МЕДИЦИНА

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DISORDERS OF HEMOSTASIS AND FIBRINOLYSIS IN PATIENTS WITH CO-MORBID NON-ALCOHOLIC FATTY LIVER DISEASE, CHRONIC KIDNEY DISEASE AND OBESITY

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The aim of the work was to find out changes in the system of homeostasis and fibrinolysis during the combined course of non-alcoholic fatty liver disease (NAFLD), depending on its form and stage of chronic kidney disease (CKD) with obesity. To achieve the goal, 444 patients were examined, including 84 patients with NAFLD with obesity of the first degree (group 1), which included 2 subgroups: 32 patients with nonalcoholic steatohepatitis (NASH) and 52 patients with nonalcoholic steatohepatitis (NASH) and 270 patients with NAFLD with degree I obesity and stage I-III CKD (group 2), including 110 patients with NASH and 160 patients with NASH. The control group included 90 patients with CKD stage I–III with normal body weight. Based on the obtained results, it was established that the maximum decrease in the prothrombin time (PTT) indicator was observed in patients with NASH and CKD – 1.9 times compared to the indicator in practically healthy persons (PHP) ($p<0.05$) with the presence of an intergroup difference; in patients with NASH without accompanying CKD, the PTC was 1.6 times lower than the indicator in PHP ($p<0.05$). In patients with non-alcoholic steatosis of the liver (NASPH), less intense changes were observed: in the group without comorbidity, the PTT was 1.2 times lower than in non-alcoholic fatty liver disease ($p<0.05$), in patients with NASH with CKD – by 1.4 times ($p<0.05$).Thus, metabolic intoxication, oxidative stress, which accompany the course of NAFLD under conditions of obesity and CKD, contribute to the activation of the kallikrein-kinin system, the formation of plasmin and thrombin with subsequent disruption of the balance between them, the development of stasis, the sludge phenomenon, the formation of platelet and erythrocyte aggregates in circulatory system.

Key words: *Nonalcoholic fatty liver disease, nonalcoholic steatosis, nonalcoholic steatohepatitis, chronic kidney disease, diabetic kidney disease, obesity, diabetes, homeostasis, fibrinolysis.*

Альона Антонів, Зоряна Коцюбійчук. Розлади гемостазу та фібринолізу у хворих із коморбідними неалкогольною жировою хворобою печінки, хронічною хворобою нирок та ожирінням

Мета роботи – виявити зміни системи гомеостазу та фібринолізу за поєднаного перебігу неалкогольної жирової хвороби печінки (НАЖХП) залежно від її форми та стадії хронічної хвороби нирок (ХХН) з ожирінням. Для досягнення поставленої мети обстежено 444 хворих, із них 84 хворих на НАЖХП з ожирінням I ступеня (1 група), які включали дві підгрупи: 32 хворих на неалкогольний стеатогепатит (НАСГ) та 52 хворих на неалкогольний стеатогепатит (НАСГ) та 270 хворих на НАЖХП з ожирінням I ступеня та ХХН I–III стадій (2 група), у тому числі 110 пацієнтів із НАСГ та 160 пацієнтів із НАСГ. Контрольну групу становили 90 хворих на ХХН I–III стадій із нормальною масою тіла. На підставі отриманих результатів установлено, що максимальне зниження показника протромбінового часу (ПТЧ) спостерігалося у хворих на НАСГ та ХХН – у 1,9 рази порівняно з показником у практично здорових осіб (ПНР) ($p<0,05$) із наявністю міжгрупової різниці; у хворих на НАСГ без супутньої ХХН ПТЧ був у 1,6 рази нижчим за показник у ПЗО ($p<0,05$). У хворих на неалкогольний стеатоз печінки (НАСП) спостерігалися менш інтенсивні зміни: у групі без супутньої патології ПТТ був у 1,2 рази нижчим, аніж при неалкогольній жировій хворобі печінки ($p<0,05$), у пацієнтів із НАСГ, із ХХН – у 1,4 рази ($p<0,05$). Таким чином, метаболічна інтоксикація, оксидативний стрес, які супроводжують перебіг НАЖХП за умов ожиріння та ХХН, сприяють активації калікреїн-кінінової системи, утворенню плазміну

та тромбіну з подальшим порушенням балансу між ними, розвитку стаз, сладж-феномен, утворення тромбоцитарних і еритроцитарних агрегатів у системі кровообігу.

