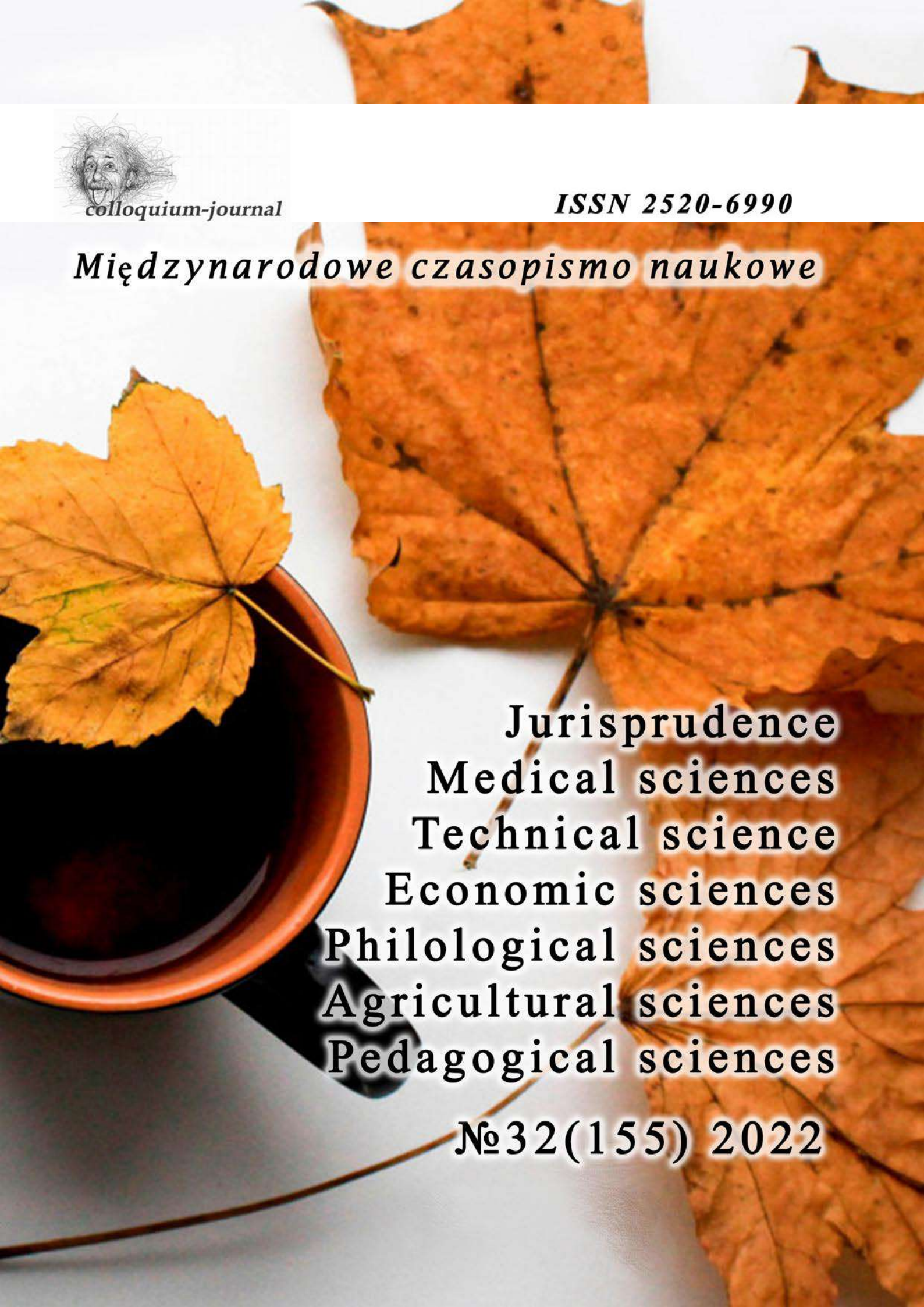

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THE ROLE OF HYDROGEN SULFIDE IN THE MECHANISMS OF MUTUAL BURDENING AND PROGRESSION OF NON-ALCOHOLIC FATTY LIVER DISEASE AND CHRONIC KIDNEY DISEASE

