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FEATURES OF THE NONALCOHOLIC STEATOHEPATITIS AND CHRONIC KIDNEY DISEASE COURSES, PATHOGENETIC CORRECTION EFFICIENCY

O.S. Khukhlina[1], A.A. Antoniv[1],O.Ie. Mandryk[1], O.B. Kuzminska[2], I.V. Dudka[1], T.V. Dudka[1]

[1]Higher State Educational Institution of Ukraine «Bukovinian State Medical University» , Chernivtsi, Ukraine
[2]Chernivtsi Emergency Medicine Hospital , Chernivtsi, Ukraine

Key words: *nonalcoholic steatohepatitis, chronic kidney disease, obesity, hydrogen sulfide, functional state of the endothelium.*

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E-mail:
oksanakhukhlina@gmail.com., antonivalona@ukr.net., quovadis@email.ua.

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The aim of the study. *To establish the mechanisms of mutual burden and progression of non-alcoholic steatohepatitis (NASH) and chronic kidney disease (CKD) in patients with obesity.*

Material and methods. *114 patients with NASH were examined against the background of I-II degree obesity, 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.*

Results. *The obtained data testify that under the conditions of the H2S deficit and hyperproduction of homocysteine for the comorbidity of NASH from CKD I-II degree the synthesis and resorption of collagen are activated, but the anabolism processes predominate as a result of the activation of the fibroblasts system, with a significant hyperproduction of acute phase proteins, fibronectin, a higher degree of hyperthyroidism and dyslipidemia with predominance of proatherogenic lipoprotein fractions, and a higher degree of endothelium dysfunction.*

Conclusions. *A significant increase in the synthesis of collagen and glycoproteins (fibronectin) in patients with NASH, which was observed on the background of obesity, was established, which is accompanied by an ineffective resorption of newly formed collagen due to inhibition of collagenolysis against activation of proteinase inhibitors (α2-MG), accompanied by hyperproduction of the fibroblast growth factor, homocysteine, endothelin-1, deficiency in the liberation of hydrogen sulfide and nitrogen monoxide.*

Ключові слова: *неалкогольний стеатогепатит, хронічна хвороба нирок, ожиріння, сірководень, функціональний стан ендотелію.*

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ОСОБЛИВОСТІ ПЕРЕБІГУ НЕАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТУ ТА ХРОНІЧНОЇ ХВОРОБИ НИРОК, ЕФЕКТИВНІСТЬ ПАТОГЕНЕТИЧНОЇ КОРЕКЦІЇ

О.С. Хухліна, А.А. Антонів, О.Є. Мандрик , О.Б. Кузьмінська, І.В. Дудка, Т.В. Дудка

Мета дослідження *— встановити механізми взаємообтяження та прогресування неалкогольної жирової хвороби печінки та хронічної хвороби нирок у хворих на ожиріння та підвищити ефективність комплексного лікування за даної поліморбідності.*

Матеріал і методи. *Обстежено 114 хворих на неалкогольний стеатогепатит (НАСГ) на тлі ожиріння I-II ступеня, у тому числі: 52 хворих на НАСГ (1-ша група) (без супровідної ХХН), 62 хворих на НАСГ із коморбідною ХХН I-II ст. (2-га група). Середній вік пацієнтів склав (45,8±3,81) років. Контрольну групу склали 20 практично здорових осіб (ПЗО) відповідного віку та статі.*

Результати дослідження та їх обговорення. *Отримані дані свідчать про те, що за умов дефіциту H2S та гіперпродукції гомоцистеїну за коморбідності НАСГ із ХХН I-II ст. активуються і синтез, і резорбція колагену, але процеси анаболізму переважають внаслідок активації сис-*

теми фібробластів, гіперпродукції гострофазових білків, фібронектину, вищим ступенем гіпер- та дисліпідемії з переважанням проатерогенних фракцій ліпопротеїнів, вищим ступенем дисфункції ендотелію.