Ключові слова: *неалкогольна жирова хвороба печінки, неалкогольний стеатоз, неалкогольний стеатогепатит, хронічна хвороба нирок, діабетична хвороба нирок, ожиріння, цукровий діабет, гомеостаз, фібриноліз.*

The urgency of the problem. Nonalcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) are the most common chronic diseases that can be caused by a variety of factors, including poor diet, lack of physical activity, genetic factors, and more. The prevalence of nonalcoholic fatty liver disease and chronic kidney disease is increasing in many countries worldwide due to lifestyle changes, including minimal physical activity, unhealthy diets, and rising rates of obesity and diabetes.

NAFLD covers the spectrum of diseases from simple steatosis to nonalcoholic steatohepatitis (NASH), which involves inflammation and ballooning degeneration of hepatocytes with the development of fibrosis and subsequent progression to cirrhosis [1-5]. Of particular concern is the increase in the frequency of hepatocellular carcinoma (HCC) in patients with NAFLD due to the high prevalence of the disease and the possibility of the development of carcinoma in the early stages of the disease, without significant fibrosis or cirrhosis, which makes its diagnosis impossible [3–6]. NAFLD is considered a hepatic manifestation of metabolic syndrome, but it can also occur independently. In particular, visceral obesity and type 2 diabetes are associated with the presence of NAFLD [5–7]. The risk of progression of steatosis to NASH and liver cirrhosis depends on several factors, including the patient's lifestyle and the severity of the metabolic syndrome, as well as genetic factors [7–9].

However, the number of studies related to the study of disorders of the fibrinolysis system and homeostasis in patients with NAFLD, CKD and obesity is insufficient.

The aim of the work was to find out changes in the system of homeostasis and fibrinolysis during the combined course of non-alcoholic fatty liver disease, depending on its form and stage of chronic kidney disease with obesity.

Research methods. To achieve the goal, 444 patients were examined, including 84 patients with NAFLD with obesity of the first degree (group 1), which included 2 subgroups: 32 patients with nonalcoholic steatohepatitis (NASH) and 52 patients with nonalcoholic steatohepatitis (NASH) and 270 patients with NAFLD with degree I obesity and stage I–III CKD (group 2), including 110 patients with NASH and 160 patients with NASH. The control group included 90 patients with CKD stage I–III with normal body weight. The diagnosis of NAFLD was established taking into account the unified clinical protocol approved by the order of the Ministry of Health of Ukraine No. 826 of November 6, 2014. Diagnosis and treatment of CKD was carried out in accordance with the recommendations of the clinical guidelines of the Institute of Nephrology of the National Academy of Sciences of Ukraine (2012).

The total coagulation potential of blood (PTC, TP), plasma fibrinolytic activity, potential plasminogen activity, fibrinogen level in blood plasma, antithrombin III activity, factor XIII activity were studied with the help of kits of reagents of the company "Simko Ltd" (Lviv) according to the methods of N. Titsa. Using reagents of the same company, the state of enzymatic and non-enzymatic fibrinolysis in blood plasma was studied. Statistical analysis of the obtained results was carried out according to the type of research conducted and the types of numerical data that were obtained. The normality of the distribution was checked using the Liliefors, Shapiro-Wilk tests and the method of direct visual evaluation of histograms of the distribution of eigenvalues. Quantitative measures that had a normal distribution are presented as mean (M) ± standard deviation (S). Discrete values are presented in the form of absolute and relative frequencies (percentage of observations to the total number of examinees). Parametric tests with Student's t-test and Fisher's F-test were used to compare data that had a normal distribution. In the case of non-normal distribution, we used: median test, calculation of the Mann-Whitney rank U-test, for multiple comparisons – the Wilcoxon T-test (in the case of research of dependent groups). Statistical and graphical analysis of the obtained results was carried out using software packages Statistica for Windows version 8.0 (Stat Soft inc., USA), Microsoft Excel 2007 (Microsoft, USA).