Антонів А.А.,
Каньовська Л.В,
Ніка В.В.
Буковинський державний медичний університет

РОЛЬ ГІДРОГЕН СУЛЬФІДУ В МЕХАНІЗМАХ ВЗАЄМООБТЯЖЕННЯ ТА ПРОГРЕСУВАННЯ НЕАЛКОГОЛЬНОЇ ЖИРОВОЇ ХВОРОБИ ПЕЧІНКИ ТА ХРОНІЧНОЇ ХВОРОБИ НИРОК

Abstract.

In patients with non-alcoholic steatohepatitis on the background of obesity and comorbidity with CKD I-II degree, the degree of fibrotic changes in the liver tissue according to the biochemical index of fibrosis exceeds those in patients with NASH without comorbid kidney disease.In patients with NASH, which arose on the background of obesity, a significant increase in the synthesis of collagen and glycoproteins (fibronectin) was observed, which was accompanied by an ineffective resorption of newly formed collagen due to inhibition of collagenolysis (CLA) on the background of activation of proteinase inhibitors (α2-MG), accompanied by hyperproduction fibroblast growth factor, homocysteine, endothelin-1, deficiency in the liberation of hydrogen sulfide and nitrogen monoxide. Under the conditions of the comorbidity of NASH from the CKN of the 1st and 2nd degrees, both collagen synthesis and resorption are activated, but the processes of anabolism prevail in spite of the compensatory activation of collagenolysis, with a significant hyperproduction of actinic-phase proteins, fibronectin, glycosaminoglycans, fibroblast growth factor and increased degradation of the extracellular matrix fucoglycoproteins and lead to progressive fibrosis of the liver and disturbance of its functions. The indicated dismetabolic manifestations of the comorbidity of NASH with CKD in a higher degree of interdependence correlate with manifestations of endothelial dysfunction (deficiency NO, hyperproduction of ET-1, homocysteine), dyslipidemia, and factors of regulation of fibrogenesis (hyperproduction of FGF and H2S deficiency).

Анотація.

У хворих на неалкогольний стеатогепатит на тлі ожиріння за коморбідності з ХХН I-II стадії ступінь фібротичних змін у печінковій тканині за біохімічним індексом фіброзу перевищує такі у хворих на НАСГ без коморбідної патології нирок.У хворих на НАСГ, що виник на тлі ожиріння, встановлено істотне підвищення синтезу колагену та глікопротеїнів (фібронектину), яке супроводжується неефективною резорбцією новоутвореного колагену внаслідок гальмування колагенолізу (КЛА) на тлі активації інгібіторів протеїназ (α2-МГ), що супроводжується гіперпродукцією фактора росту фібробластів, гомоцистеїну, ендотеліну-1, дефіцитом ліберації гідрогену сульфіду та монооксиду нітрогену. За умов коморбідності НАСГ із ХХН I-II ст. активуються і синтез, і резорбція колагену, але процеси анаболізму переважають, незважаючи на компенсаторну активацію колагенолізу, із істотнішою гіперпродукцією гострофазових білків, фібронектину, глікозаміногліканів, фактора росту фібробластів та підвищеною деградацією фукоглікопротеїнів позаклітинного матриксу і призводять до прогресуючого фіброзування печінки та порушення її функцій. Зазначені дисметаболічні прояви за коморбідності НАСГ із ХХН у вищому ступені взаємозалежності корелюють з проявами ендотеліальної дисфункції (дефіцит NO, гіперпродукція ET-1, гомоцистеїну), дисліпідемії та чинниками регуляції фіброгенезу (гіперпродукція ФРФ та дефіцит H2S).

