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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

THE INFLUENCE OF HYPERCHOLESTEROLEMIA AND CONCOMITANT STATIN THERAPY ON THE STATE OF PLATELET-PLASMA HEMOSTASIS IN PATIENTS WITH ESSENTIAL HYPERTENSION AND NON-ALCOHOLIC FATTY LIVER DISEASE

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Non-alcoholic fatty liver disease (NAFLD) has been shown to be associated with an increased risk of cardiovascular disease (CVD) and mortality. The debate over causation between NAFLD and CVD is ongoing today; however, NAFLD is at least a marker of risk, and therefore attention and control of CVD risk factors is important. In addition, the existence of links between NAFLD and various stages of the atherosclerotic process and the structural and functional state of the cardiovascular system, including endothelial dysfunction and atherogenic dyslipidemia [1,2].

The liver plays an important role in the development of atherogenic dyslipidemia, as changes in lipid metabolism begin at the hepatocyte level. All statins inhibit the activity of HMG-CoA reductase, resulting in an increase in the number of LDL receptors in hepatocytes, increased LDL uptake and thus reduce the level of circulating LDL. In addition, it reduces the content of intracellular cholesterol in the liver, which provides a lipid-lowering effect of statins [3].

According to a recent retrospective analysis of the GREACE study, statins have a positive effect on aminotransferase levels and improve the prognosis of cardiovascular events in patients with elevated aminotransferases in NAFLD [4]. A retrospective analysis of the IDEAL study also revealed the benefits of using statins in patients with elevated ALT levels [5].

Although elevated aminotransferases are not uncommon in patients receiving lipid-lowering therapy, severe liver damage by statins is quite rare in clinical practice [6–8]. Therefore, the use of statins in NAFLD is not only safe, but also recommended by international societies for the study of liver disease [9, 10], in particular the American Association for the Study of Liver Diseases (AASLD) [1].

Given the prevalence of atherogenic dyslipidemias and their proven effect on the development of thrombotic cardiovascular complications in patients with NAFLD, it is important to understand the role of platelets and hemostatic activity in the blood. In addition, the production of peripheral platelets is regulated mainly by the glycoprotein hormone thrombopoietin, which is mainly synthesized in the liver. According to recent studies, people with NAFLD have a significantly increased risk of decreased platelet counts compared to those without NAFLD [11]. Therefore, the question of the nature of the high frequency of thrombotic complications in such patients and the possibility of their prevention remains open.

Due to the lack of a clear understanding in the modern scientific world of pathophysiological changes in this process, we analyzed the impact of changes in lipid profile and concomitant statin therapy on platelet-plasma hemostasis in patients with hypertension as a major risk factor for cardiovascular events and concomitant.

Objective -to determine the state of platelet-plasma hemostasis in patients with essential hypertension and concomitant non-alcoholic fatty liver disease.

Material and methods. The study was conducted on the clinical basis of the Department of Propaedeutics of Internal Medicine №1 Bogomolets National Medical University of the Kyiv Clinical Hospital by Rail №2 of Ukrainian Railways. 152 patients were examined: 72 men and 80 women. The majority of patients were women - 80 people (52.6%), men among the surveyed were 72 people (47.4%). Patients were divided into groups: Group I - patients with stage II HT without signs of liver damage (46 people, median and interquartile age range of the subjects was 58.00 [51.00; 63.00] years); Group II - patients with NAFLD without HT (54 individuals, median and interquartile range of the subjects were 54.00 [43.00; 58.00] years); Group III - patients with stage II HT with NAFLD (52 individuals, median and interquartile range of the subjects were 57.50 [48.00; 64.50] years).

The control group consisted of 15 practically healthy individuals comparable in age and sex (median and interquartile age range of the surveyed were 49.00 [42.00; 55.00] years, who underwent preventive examination).

To achieve this goal, a study of spontaneous and induced platelet aggregation was performed. Platelet aggregation capacity was studied using a 230-LA aggregation laser analyzer (Biola Research and Production Company, Russia). Spontaneous and induced platelet aggregation was studied using inducers: adenosine 5-diphosphate (ADP), arachidonic acid (AA), collagen, adrenaline (NPO-Renam, Russia) [12, 13]. Coagulation activity, anticoagulant were also studied. and fibrinolytic potential of blood in the examined patients [13, 14]. The critical level of significance in testing statistical hypotheses was assumed to be 0.05. Non-parametric statistical methods were used to analyze the indicators of anticoagulant and fibrinolytic hemostasis: U-Mann-Whitney test, Kruskal-Wallis H-test, as small sample sizes were used, and values in groups did not obey the law.

Results and discussion. Among 152 people, hypercholesterolemia (total cholesterol ≥5 mmol/l) was found in 68 (44.7%) people), hypertriglyceridemia (triglycerides ≥1.7 mmol/l) in 40 (26.4%) people, the majority were who had HT and the combined course of HT with NAFLD.