Research results and their discussion. Based on the obtained results, it was established that the maximum decrease in the prothrombin time (PTT) indicator was observed in patients with NASH and CKD – 1.9 times compared to the indicator in practically healthy persons (PHP) ($p<0.05$) with the presence of an intergroup difference; in patients with NASH without accompanying CKD, the PTC was 1.6 times lower than the indicator in PHP ($p<0.05$). In patients with non-alcoholic steatosis of the liver (NASPH), less intense changes were observed: in the

group without comorbidity, the PTT was 1.2 times lower than in non-alcoholic fatty liver disease ($p<0.05$), in patients with NASH with CKD – by 1.4 times ($p<0.05$). In patients with isolated CKD, the decrease in PTT was 1.4 times ($p<0.05$) (Table 1). During the study of the 3rd phase of coagulation hemostasis, it was established that the content of fibrinogen in the blood of patients was reduced: in patients with NASH and NASH with CKD – by 1.4 and 2.0 times, respectively ($p<0.05$) against an increase of 1,2 times in patients with isolated CKD ($p<0.05$); in patients with NASP, the decrease was 12.7% and 17.1% ($p<0.05$), the indicator probably differed when compared in the intergroup aspect ($p<0.05$). Insufficiency of the synthesis of blood coagulation factor I in the liver and/or activation of the hemostasis system, which is manifested by a decrease in the content of fibrinogen in the blood of patients with NAFLD with CKD and obesity, indicates a response to inflammation, the development of hypercoagulation, the formation of microthrombi, thereby involving a certain amount of fibrinogen in this process.

When analyzing the anticoagulation potential of blood, a decrease in TT was found in all groups of patients, with the maximum percentage decrease in patients with NASH with CKD – 1.7 times ($p<0.05$) compared to the PHP group, however, in patients with NASH, TT is also likely decreased by 1.5 times ($p<0.05$) with a probable intergroup difference ($p<0.05$). It should be taken into account that in patients with NASP with CKD, the TT index was reduced by 1.4 times ($p<0.05$), and in patients with CKD without comorbid conditions – by 1.2 times ($p<0.05$). In patients with NASP, the changes were not probable ($p>0.05$).

The results of the study established the inhibition of ATIII activity in all comparison groups with the maximum inhibition in patients with NASH with CKD – 1.4 times ($p<0.05$) against a decrease of 1.3 times in patients with NASH (Table 1). In the groups of patients with NASP and NASP with CKD, a moderate difference was not established. The study of blood fibrinolytic activity showed that plasma SFA in patients of all groups was probably lower than the control indicators: in patients with NASH – by 7.1%, patients with NASH with CKD – by 14.9%, patients with NASH – by 17.2%, patients with NASH with CKD – by 18.9%, patients with

Таблиця 1

Changes in indicators of hemostasis and fibrinolysis in patients with non-alcoholic steatosis of the liver and steatohepatitis depending on comorbidity with CKD, during its isolated course (M ± m)