Keywords: *nonalcoholic steatohepatitis, chronic kidney disease, hydrogen sulfide, proteolysis, functional state of the endothelium.*

Ключові слова*: неалкогольний стеатогепатит, хронічна хвороба нирок, гідроген сульфід, протеоліз, функціональний стан ендотелію.*

The steady increase in the frequency of cases of comorbid flow of non-alcoholic steatohepatitis (NASH) on the background of obesity and chronic kidney disease (CKD) in persons of working age in Ukraine and in the world [5, 6, 8] necessitates conducting research on mechanisms of mutual burden and the search for new factors of pathogenesis of progression of this comorbid pathology [2, 3, 4]. The role of hydrogen sulfide (H2S) in the development of fibrosis has only recently been noted. Studies have shown that H2S dose-dependent plays a role in the development of fibrosis in the lungs, liver, kidneys and myocardium [9,

10, 12]. The results of the researches show that the processes of fibrosing of organs in a strong interdependence correlate with the violation of the endogenous synthesis of H2S, and with the decrease in the activity of H2S-generating enzymes in plasma and directly in tissues [10, 11, 14]. Stimulation and recovery of exogenous H2S synthesis reduces the severity of fibrosis in various experimental animal models [12]. Animal models of fibrosis of various organs demonstrated a significant reduction in endogenous H2S levels in plasma and tissues, and inhibition of H2S-producing enzymes, while the introduction of exogenous H2S may inhibit the development of fibrosis [9, 13, 14]. Based on the established data, it will be possible to justify methods to correct the established disorders.

The aim of the study. To establish the role of hydrogen sulfide in the mechanisms of mutual burden and progression of non-alcoholic steatohepatitis and chronic kidney disease in patients with obesity based on the study of protein and carbohydrate-protein components of the extracellular matrix, proteinase-inhibitor system, lipid profile of the blood and the functional state of the endothelium.

Materials and methods of research. 114 patients with NASH were examined on the background of obesity of I-II degree, including: 52 patients with NASH (group 1) (without accompanying CKD), 62 patients with NASH with a comorbid CKD I-II degree (group 2). The average age of patients was (45.8 ± 3.81) years. The control group consisted of 20 practically healthy persons (PHPs) of the corresponding age and sex.

The diagnosis of NASH was established in accordance with a unified clinical protocol approved by the Ukranian Ministry Of Health, Order No. 826 dated on November 6, 2014, in the presence of criteria for the exclusion of chronic diffuse liver disease of viral, hereditary, autoimmune or medicinal origin as causes of cytolytic, cholestatic syndromes, as well as the results of the ultrasonography survey. Diagnosis and treatment of CKD were performed according to the recommendations of the clinical guidelines of the State Institute "Institute of Nephrology, NAMS of Ukraine" (2012). Changes in the metabolism of the components of the extracellular matrix were determined by the free oxyproline content in blood (FOP) by S.S. Tetyanets (1985) and protein-bound oxyproline (PBOP) by M.S. Osadchuk (1979), hexosamines (HA) by O.G. Arkhipova (1988), seromucoid (SM), sialic acids (SC) with the help of Danish Ltd (Lviv) kits, ceruloplasmin (CP) by the method of MR. Revina (1976). The content of the matrix metalloproteinase-1 (MMP-1) and the tissue inhibitor MMP-1 (TIMMP-1), the fibroblast growth factor (FGF), was determined by the enzyme-linked immunosorbent assay (ELISA) (DRG System). The content of H2S in blood was determined by the spectrophotometric method [25]. The state of proteolytic activity of blood plasma was studied by the total activity of blood serum proteinases - according to M. Kunitz (1975), the intensity of lysis of low molecular weight proteins (azo-albumin), macromolecular proteins (azocasein) and collagen (lysis of azocol) with the help of the Danish Ltd (Lviv) reagents. The state of the proteinase-inhibitor system was studied by the presence of α2-MG blood serum in the blood plasma α1-IP (Danish Ltd, Lviv).

The lipid profile of the blood was studied based on the content of common lipids, total cholesterol (TC), triacylglycerols (TG), low density lipoprotein cholesterol (LDL), high density lipoprotein (HDL), and atherogenicity index (AI). The functional state of the endothelium was studied by the content of the metabolites nitrogen monoxide (NO) (nitrites / nitrates), endothelin-1, homocysteine by the ELISA method (AXIS-SHIELD (Norway)) in the blood.