In the analysis of lipid spectrum data on total cholesterol (General cholesterol), triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL), it was found that in the group of patients with HT the level of total cholesterol was the highest - 5.9 [5.2; 6.9] mmol/l, which was 11.3% ($p<0.05$) more than in patients with NAFLD (5.3 [4.3; 5.8] mmol/l), and 7.3% ($p<0.05$) exceeded the value in the combined course of these diseases (5.5 [4.7; 6.2]). The highest values of triglycerides were found in patients with comorbid course of HT and NAFLD - 2.06 [1.36; 2.69] mmol/l, instead in patients with HT and in the NAFLD group, they seemed to correspond to normal triglyceridemia levels (1.58 [1.22; 2.28] and 1.17 [0.84; 1.94], respectively). However, the distribution of obesity revealed hypertriglyceridemia in patients with HT and BMI ≥30 kg/m^2 (1.87 [1.36; 3.1] mmol/l). Thus, the tendency to hypercholesterolemia was determined in all groups, while hypertriglyceridemia only in the presence of a combined course of hepatic steatosis and HT.

Similar changes were found in the study of LDL levels, which was the highest among patients with a combined course of HT

and NAFLD - 3.55 [2.7; 4.2] mmol/l, and slightly lower in patients with NAFLD in the absence of concomitant HT (3.4 [3.1; 3.4] mmol/l). In patients with HT of the II degree, on the contrary, the indicator was 2.5 [1.7; 3.7] mmol/l. In contrast to LDL, in patients with NAFLD, the level of HDL was the lowest, and was equal to 1.0 [0.7; 1.2] mmol/l in isolated flow and 1.1 [1.0; 1.3] mmol/l in the combination of NAFLD and HT of the II degree, which confirmed the presence of a shift of the lipid spectrum towards atherogenicity in patients with hepatic steatosis. In contrast to other groups, patients with HT HDL exceeded 1.6 [1.4; 1.6] mmol/l. Given the above, note the changes in the lipid profile in patients with NAFLD who meet the criteria of the atherogenic lipid triad: an increase in triglycerides and LDL with a simultaneous decrease in HDL. At the same time the most expressed dyslipidemic deviations were observed at a comorbid course of HT of the II century. and NAFLD. Instead, in patients with independent HT we observed only hypercholesterolemia at normal values of triglycerides, LDL and HDL. Thus, the tendency to atherogenic dyslipidemia observed in patients with NAFLD corresponded to the data described in the literature [1].

In the next step, we decided to investigate the possible relationship between the increase in total cholesterol, according to the latest recommendations for dyslipidemia ESC 2019 [15] and the state of platelet and plasma hemostasis in the studied patients.

Analyzing the value of platelet hemostasis, there was no significant difference in the level of induced aggregation in patients with normal and elevated cholesterol levels. However, it should be emphasized that the degree of spontaneous aggregation was significantly higher in patients with hypercholesterolemia - by 32.4% ($p<0.05$) (3.31 [2.10; 3.90] vs. 2.5 [1.75 ; 3.04]).

It should be noted that we separately performed the distribution of patients according to the values of aggregation, which significantly exceeded the average of healthy individuals. This allowed us to detect a more pronounced and statistically significant increase in the frequency of high degrees of spontaneous and induced aggregation in patients with total cholesterol ≥5 mmol/l.

The results of the analysis proved that hypercholesterolemia was associated with a high degree of spontaneous aggregation - more than 1.0%, the odds ratio was 2.4 (0.495-11.64) ($p=0.044$) under conditions of very high sensitivity (Se = 94, 1%), but low specificity (Sp=21.1%) of this method. Also, hypercholesterolemia was associated with a high degree of AA-induced platelet aggregation - more than 50%, the odds ratio reached 3.2 (0.985-10.68) ($p=0.046$) with high specificity (Sp= 81%) and average sensitivity values of the method (Se = 43.3%). Patients with cholesterol ≥5 mmol/l were twice as likely to have high levels of ADP-induced - more than 70% (HS = 2.051 (0.539-7.808); p= 0.285; Se = 23.5%, Sp= 87%) and adrenaline. induced aggregation - more than 20% (HS = 2,063 (0,323-13,198); p= 0,436; Se = 95,6%, Sp= 8,7%), instead, the prevalence of high degrees of collagen-induced activity (more than 30%) of platelets at high cholesterol levels was almost equal to the frequency of such indicators in cholesterol <5 mmol/l (Table 1).

Thus, despite virtually identical indicators of platelet functional activity in the subgroups of high and low cholesterol, the distribution of the frequency of very high degrees of aggregation revealed thrombophilic changes in patients with hypercholesterolemia.

The next step was to assess plasma hemostasis depending on the presence of hypercholesterolemia.

During the evaluation of plasma hemostasis in patients with high and normal cholesterol levels, it was found that the level of fibrinogen was higher by 13.5% ($p<0.05$) precisely in the case of hypercholesterolemia (86.5% [78.1; 96.0] and 94.0% [82.0; 108]), while there was a decrease in antithrombin III by 8.7% ($p<0.05$) in patients with high cholesterol [86.5% [78.1; 96.0] and 94.0% ([82.0; 108]). Other indicators of plasma hemostasis did not show significant differences depending on the level of cholesterol. Therefore, hypercholesterolemia was accompanied by a decrease in anticoagulant activity, while promoting coagulation at the end links of blood clotting.