Indicators, unit measurement	PHP, n=30	Groups of examined patients				
		NASP, n=32	NASH, CKD, n=110	NASH, n=52	NASH, CKD, n=160	CKD, n=90
PTT, s.	22,14± 0,47	18,21± 0,32*	16,23± 0,13*/**	14,26± 0,21*/**	12,18± 0,25*/***/#	17,27± 0,29 */***/##
Fibrinogen, g/l	3,62±0,11	3,26±0,15*	3,18±0,12*	2,71±0,18*/**	1,78± 0,10 */***/#	4,28± 0,09*/***/##
TT, s	16,76± 0,87	15,82± 0,36	12,45± 0,23*/**	11,92± 0,24*/**	10,35± 0,15 */***/#	13,25± 0,20*/***/##
AT III, %	95,50± 2,01	83,06± 3,16*	76,38±3,24*	74,02± 2,85*	67,27± 2,25*/***	80,29±3,29 */##
SFA, E440/ ml/h	1,68± 0,02	1,57±0,02*	1,46±0,01*	1,40± 0,01*/**	1,36± 0,004*/***/#	1,53± 0,01*/***/##
NFA, E440/ ml/h	0,49± 0,02	0,61±0,01*	0,64± 0,003*	0,69± 0,004*/**	0,76± 0,01*/***/#	0,58± 0,002 */***/##
FFA, E440/ ml/h	1,20± 0,01	0,99±0,01*	0,83± 0,01*/**	0,72± 0,004*/**	0,63± 0,01*/***/#	0,94± 0,01*/***/##
HDF, min.	19,46± 0,19	23,53± 1,34*	30,25± 1,19*/**	34,55± 1,15*/**	38,32± 1,28*/***	29,38±1,07 */##
XIII factor, %	99,92± 2,46	97,34± 2,42	83,52±1,14*	70,92± 1,15*/**	69,19± 1,29*/***	80,26±2,35*/##
PAP, min.	16,24± 0,28	18,32± 0,22*	22,21± 0,18*/**	26,39± 0,13*/**	30,16± 0,12*/***/#	25,01± 0,11*/***/##

Notes: * – the difference is probable in comparison with the indicator in the PZO ($p<0.05$);

** – the difference is probable in comparison with the indicator in patients with NASP ($p<0.05$);

*** – the difference is probable in comparison with the indicator in patients with NASH ($p<0.05$);

– the difference is probable in comparison with the indicator in patients with NASP with CKD ($p<0.05$);

– the difference is probable in comparison with the indicator in patients with NASH with CKD ($p<0.05$).

CKD – by 10.6% ($p<0.05$) with the presence of a probable intergroup difference between groups with comorbidity and isolated course of CKD ($p<0, 05$). SFA inhibition occurred due to a decrease in FFA: in patients with NASH, the indicator was probably 1.2 times lower than in controls, in patients with NASH with CKD – by 1.4 times, in patients with NASH – by 1.7 times, in the group of patients on NASH with CKD – 1.9 times, while in the group of patients with CKD, FFA inhibition was registered – 1.3 times ($p<0.05$). At the same time, NFA in patients of all groups increased compared to the PZO group: respectively, in patients with NASH – by 1.2 times, in patients with NASH with CKD – by 1.3 times, in patients with NASH – by 1.4 times, in the group of patients with NASH with CKD – 1.5 times, while in the group of patients with CKD, NFA activation was registered – 1.2 times ($p<0.05$), with the presence of a probable difference between the groups with comorbidity and isolated course of CKD ($p<0.05$). That is, in patients with NASH with CKD, NFA acquired a compensatory maximum intensity ($p<0.05$). At the same time, there was a probable decrease in the activity of Hageman-dependent fibrinolysis: respectively, in patients with NASH – by 1.2 times, in patients with NASH with CKD – by 1.6 times, in patients with NASH – by 1.8 times, in the group patients with NASH with CKD – by 1.9 times, while in the group of patients with CKD, the decrease in the activity of Hagemann-dependent fibrinolysis (HDF) was 1.5 times ($p<0.05$) with the presence of a probable difference between groups with comorbidity and the isolated course of CKD ($p<0.05$). The activity of fibrin-stabilizing factor in patients with NASH and NASH with CKD decreased by 1.4 and 1.5 times, respectively ($p<0.05$), which indicates a violation of the postcoagulation phase of blood coagulation. In the groups of patients with NSAID, changes were unlikely, and in patients with NSAID with CKD and isolated CKD, the decrease was 1.2 times ($p<0.05$) (Table 1).

