetylation type with liver disease development. As part of the study, patients filled the questionnaire to assess xenobiotic load. The rs1495741 polymorphism was detected by real-time PCR. Significant differences were revealed in the criptogenic liver cirrhosis and non-alcoholic fatty liver disease groups in patients consuming fried and smoked foods (OR: 5,49 at p<0,05); in combination with older age (>55) the risk increases by 7.57 times (p<0,05). However, no association of the rs1495741 polymorphism with the development of liver diseases was identified.

Keywords: N-acetyltransferase 2, polymorphism, cryptogenic liver cirrhosis, non-alcoholic fatty liver disease.

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Introduction. One of the causes for high mortality in the Russian Federation is the liver cirrhosis, associated with hepatitis virus infection and alcohol abuse. Previously, in approximately 10% of cases, it was not possible to identify the etiological cause of the disease, which led to a diagnosis of cryptogenic liver cirrhosis (CLC). The development of molecular genetic diagnostics in combination with laboratory and instrumental methods has led to a decrease in the proportion of CLC in the structure of cirrhosis [4]. In addition, studies have shown that most people with CLC are likely to have an outcome of active fibrosis in non-alcoholic steatohepatitis, a severe form of non-alcoholic fatty liver disease (NAFLD) [18].

Currently, the population is faced with a variety of foreign chemicals (xenobiotics): pharmaceuticals, household chemicals and products of human economic activity, including food additives. The liver plays the main role in the neutralization and biotransformation of xenobiotics. One of the enzymes in the second phase of detoxification is N-acetyltransferase 2 (NAT2), which is involved in the acetylation of arylamines and hydrazines [9]. The enzyme gene is localized on chromosome 8 (8p22) and has several single nucleotide polymorphisms (SNP), the combination of which led to the existence of two haplotypes, slow and rapid acetylation, in the population [8]. The *NAT2* genotype can be identified by SNP detection in polymerase chain reaction (PCR) or gene sequencing. The simplest and the most sensitive methods is real-time PCR genotyping of tagSNP (rs1495741), which correlates with acetylation type [2, 5].

Scientists described the role of slow acetylation alleles in the development of drug-induced hepatitis when using anti-tuberculosis drugs. It is known that rapid acetylation alleles are associated with a high risk of transformation of hepatitis into cirrhosis and hepatocellular carcinoma (HCC) in the presence of provoking environmental factors in patients with chronic viral and alcoholic hepatitis [10, 12, 13]. Considering that the expression of NAT2 has the highest level in the liver, it can be assumed that, depending on the rate of acetylation, toxic substances accumulate in liver cells, which form a focus of chronic inflammation under conditions of constant increased load of xenobiotics [19]. Taking into account the increasing influence of exogenous chemicals on the human body, it seems relevant to study the role of gene polymorphisms that determine the activity of xenobiotic metabolic enzymes in the development of CLC and NAFLD.

The aim of this study is to evaluate