Given the influence of NAFLD on the development of atherogenic dyslipidemias, which further contributes to the occurrence of cardiovascular complications, we analyzed the effect of statin treatment on the state of platelet-plasma hemostasis. Among the 152 examined patients, 52 (34.2%) people received statin treatment. At the time of the study, 21 (40.3%) individuals of patients were receiving rosuvastatin, of which 16 (76.2%) individuals at a dose of 10 mg, and 5 (23.8%) patients- 20 mg; 27 (51.9%) people received atorvastatin at a dose of 40 mg and 4 (7.7%) - simvastatin 80 mg. When evaluating the use of statin therapy in each of the surveyed groups, it was noted that among the surveyed groups of HT 17 (35.4%) people received lipid-lowering therapy, the lowest percentage of patients treated with statins - 14 (25.9%) people, and the largest number of patients on statin therapy - 21 (38.9%) people - was among patients with a combined course of HT and NAFLD.

We conducted a comparative analysis of platelet-plasma hemostasis in view of the use of statin therapy in the treatment of the examined groups of patients.

When analyzing the degree of spontaneous platelet aggregation, it should be noted that in all patients it was significantly higher than the control values (0.75 [0.47; 1.14]), regardless of statin therapy. It was also found that there was no significant difference between the degree of spontaneous aggregation in patients receiving statins and those who did not receive this treatment in any of the groups except the cohort with comorbid HT and NAFLD, where patients on statin therapy had 16.5% ($p<0.05$) lower degree of spontaneous aggregation than patients who did not receive this treatment (2.85 [2.29; 3.54] and 3.32

Table 1. Influence of hypercholesterolemia on the frequency of high degree of platelet aggregation

Risk factor	OR	95% CI	χ2	p	Se	Sp	φ
Spontaneous> 1.0%	4,267	0,956-19,039	2,478	0,044	0,941	0,211	0,217
ADP> 70.0%	2,051	0,539-7,808	0,597	0,285	0,235	0,870	0,112
AA >50,0%	3,243	0,985-10,679	3,040	0,046	0,433	0,810	0,213
Collagen> 30.0%	1,019	0,324-3,201	0,067	0,975	0,221	0,783	0,003
Adrenaline> 20%	2,063	0,323-13,198	0,063	0,436	0,956	0,087	0,082

note: OR - odds ratio, 95% CI - confidence interval, χ2 - criterion Hi-square with Yates correction, Se - sensitivity, Sp - specificity, φ - strength of the relationship between risk factor and consequence

[2.73; 3.92]). Thus, the results of the analysis proved that the use of statins significantly reduced the degree of spontaneous aggregation in patients with comorbid course of HT and NAFLD both in comparison with the subgroup without statin therapy and in patients with NAFLD without concomitant HT who received lipid-lowering therapy.

Analysis of the degree of ADP-induced platelet aggregation showed that significant differences from control (45.0 [36.5; 52.6]) were found only in patients with NAFLD, in groups II and III, and, it should be noted, there was an increase in aggregation in both patients taking statins and those not receiving this treatment.

Assessing the degree of AA-induced platelet aggregation, we noted significantly lower values in the NAFLD group and in patients with comorbid course of HT and NAFLD for control (36.70 [31.99; 42.6]). At the same time, this indicator significantly exceeded the indicators of healthy people in patients with HT both with the use of statin therapy and without its use. However, only in the NAFLD group did patients receiving statins have a significantly lower degree of AA-induced aggregation against patients without lipid-lowering therapy (by 54.0%, p<0.001) (17.2 [13.6; 20.71] and 26.48 [20.20; 36.50]).

Changes in the degree of collagen-induced aggregation relative to control were found only in patients with grade II HT combined with NAFLD, whose treatment regimen included statins. It was 82.0% (p<0.05) (12.8 [10.14; 16.25]) lower than the control values (23.30 [16.18; 25.1]). Nevertheless, differences in the degree of collagen-induced aggregation were not found in any of the studied groups of patients on statin therapy and without lipid-lowering treatment. However, the analysis of the total population of the examined revealed a decrease in the degree of collagen-induced aggregation by 38.7% (p<0.05) in a subgroup of patients treated (15.5 [11.4; 28.70] against 21,5 [16,4; 28,1]), which demonstrated the stabilizing effect of statins on the vascular wall. Thus, treatment with statins led to a significant reduction in the overall cohort of subjects.

Analysis of adrenaline-induced platelet aggregation showed that in all patients they were significantly higher than control values, regardless of the use of statins. However, as in the analysis of ADP-induced aggregation, the comparison did not reveal a significant difference between the values of the degree of adrenaline-induced aggregation when taking statins and in the absence of them in treatment.

The next step was to determine the effect of statin therapy on the state of plasma hemostasis among the examined groups of patients.