A probable decrease in PAP was found in patients with CKD: in patients with NASH – by 1.2 times, in patients with NASH with CKD – by 1.5 times, in patients with NASH – by 1.7 times, in patients with NASH with CKD – in 2.0 times, in the group with CKD without comorbidity – the decrease was 1.6 times ($p<0.05$) with the presence of a probable difference between the groups with comorbidity and the isolated course of CKD ($p<0.05$) (Table 1).

The results of the study of the factors of coagulation hemostasis, anticoagulation and fibrinolytic systems indicate the formation of a hypercoagulable syndrome in patients with NAFLD with obesity, which deepens with the addition of CKD.

To assess the dependence of disorders of hemostasis and fibrinolysis in patients with comorbid NAFLD, obesity, CKD, depending on the stage of CKD, a cluster analysis was performed, the results of which are shown in Table 2. Thus, in patients with NASP and CKD, depending on the stage of CKD, a probable decrease in PTT was established when progressing from II to III stage of CKD ($p<0.05$) (Table 2), a tendency to increase the content of fibrinogen in the blood ($p>0.05$), a probable decrease in the activity of AT III during the progression from II to III stage of CKD ($p<0.05$), a probable decrease in SFA and FFA during progression from II to III stage of CKD ($p<0.05$), which contributed to a significant probable increase in NFA from I to II and from II to III stage of CKD ($p<0.05$), inhibition of Hagemann-dependent fibrinolysis from II to III stage of CKD ($p<0.05$), a probable decrease in factor XIII activity during progression from II to III stage of CKD ($p<0.05$) and a significant decrease in PAP, which probably decreased from I to II and from II to III stages of CKD ($p<0.05$). The obtained results indicate a significant contribution of CKD to the formation of hemostasis disorders and, in general, to the pathogenesis of NASP progression against the background of obesity.

In patients with NASH and CKD, depending on the stage of CKD, there was a probable decrease in PTT with progression from II to III stage of CKD ($p<0.05$) (Table 2), an increase in the content of fibrinogen in the blood with progression from II to III stage of CKD ($p <0.05$), probable decrease in TT and AT III activity during progression from II to III stage of CKD ($p<0.05$), probable decrease in SFA during progression from II to III stage of CKD ($p<0.05$), which occurred due to a decrease in FFA from I to II stage and from II to III stage of CKD ($p<0.05$), which was accompanied by a probable increase in NFA from II to III stage of CKD ($p<0.05$), a probable decrease in the activity of factor XIII during progression from II to III stage of CKD ($p<0.05$) and a decrease in PAP, which also probably decreased from I to II, II to III stage of CKD ($p<0.05$).

The analysis of indicators of hemostasis and fibrinolysis in examined patients with NASH depending on the stage of CKD showed that as the stage of CKD increases, clotting activity increases, with the exception of fibrinogen content (most likely due to consumption coagulopathy), the activity of factors of the anticoagulation system decreases, the

Table 2

Changes in indicators of the hemostasis system and fibrinolysis in patients with non-alcoholic steatosis of the liver and steatohepatitis depending on the stage of CKD, (M±m)