Statistical processing of the results of the research was carried out using parametric and nonparametric methods of variation statistics. The normal distribution was checked using the Shapiro-Uilka test and the method of direct visual evaluation of eigenvalues distribution histograms. Quantitative indices having a normal distribution are represented as mean (M) ± standard deviation (S). In a nonparametric distribution, the data is presented as median (Me) as position, upper (Q75) and lower quartile (Q25) as a measure of scattering. For comparisons of data that had a normal distribution pattern, parametric tests were used to estimate the Student's t-criterion, Fisher's F-criterion. To estimate the degree of dependence between variables, Pearson correlation analysis using parametric distribution and Spearman rank correlation coefficient were used. To compare discrete values in independent groups, the criterion $\chi 2$ of maximum probability (log-likelihood) (MP $\chi 2$) was used; for calculating the pairs of discrete values, the calculation of the modification of Fisher's exact criterion (mid-p) was used. The evaluation of treatment efficacy was based on the effects of treatment, absolute (AR) and relative (RR) therapeutic effects, therapeutic benefits - absolute risk difference (ARR), relative risk changes (RRR), as well as odds ratios (ORs), calculated confidence intervals and the criterion of reliability for RR and OR. Statistica for Windows version 8.0 (Stat Soft inc., USA), Microsoft Excel 2007 (Microsoft, USA) software packages were used for statistical and graphical analysis of the obtained results.

Results of the research and their discussion. The obtained results of researches indicate that the patients with NASH with CKD found significant activation of fibrous reactions. Thus, the average indicator of the total biochemical fibrotest in patients with NASH in group 1 exceeded the index in PHP by 1.6 times ($p < 0,05$), in group 2 by 2,6 times ($p < 0,05$) (Table 1) .

Table 1

Indicators of the connective tissue components state, proteolysis, functional state of the endothelium and their regulation in patients with non-alcoholic stethohepatitis, obesity and comorbidity with chronic kidney disease of the I-II stage

Indicators, units measurement	PHP (n=20)	Groups of patients surveyed	
		Group 1 (n=52)	Group 2 (n=62)
FibroTest, c.u.	0,18±0,01	0,29±0,02*	0,46±0,01 */**
PBOP, μmol/l	41,48±3,72	64,72±2,38*	83,50±3,73 */**
FOP, μmol/l	12,39±0,34	10,31±0,50 *	17,38±0,54 */**
HA, mmol/l	5,54±0,02	6,77±0,12*	8,52±0,27 */**
SC, mmol/l	1,92±0,02	2,42±0,03*	2,85±0,02 */**
collagenolysis, c.u.	0,84±0,01	0,73±0,01 *	0,93±0,01 */**
ceruloplasmin, mmol/l	12,63±0,12	17,86±0,52*	23,83±1,13 */**
fibronectin, μg/ml	334,94±12,04	424,21±13,35*	525,30±22,19 */**
α_2-MG, mmol/l	2,35±0,12	4,93±0,13*	6,34±0,14 */**
FGF, nmol/l	17,92±1,07	36,13±2,52 *	53,23±2,29 */**
lysis AA, E440/ml×hour	2,41±0,02	3,65±0,03 *	3,99±0,02 */**
H2S, μmol/l	74,2±3,1	43,7±2,4 *	23,5±1,7 */**
Homocysteine, μmol/l	9,9±0,42	30,6±1,04 *	62,8±1,97 */**
NO, μmol/l	17,62±1,43	9,54±0,53 *	7,12±0,38 */**
ET-1, pmol/l	6,01±0,94	13,27±1,02 *	15,25±0,76 */**
Note: * - changes are probable compared to the index in the PHP (P <0,05); ** - changes are probable in comparison of indicators in patients of group 1 (P <0,05).			