When analyzing the rate of clot formation during PTT, it should be noted that it was significantly higher than the control values (19.25 [18.6; 19.9]) only in patients who did not receive concomitant statin therapy and had hepatic steatosis, ie in groups II and III. Thus, we observed a 23.4% (p<0.001) (15.6 [14.2; 16.8]) reduction in clot formation time in the NAFLD group and a 16.0% reduction (p<0.05) (16.6 [13.6; 19.4]) in the group of combined HT and NAFLD. Determination of the effect of lipid-lowering therapy revealed that patients with NAFLD without statin treatment 19.2% (p<0.01) formed a clot faster than patients receiving lipid-lowering therapy [18.6 [16.3; 20.9] against 15.6 [14.2; 16.8]). Analysis of the results of PTT of all examined patients showed a reduction in time by 13.3% (p<0.01) in patients who did not receive statin therapy [18.8 [16.3; 21.0] against 16.6 [14.2; 19.3]). Therefore, the presence of statins in the treatment regimen led to a prolongation of the clot formation time at the initial stage of blood coagulation by the external mechanism of coagulation in patients with NAFLD and in the general population of subjects.

The study of INR found that the values were significantly lower compared to the control (0.83 [0.79; 0.89]), only in patients with NAFLD in the absence of statin treatment - by 15.3% (p<0.001) (0.72 [0.68; 0.81]). It should be noted that in this subgroup there was a significant decrease in INR - by 9.7% (p<0.05) - compared with patients with NAFLD who received lipid-lowering therapy [0.79 [0.72; 0.93] against 0.72 [0.68; 0.81]). Thus, the value of INR was most affected in patients with NAFLD who were not treated with statins - these patients had the lowest INR.

Table 2. Comparison of platelet hemostasis in patients depending on the presence of concomitant statins in therapy (Me [25%; 75%])

	I group			II group			III group			**Total**		
	Statins (+)	**Statins (-)**	p	**Statins (+)**	**Statins (-)**	p	**Statins (+)**	**Statins (-)**	p	**Statins (+)**	**Statins (-)**	p
Spontaneous aggregation, degree,%	1,54*** [1,26; 2,61]	1,72*** [1,25; 2,87]	>0,05	3,58*** [3,02; 4,28]	3,02*** [2,42; 3,68	>0,05	2,85*** [2,29; 3,54]	3,32*** [2,73; 3,92	<0,05	2,76*** [2,18; 3,50]	2,88*** [2,19; 3,54]	>0,05
ADP-induced aggregation, degree,%	48,2 [37,3; 73,20]	45,9 [37,4; 78,50]	>0,05	66,5*** [56,4; 79,00]	59,5*** [50,2; 69,25]	>0,05	53,4** [49,40; 64,70]	56,0* [44,2; 64,60]	>0,05	57,7** [45,6; 69,15]	56,7** [45,3; 69,3]	>0,05
AA-induced aggregation, degree,%	64,2*** [61,1; 75,00]	51,7** [42,1; 63,40]	>0,05	17,2*** [13,6; 20,71]	26,48* [20,20; 36,50]	<0,001	28,6* [17,08; 39,12]	25,3* [19,4; 36,00]	>0,05	33,7 [17,7; 59,50]	31,8 [23,5; 45,5]	>0,05
Collagen-induced aggregation, degree,%	23,1 [11,3; 31,30]	23,4 [10,5; 33,60]	>0,05	27,8 [24,2; 39,30]	23,75 [14,81; 28,55]	>0,05	12,8* [10,14; 16,25]	12,5 [11,80; 22,49]	>0,05	15,5 [11,4; 28,70]	21,5 [16,4; 28,1]	<0,05
Adrenaline - induced aggregation, degree,%	44,8*** [35,2; 50,30]	34,9*** [31,3; 52,10]	>0,05	41,8*** [33,1; 54,40]	44,2*** [37,20; 52,70]	>0,05	30,4* [23,40; 32,60]	29,6** [25,0; 36,40]	>0,05	34,6*** [28,6; 49,25]	37,9*** [29,5; 51,1]	>0,05

*The degree of probability of indicators relative to the control group: * - p<0.05; ** - p<0.01; *** - p<0.001*

Determining the difference in the duration of thrombin time (TT) showed a shortening of the clot formation time in both subgroups of the NAFLD group compared with the control values (10.8 [10.1; 11.2]). However, a decrease in TT by 12.2% ($p<0.05$) was observed in the subgroup receiving statins among patients with NAFLD (8.2 [7.70; 8.60] vs. 9.20 [8.40; 10, 10]).

Treatment with statins did not have a significant effect on other indicators of the coagulation of hemostasis: APTT, fibrinogen, RFMC, although there were significant differences in the values of these indicators against control, which reflected the general trend of groups of patients with HT, NAFLD and their combination, regardless of treatment statins.