Indexes, unit measurement	PHP (n=30)	Groups of examined patients					
		Patients with NSAID, CKD (n=110)			Patients with NASH, CKD (n=160)		
		I st. (n=45)	II st., (n=36)	III st. (n=29)	I st., (n=63)	II st., (n=52)	III st. (n=45)
PTT, s.	22,12± 0,46	16,94± 0,21*	16,63± 0,15*	14,89± 0,23*/**	11,82± 0,13*	11,43± 0,25*	11,03±0,16*/**
Fibrinogen, g/l	3,81± 0,12	3,14± 0,10 *	3,18± 0,07 *	3,26± 0,09*	1,72± 0,05*	1,86±0,09*	1,95±0,04*/**
TT, s	16,95± 0,87	12,44± 0,10*	12,32± 0,11*	12,23± 0,07*	10,65± 0,13*	10,26± 0,12 *	10,11± 0,07*/**
AT III, %	95,48± 2,01	84,15± 3,08*	78,31± 3,11*	70,45± 2,23*/**	71,58± 2,36*	68,25± 2,20*	59,96± 2,13*/**
SFA, E440/ ml/h	1,69± 0,02	1,49± 0,01*	1,47± 0,01*	1,43± 0,01*/**/***	1,39± 0,01*	1,38± 0,004*	1,35±0,01*/**/***
NFA, E440/ ml/h	0,49± 0,02	0,62± 0,002*	0,64± 0,002*/**	0,66± 0,001 */**/***	0,74± 0,004 *	0,76± 0,01*	0,79± 0,003*/**/***
FFA, E440/ ml/h	1,20± 0,01	0,87± 0,01*	0,85± 0,004*	0,82± 0,003*/**/***	0,66± 0,003*	0,63± 0,01*/**	0,59± 0,004*/**/***
HDF, min.	19,45± 0,19	28,14± 1,21 *	30,23± 1,09 *	34,21± 0,78*/**	36,16± 1,23*	38,32± 1,15*	39,36±1,11*
XIII factor, %	99,91± 2,45	86,14± 1,25*	83,40± 1,15*	79,52± 1,10*/**	69,54± 1,18*	68,28± 1,22*	62,82± 1,15 */**/***
PAP, min.	15,23± 0,27	21,43± 0,13*	22,28± 0,15*/**	23,42± 0,14*/**/***	29,46± 0,15*	30,18± 0,11*/**	30,93± 0,16*/**/***

Notes: 1.* – changes are probable in comparison with the indicator in PZO ($p<0.05$);
2.** – changes are probable in comparison with the indicator in the group of patients of the 1st stage of CKD ($p<0.05$);
3.*** – changes are probable in comparison with the indicator in the group of II stage CKD patients ($p<0.05$).

total and enzymatic activity of fibrinolysis decrease, and the non-enzymatic increases compensatory. The correlation analysis between hemostasis indicators and lipid homeostasis indicators indicates the presence of an inverse interdependence between the content of CH, TG, IA, leptin and the content of fibrinogen ($p<0.05$), the content of ATIII in the blood ($p<0.05$), factor XIII ($p<0.05$), SFA, FFA ($p<0.05$), PAP ($p<0.05$) (tables 6.3, 6.4). Correlation analysis between indicators of hemostasis and indicators of glucose homeostasis indicates the presence of an inverse interdependence between the content of postprandial glucose in the blood and PCT, the content of fibrinogen ($p<0.05$), ATIII ($p<0.05$), factor XIII ($p<0.05$), SFA, FFA ($p<0.05$), PAP ($p<0.05$).

The consequence of significant activation of hemocoagulation against the background of SFA suppression is local blood coagulation in the arteries. The function of Hageman-dependent fibrinolysis is to regularly rid the circulatory system of fibrin clots formed under conditions of inflammation. The results of our study indicate a decrease in the rate of enzymatic, Hageman-dependent fibrinolysis, which is the cause of compensatory activation of NFA. Slowing of blood circulation in the liver and kidneys due to the formation of microthrombi in the microcirculatory channel contributes to the deepening of hypoxia, the formation of ROS and free radicals, followed by damage to the cell membranes of hepatocytes, cytolysis, a decrease in GFR and the closing of the "vicious" circle of the pathogenesis of the progression of NAFLD and CKD.

Conclusions. Thus, metabolic intoxication, oxidative stress, which accompany the course of NAFLD under conditions of obesity and CKD, contribute to the activation of the kallikrein-kinin system, the formation of plasmin and thrombin with subsequent disruption of the balance between them, the development of stasis, the sludge phenomenon, the formation of platelet and erythrocyte aggregates in circulatory system.

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