The analysis of the intensity of fibrous reactions in patients with NASH, depending on the presence of a comorbid CKD, indicates a probable increase in the content of PBOP in the blood of patients in group 1 - 1.6 times in comparison with PHP (p <0.05), in patients with group 2 - in 2, 0 times (p <0.05). At the same time, the index of blood in the blood of the FOP (Table 1), which is the biochemical marker of collagen catabolism, in patients with NASH in group 1 was 1.2 times lower than that in PHP (p <0.05). At the same time, in group 2 patients, the FOP content in the blood exceeded the data in the PHP by 1.4 times (p <0.05), indicating an increase in collagen degradation in the background of its high synthesis.

In patients of the group 2, a reliable increase in blood collagenolysis was found, the intensity of which exceeded the index in PHP by 10.7% (p <0.05), in patients of group 1 - collagenolysis was reduced by 13.1% (p <0.05) with the presence of a probable intergroup difference (p <0,05). We determined the probable increase in the content of α2-MG in the blood of patients in group 2 (2.7 versus 2.1 in patients in group 1, p <0.05).

Indicators of ceruloplasmin content indicate a probable increase in patients in all groups of observation (p <0.05) with a probable prevalence in patients with group 2 (1.9 versus 1.4 times in group 1, p <0.05). The content of fibronectin in the blood was elevated in patients with the group 2 (1.6 times, p <0.05), whereas in patients with 1 group its growth was 1.4 times (p <0.05) in comparison with indicator in PHP. The established disturbances in the balance of collagen catabolism analysis were accompanied by a significant increase in the content of FGF in the blood - 3.1 times in group 2, compared with 2.1 times in group 1, p <0.05). This phenomenon explains the induction of the phenomenon of "sinusoidal capillarisation" in patients with NASH with the activation of peri-sinusoidal star-shaped Ito cells, their transformation into myofibroblast-like cells with hyperproduction of collagen in the Disse space, the development of fibrosis against the background of aseptic inflammation around dystrophitically altered (steatosis) hepatocytes, narrowing of sinusoids and formation progressive portal circulation disorder [3, 4, 6, 15, 34]. As the data show, for the comorbidity of NASH, obesity with CKD, these phenomena are more pronounced and increase faster in comparison with the course of NASH only against the background of obesity. The intensity of lysis of low molecular weight proteins also in patients in group 2 was higher: respectively 1.7 times against 1.5 times in patients in group 1 (p <0.05). The content of H2S in blood in patients of both groups was reduced: 1.7 times and 3.2 times, respectively (p <0.05) compared to the PHP index. Indicators of the functional state of the endothelium indicate its significant dysfunction: blood NO content was significantly reduced in patients of both groups with a significant deficit in patients of group 2 : 2.5 times versus 1.8 times in group 1 (p <0.05) , the content of the ET-1 in blood, on the contrary, exceeded the index in PHP by 2.2 and 2.5 times, respectively (p <0.05), indicating a significant predominance of vasoconstrictors and a deficiency of the endothelie releasing factor and contributing to hypoxia, ischemia of the liver and kidney parenchyma, and are additional factors of damage due to oxygen and energy starvation [14, 21, 24]. The content of homocysteine in the blood increased significantly in patients of both groups, respectively, in 3,1 and 6,4 times (p <0,05), that in patients of group 2 in strong interdependence (r =0,65-0,85, p <0,05)) correlated with the parameters of hyperlipidemia: TCH, TG, CH LDL, AI (p <0.05) and endothelial dysfunction: NO (r = -0.74, p <0.05), ET-1 (r = 0.63, p <0.05), as well as with H2S content (r = -0.79, p <0.05).

The interdependence of the above mentioned changes in homeostasis indices of the components of the connective tissue extracellular matrix and the content of H2S in blood confirms the existence of established correlation relationships (Table 2).