Interestingly, during the analysis of anticoagulant hemostasis, despite the absence of probable discrepancies with control, it was in the NAFLD group that statins showed a difference in the effect on BP III, and a similar difference was observed in the general population. Thus, in the general cohort, the use of statins increased the activity of blood pressure III by 10.7% ($p<0.01$) (98.5 [83.6; 106.0] against 89.0 [81.0; 95.0]), but in the NAFLD group this difference was more significant - by 14.3% ($p<0.001$) BP III was more active in patients receiving lipid-lowering therapy (104.0 [102.0; 106.0] vs. 91.0 [85, 5; 94.0]). Thus, statin treatment significantly increased the activity of the anticoagulant link of hemostasis in the general population of subjects and among patients with NAFLD.

Indicators of the fibrinolytic system had significant deviations from control values in all groups, showing a decrease in fibrinolysis activity, but the difference between subgroups depending on concomitant statin therapy did not become statistically significant.

The next step was to compare the indicators of platelet-plasma hemostasis directly in the group of combined course of HT and NAFLD depending on cholesterol levels and the presence of statins in the treatment regimen of these patients.

Interesting was the fact that the degree of aggregation in patients with a combination of HT and NAFLD, which achieved the target values of cholesterol due to the appointment of statins, did not differ from those who had cholesterol levels <5.0 mmol/l without the use of lipid-lowering therapy. It was noticed that among patients with comorbid course of HT and NAFLD, statins showed an effect in patients with high cholesterol. Thus, their spontaneous aggregation was 17.1% ($p<0.05$) lower than in patients who did not receive statins and had high cholesterol (2.80 [2.29; 3.23] vs. 3.28 (2.47; 4.85]), and the degree of collagen-induced aggregation decreased by 33.7% ($p<0.05$) (12.76 [10.90; 14.75] vs. 17.06 [14.07; 21.35]) in patients on statin therapy with cholesterol levels ≥5.0 mmol/l. Thus, we can conclude that in patients with hypercholesterolemia with a combination of HT with NAFLD, statin treatment reduced spontaneous and collagen-induced platelet aggregation even when cholesterol targets were not met. At the same time, the values of spontaneous and induced platelet aggregation did not differ depending on the intake of statins, if cholesterol levels did not exceed 5.0 mmol/l.

The analysis of plasma hemostasis in the group of combined course of HT of the II century is carried out. and NAFLD showed that in the case of normal cholesterol levels, the clot formation time was significantly prolonged in the first stage of thrombus formation, especially in patients who reached normal cholesterol levels due to statin therapy, which can be considered as an antithrombogenic effect of lipid-lowering therapy.

Therefore, we observed a prolongation of PTT by 32.5% ($p<0.05$) (21.2 c [20.5-23.7] vs. 16.0 c [13.4-18.9]), INR on 25.4% ($p<0.05$) (0.89 [0.75-0.97] vs. 0.71 [0.65-0.79]) and TT by 23.2% ($p<0, 05$) (12.2 c [9.8-12.5] vs. 9.9 c [9.2-10.4]). Instead, in the subgroup with hypercholesterolemia, statins increased the activity of the anticoagulant hemostasis - blood pressure III increased by 3.1% ($p<0.05$) (108.0% [96.0-126.0] vs. 100.5% [90 Thus, in patients with stage II HT combined with NAFLD, statins reduced the thrombogenic potential of blood, affecting mainly the primary link of plasma hemostasis in the case of effective therapy, and in case of failure to achieve target values of cholesterol, mostly anticoagulant. hemostasis system.

Summarizing the results of our analysis, we can state that the atherogenic nature of the changes in the lipid profile was diagnosed both in patients with NAFLD and in their combined course. At the same time the most expressed dyslipidemic deviations were observed at a comorbid course of HT of the II century. and NAFLD, what has been proven earlier [9]. Instead, in patients with independent HT we observed only hypercholesterolemia at nonatherogenic triglycerides, LDL, and HDL.

Analyzing the value of platelet hemostasis in patients with normal and elevated cholesterol levels and we found that the degree of spontaneous aggregation was significantly higher in patients with hypercholesterolemia. In addition, hypercholesterolemia was associated with higher platelet function. That is, an increase in cholesterol levels can be seen as an additional risk factor for increased platelet aggregation. Changes in plasma hemostasis also had a shift to the prothrombogenic side: hypercholesterolemia was accompanied by a decrease in anticoagulant activity and activation of coagulation at the end links of blood coagulation. The described changes correspond to the literature data [12].

After analyzing the effect of statin therapy on the state of platelet-plasma hemostasis, it was found that the use of statins significantly reduced the degree of spontaneous aggregation in patients with comorbid course of HT and NAFLD. Under the influence of lipid-lowering therapy, AA-induced aggregation was also reduced in patients with independent NAFLD, indicating a decrease in platelet response to proinflammatory prostaglandins. Statin treatment also markedly reduced the degree of collagen-induced aggregation in patients with comorbid HT and NAFLD, and led to a significant decrease in this indicator in the general cohort of subjects, indicating a decrease in prothrombogenic response in case of damage to the vascular wall or destabilization of atherosclerotic plaque. In addition, the use of statins in the treatment of dyslipidemia was accompanied by a decrease in the coagulation activity of hemostasis and an increase in the anticoagulant potential of the blood.

Thus, the results of the analysis showed that patients with hypercholesterolemia have procoagulant and prothrombogenic blood activity, but against the background of statin treatment there is a decrease in platelet aggregation, blood coagulation potential and increased activity of anticoagulant hemostasis.

Research limitations.

The limitations of the study are related to the small groups of patients.

Prospects for further research. Prospects for further research are the study of platelet-plasma hemostasis in hypertriglyceridemia, high LDL levels, the effect of fibrates on the state of hemostasis.

Conclusions.

1. The atherogenic nature of changes in the lipid profile is diagnosed both in patients with hypertension and in patients with NAFLD and in their combined course.

2. Hypercholesterolemia is associated with higher platelet function, hyperfibrinogenemia, decreased anticoagulant potential of the blood, so such changes in the lipid profile can be considered as an additional risk factor for prothrombogenic blood changes.

3. The use of lipid-lowering therapy reduces the degree of spontaneous aggregation in the comorbid course of HT and NAFLD, leads to a significant decrease in collagen-induced aggregation in the total cohort of subjects and a combination of HT with NAFLD, as well as to reduce the degree of AA-induced aggregation in patients with NAFLD, which suggests the presence of pleiotropic antithrombotic effect of statins.

4. The use of statins in the treatment of dyslipidemia reduces the coagulation activity of hemostasis and enhances the anticoagulant potential of the blood, to a greater extent this effect is observed in patients with NAFLD and patients with HT, combined with NAFLD, which explains the prophylactic effect of statin therapy in cardiac thrombotic complications.

5. In patients with comorbid course of HT and NAFLD on statin therapy, and without lipid-lowering therapy, the values of spontaneous and induced platelet aggregation do not differ if cholesterol levels do not exceed 5.0 mmol/l. However, in patients with hypercholesterolemia, statin treatment reduced spontaneous and collagen-induced platelet aggregation even when the target cholesterol values were not met, thus reducing the prothrombogenic potential of the blood.

6. Treatment with statins in patients with combined HT and NAFLD is accompanied by a decrease in the activity of the coagulation unit in the case of reaching a cholesterol level <5 mmol/l. However, despite the failure of these patients to achieve cholesterol targets, statin therapy increases the anticoagulant activity of the blood. Thus, the inclusion of statins in the treatment of patients with HT and NAFLD demonstrates an additional antithrombotic effect.

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SUMMARY

THE INFLUENCE OF HYPERCHOLESTEROLEMIA AND CONCOMITANT STATIN THERAPY ON THE STATE OF PLATELET-PLASMA HEMOSTASIS IN PATIENTS WITH ESSENTIAL HYPERTENSION AND NON-ALCOHOLIC FATTY LIVER DISEASE

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The liver plays an important role in the development of atherogenic dyslipidemia, since changes in lipid metabolism begin at the hepatocyte level. Given the prevalence of dyslipidemias and their proven effect on the development of thrombotic cardiovascular complications in patients with non-alcoholic fatty liver disease (NAFLD), it is important to understand the role of platelets and hemostatic blood activity.

Objective - to determine the state of platelet-plasma hemostasis in patients with essential hypertension, with concomitant non-alcoholic fatty liver disease.

152 patients were examined: 72 men and 80 women. Three groups were identified: I - 46 patients with hypertension stage II, II - 54 patients with NAFLD without hypertension, Group

III - 52 patients with hypertension stage II with concomitant NAFLD. The total amount of spontaneous and induced platelet aggregation ability, coagulation activity, anticoagulant and fibrinolytic potential of blood was studied.

The degree of spontaneous aggregation was significantly higher in patients with hypercholesterolemia - by 32.4% (p<0.05). that the level of fibrinogen was higher by 13.5% (p<0.05) precisely in hypercholesterolemia. In a cohort with a comorbid course of hypertension and NAFLD, patients on statin therapy had a 16.5% (p<0.05) lower degree of spontaneous aggregation than patients who did not receive this treatment. In patients with NAFLD without statin treatment, prothrombin time (PTT) was shortened by 19.2% (p<0.01) and international normalization ratio (INR) by 15.3% (p<0.01) than in patients who received lipid-lowering therapy. A decrease in thrombin time (TT) by 12.2% (p<0.05) was observed in the subgroup receiving statins among NAFLD patients. The use of statins in the general cohort increased the activity of antithrombin (AT) III by 10.7% (p<0.01), and in the NAFLD group by 14.3% (p<0.001). In patients with essential hypertension (HT) and NAFLD with a high level of cholesterolemia, spontaneous aggregation was 17.1% (p<0.05) less than in patients who did not receive statins and had high cholesterol levels, and the degree of collagen-induced aggregation decreased by 33.7% (p<0.05). In the subgroup with hypercholesterolemia, statins contributed to an increase in PTT by 32.5% (p<0.05), INR by 25.4% (p<0.05), and thrombin time - by 23.2% (p<0.05) and increased the activity of the anticoagulant link of hemostasis - the level of AT III increased by 3.1% (p<0.05)

Hypercholesterolemia is associated with a higher functional activity of platelets, hyperfibrinogenemia. Statin therapy in patients with HT stage. and NAFLD is accompanied by a decrease in the activity of spontaneous aggregation, the coagulation link and increases the anticoagulant potential of the blood.