Table 2

The matrix of correlation relations between the content of the extracellular matrix components, proteolysis, collagenolysis and indicators of the functional state of the liver, the lipid profile of the blood, the functional state of the endothelium, and the content of hydrogen sulfide in the blood of patients with non-alcoholic steatohepatitis with CKD (r, p)

Indicators	AST	ALT	GGT	TC	TG	LDL	H2S	Homocysteine	NO	ET-1
FOP	0,39*	0,43*	0,10	0,33*	0,35*	0,38*	-0,59*	0,43 *	-0,34*	0,22
PBOP	0,46*	0,53*	0,54*	0,39*	0,42*	0,51*	-0,67*	0,65*	-0,57*	0,53*
HA	0,34*	0,37*	0,23	0,16	0,15	0,18	-0,53*	0,54*	-0,38*	0,43*
SC	0,51*	0,55*	0,36*	0,20	0,22	0,25	-0,57*	0,58*	-0,31*	0,37*
fibronectin.	0,53*	0,59*	0,43*	0,37*	0,32*	0,38*	-0,68*	0,63*	-0,45*	0,33*
Lysis AA	0,44*	0,45*	0,21	0,17	0,09	0,11	-0,44*	0,24	-0,37*	0,34*
CLA	0,41*	0,45*	0,32*	0,21	0,17	0,08	-0,43*	0,27	-0,33*	0,37*
MMP-1	0,44*	0,47*	0,38*	0,19	0,16	0,13	-0,49*	0,19	-0,35*	0,36*
FGF	0,49*	0,57*	0,54*	0,41*	0,47*	0,53*	-0,75*	0,66*	-0,58*	0,57*

Note: * - statistically significant correlation coefficient ($p < 0,05$).

Under the conditions of the deficit of H2S and hyperproduction of homocysteine for the comorbidity of NASH with CKD I-II degree, the synthesis and resorption of collagen are activated, but the anabolism processes are dominated by the activation of the fibroblast system, hyperproduction of the FGF, with a significant hyperproduction of the acute phase proteins, fibronectin, GA, and an increased degradation of extracellular matrix fucoglycoproteins, a higher degree of hyperthyroidism and dyslipidemia with a predominance of proatherogenic fractions of lipoproteins, an increase in AI $p < 0.05$), the highest degree of endothelium dysfunction (NO deficiency and ET-1 deficiency ($p < 0.05$)). The protective role of H2S in the progression of fatty liver disease is due to its antioxidant, antiapoptotic, anti-inflammatory, vasodilatory and antihypoxant effects, the ability to stimulate angiogenesis, reduce the content of proatherrogenic lipoproteins in the bloodstream and inhibit the activity of fibroblasts [3, 9, 10].

All of the above factors are likely risk factors and direct links in the pathogenesis of the progression of NASH and the CKD [3, 4, 5, 6, 7, 8, 13, 14, 15, 19, 20, 23], which need to be influenced by adequate medication support [3].

Conclusions.

In patients with non-alcoholic steatohepatitis on the background of obesity and comorbidity with CKD I-II degree, the degree of fibrotic changes in the liver tissue according to the biochemical index of fibrosis exceeds those in patients with NASH without comorbid kidney disease.In patients with NASH, which arose on the background of obesity, a significant increase in the synthesis of collagen and glycoproteins (fibronectin) was observed, which was accompanied by an ineffective resorption of newly formed collagen due to inhibition of collagenolysis (CLA) on the background of activation of proteinase inhibitors (α2-MG), accompanied by hyperproduction fibroblast growth factor, homocysteine, endothelin-1, deficiency in the liberation of hydrogen sulfide and nitrogen monoxide. Under the conditions of the comorbidity of NASH from the CKN of the 1st and 2nd degrees, both collagen synthesis and resorption are activated, but the processes of anabolism prevail in spite of the compensatory activation of collagenolysis, with a significant hyperproduction of actinic-phase proteins, fibronectin, glycosaminoglycans, fibroblast growth factor and increased degradation of the extracellular matrix fucoglycoproteins and lead to progressive fibrosis of the liver and disturbance of its functions. The indicated dismetabolic manifestations of the comorbidity of NASH with CKD in a higher degree of interdependence correlate with manifestations of endothelial dysfunction (deficiency NO, hyperproduction of ET-1, homocysteine), dyslipidemia, and factors of regulation of fibrogenesis (hyperproduction of FGF and H2S deficiency).

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