Keywords: non-alcoholic fatty liver disease, platelet aggregation, plasma hemostasis; fibrinolysis; coagulation hemostasis; hypertonic disease; dyslipidemia; statin therapy.

РЕЗЮМЕ

ВЛИЯНИЕ ГИПЕРХОЛЕСТЕРИНЕМИИ И СОПУТСТВУЮЩЕЙ СТАТИНОТЕРАПИИ НА СОСТОЯНИЕ ТРОМБОЦИТАРНО-ПЛАЗМЕННОГО ГЕМОСТАЗА У ПАЦИЕНТОВ С ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ И НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ

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Цель исследования - определить состояние тромбоцитарно-плазменного гемостаза у пациентов с гипертонической болезнью и сопутствующей неалкогольной жировой болезнью печени.

Обследовано 152 пациента: 72 мужчин и 80 женщин. Выделены три группы: I группа - 46 больных гипертонической болезнью (ГБ) II стадии, II группа - 54 пациента с неалкогольной жировой болезнью печени (НАЖБП) без ГБ, III группа - 52 пациента с ГБ II стадии с сопутствующей НАЖБП. Проведено исследование общего количества спонтанной и индуцированной агрегационной способности тромбоцитов, коагуляционной активности, антикоагулянтного и фибринолитического потенциала крови.

Степень спонтанной агрегации оказалась существенно выше у пациентов с гиперхолестеринемией - на 32,4% (p<0,05), уровень фибриногена - выше на 13,5% (p<0,05) именно при гиперхолестеринемии. У пациентов с коморбидным течением ГБ и НАЖБП, которые находились на статинотерапии, степень спонтанной агрегации была на 16,5% (p<0,05) ниже, чем у больных, не получавших данного лечения. У пациентов с НАЖБП без лечения статинами протромбиновое время (ПТВ) сокращалось на 19,2% (p<0,01), международное нормализованное отношение (МНО) - на 15,3% (p<0,01), в сравнении с больными, получавшими липидоснижающую терапию. Среди больных НАЖБП, получавших статины, наблюдалось уменьшение тромбинового времени (ТВ) на 12,2% (p<0,05). Применение статинов в общей когорте повышало активность антитромбина III (АТ) на 10,7% (p<0,01), а в группе НАЖБП - на 14,3% (p<0,001). У пациентов с ГБ и НАЖБП с высоким уровнем холестеринемии спонтанная агрегация была на 17,1% (p<0,05) меньше, чем у пациентов, не получавших статины, и имевших высокий уровень холестерина, а степень коллаген-индуцированной агрегации уменьшилась на 33,7% (p<0,05). В группе с гиперхолестеринемией статины способствовали удлинению ПТВ на 32,5% (p<0,05), МНО - на 25,4% (p<0,05), тромбиновое время - на 23,2% (p<0,05) и повышали активность антикоагулянтного звена гемостаза - уровень АТ III увеличился на 3,1% (p<0,05)

Гиперхолестеринемия ассоциируется с более высокой функциональной активностью тромбоцитов и гиперфибриногенемией. Статинотерапия у пациентов с ГБ II ст. и НАЖБП сопровождается уменьшением активности спонтанной агрегации, коагуляционного звена и повышает антикоагулянтный потенциал крови.

რეზიუმე

ჰიპერქოლესტერინემიის და თანმხლები სტატინოთერაპიის გავლენა თრომბოციტულ-პლაზმური ჰემოსტაზის მდგომარეობაზე პაციენტებში ჰიპერტონიული დაავადებით და ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადებით

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დისლიპიდემიის გავრცელების და გულ-სისხლძარღვოვანი თრომბოზული გართულებების განვითარებაზე მისი დადასტურებული ეფექტის გათვალისწინებით, პაციენტებში ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადებით (დაცდ) თრომბოციტების და სისხლის ჰემოსტაზური აქტივობის როლის გარკვევა მეტად მნიშვნელოვანია.

კვლევის მიზანს წარმოადგენდა თრომბოციტულ-პლაზმური ჰემოსტაზის მდგომარეობის შეფასება პაციენტებში ჰიპერტონიული დაავადებით და ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადებით.

გამოკვლეულია 152 პაციენტი – 72 მამაკაცი და 80 ქალი. გამოიყო სამი ჯგუფი: I ჯგუფი – 46 პაციენტი ჰიპერტონიული დაავადების II სტადიით, II ჯგუფი – 54 პაციენტი დაცდ-ით ჰიპერტონიული დაავადების

გარეშე, III ჯგუფი – 52 პაციენტი ჰიპერტონიული დაავადების II სტადიით და ღაცდ-ით. შესწავლილია თრომბოციტების სპონტანური და ინდუცირებული აგრეგაციის უნარი, სისხლის ანტიკოაგულაციური და ფიბრინოლიზური პოტენციალი. სპონტანური აგრეგაციის ხარისხი აღმოჩნდა მნიშვნელოვანდ უფრო მაღალი პაციენტებში ჰიპერქოლესტერინემიით – 3,4%-ით (p<0,05), ხოლო ფიბრინოგენის დონე – 13,5%-ით მეტი (p<0,05). პაციენტებში ჰიპერტონიული დაავადების და ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადების კომორბიდული მიმდინარეობით, რომლებიც იმყოფებოდნენ სტატინოთერაპიაზე, სპონტანური აგრეგაციის უნარი იყო 16,5%-ით (p<0,05) უფრო დაბალი, ვიდრე პაციენტებში აღნიშნული მკურნალობის გარეშე. პაციენტებში ღაცდ-ით სტატინებით მკურნალობის გარეშე პროთრომბინის დრო შემცირდა 19,2%-ით (p<0,01), INR – 15,3%-ით (p<0,01), ვიდრე პაციენტებში, რომლებიც იღებდნენ ლიპიდდამაქვეითებელ მკურნალობას. პაციენტებში ღაცდ-ით და სტატინების მიღებით აღინიშნებოდა თრომბოციტული დროის შემცირება 12,2%-ით (p<0,05). სტატინების გამოყენება საერთო კოჰორტაში ზრდიდა ანტითრომბინ III-ის აქტივობას 10,7%-ით (p<0,01), ხოლო ჯგუფში ღაცდ-ით - 14,3%-ით (p<0,001). პაციენტებში ჰიპერტონიით, ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადებით და ქოლესტერინემიის მაღალი დონით სპონტანური აგრეგაცია იყო 17,1%-ით (p<0,05) უფრო ნაკლები, ვიდრე პაციენტებში, რომლებიც არ იღებდნენ სტატინებს და ჰქონდათ ქოლესტერინის მაღალი დონე, ხოლო კოლაგენ-ინდუცირებული აგრეგაციის დონე შემცირდა 33,7%-ით (p<0,05). ჯგუფში ქოლესტერინემიით სტატინები ხელს უწყობდნენ პროთრომბინის დროის გახანგრძლივებას 32,5%-ით (p<0,05), INR-ისა - 25,4%-ით (p<0,05), თრომბული დრო - 23,2%-ით (p<0,05) და ზრდიდნენ ჰემოსტაზის ანტიკოაგულაციური რგოლის აქტივობას – ანტითრომბინ III-ის დონემ მოიმატა 3,1%-ით (p<0,05).

ჰიპერქოლესტერინემია ასოცირდება თრომბოციტების უფრო მაღალ ფუნქციურ აქტივობასთან და ჰიპერფიბრინოგენემიასთან. სტატინოთერაპია პაციენტებში ჰიპერტონიული დაავადების II სტადიით და ღაცდ-ით განსაზღვრავს კოაგულაციური რგოლის და სპონტანური აგრეგაციის შემცირებას და სისხლის ანტიკოაგულაციური პოტანციალის ზრდას.

APPLICATION OF HYPOXIC TRAINING IN ELDERLY PATIENT WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE: IMPACT ON THE STATE OF MICROCIRCULATION

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Hypoxia is both a cause and a characteristic syndrome of aging. Age-related hypoxic changes contribute to the development of pathological processes, in particular, diseases of the respiratory system [2,7,11]. Therefore, the development of lung pathology, in particular, chronic obstructive pulmonary disease (COPD) in old age is understandable.

COPD as one of the leading causes of morbidity and mortality continues to attract the attention of many researchers. This is due to the continued spread of this pathology, as well as the lack of effectiveness of treatment [5,9,10]. Along with smoking, air pollution, population aging has a significant impact on the incidence of COPD [9,10]. Moreover, the proportion of elderly patients in the age structure of COPD continues to grow [9].

In the development of COPD, along with other pathogenetic processes, the relationship between disorders of external respiration and the functioning of the cardiovascular system, in particular, its microcirculatory system [4,13]. According to some authors, there is a direct link between COPD and various pathological conditions of the cardiovascular system [1,13]. Disorders of microcirculation and endothelial function are essential in the mechanisms of development of disorders of the cardiorespiratory system in COPD [4,13].

Microcirculation disorders in patients with COPD primarily affect the elderly. This is due to changes in microvessels, decreased vascularization with aging, which can cause tissue hypoxia [3,7].

Thus, the implementation of therapeutic measures aimed at improving endothelial function and the functioning of the microcirculatory system in patients with COPD, especially the elderly, is relevant and justified.

The choice of treatment tactics in elderly patients with COPD requires a balanced approach, taking into account the benefits and risks of therapeutic effects [5,9]. The use of drug therapy in the elderly is often limited or impossible. Therefore, in the elderly and senile age, drug-free treatment methods attract attention. The advantage of these treatments, in particular, is the complexity, physiology, low risk of side effects.

Among drug-free treatments, hypoxic training has become widely accepted. The use of hypoxic training is based on the development of adaptation to hypoxic effects. But due to cross-