Висновки. *У хворих на неалкогольний стеатогепат, що виник на тлі ожиріння, встановлено істотне підвищення синтезу колагену та глікопротеїнів (фібронектину), яке супроводжується неефективною резорбцією новоутвореного колагену внаслідок гальмування колагенолізу на тлі активації інгібіторів протеїназ (α2-макроглобулінів), що супроводжується гіперпродукцією фактора росту фібробластів, гомоцистеїну, ендотеліну-1, дефіцитом ліберації гідрогену сульфіду та монооксиду нітрогену.*

Ключевые слова: *неалкогольный стеатогепатит, хроническая болезнь почек, ожирение, сероводород, функциональное состояние эндотелия.*

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ОСОБЕННОСТИ ТЕЧЕНИЯ НЕАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТА И ХРОНИЧЕСКОЙ БОЛЕЗНИ ПОЧЕК, ЭФФЕКТИВНОСТЬ ПАТОГЕНЕТИЧЕСКОЙ КОРРЕКЦИИ

О.С. Хухлина, А.А. Антонив, О.Е. Мандрик, О.Б. Кузминская, И.В. Дудка, Т.В. Дудка

Цель исследования *– определить механизмы взаимообтяжения и прогрессирования неалкогольной жировой болезни печени и хронической болезни почек у больных ожирением и повысить эффективность комплексного лечения при данной полиморбидности.*

Материал и методы. *Обследовано 114 больных неалкогольным стеатогепатитом (НАСГ) на фоне ожирения I-II степени, в том числе 52 больных НАСГ (1-ая группа) (без сопроводительной ХБП), 62 больных НАСГ с коморбидной ХБП I-II ст. (2-ая группа). Средний возраст пациентов составил (45,8±3,81) лет. Контрольную группу составили 20 практически здоровых лиц (ПЗЛ) соответствующего возраста и пола.*

Результаты исследования и их обсуждение. *Полученные данные свидетельствуют о том, что в условиях дефицита H2S и гиперпродукции гомоцистеина при коморбидности НАСГ с ХБП I-II ст. активируются и синтез, и резорбция коллагена, но анаболические процессы преобладают в результате активации фибробластов, гиперпродукции острофазовых белков, фибронектина, высокой степенью гипер- и дислипидемии с преобладанием проатерогенных фракций липопротеинов, высокой степенью дисфункции эндотелия.*

Выводы. *У больных неалкогольным стеатогепатитом, возникшим на фоне ожирения, установлено существенное повышение синтеза коллагена и гликопротеинов (фибронектин), которое сопровождается неэффективной резорбцией вновь образованного коллагена вследствии торможения колагенолиза на фоне активации ингибиторов протеиназ (α2-макроглобулина), что сопровождается гиперпродукцией фактора роста фибробластов, гомоцистеина, эндотелина-1, дефицитом либерации водорода сульфида и оксида азота.*

Relevance of the problem. The steady increase in the frequency of cases of comorbid flow of non-alcoholic steatohepatitis (NASH) against the background of obesity and chronic kidney disease (CKD) in persons of working age in Ukraine and in the world [1-8] necessitates conducting research on mechanisms of mutual burden and the search for new factors of pathogenesis of progression of this comorbid pathology [1-5, 7, 8]. 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 [5, 7, 8]. 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 [1-4, 5].

Liver fibrosis is a dynamic process that occurs in

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).			

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).										

response to various stimulators, which leads to the destruction of the architecture of the liver parenchyma, with subsequent excessive deposition of the components of the extracellular matrix (ECM), the formation of fibrous tissue, and pathological regeneration with the formation of cirrhosis (the final pathological stage of liver fibrosis)

[1-3, 9]. In patients with cirrhosis of the liver significant inhibitory expression / activity of CBS and CSE and decreased levels of H2S in plasma [2, 5, 7, 10].

The aim of the study. To establish mechanisms of mutual burden and progression of non-alcoholic fatty liver disease and chronic kidney disease in patients with obesity and to increase the efficiency of complex treatment for this polymorbidity.

Material and methods. 114 patients with NASH were examined against 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. patients with NASH with CKD group 2A (30 patients) received S-adenosylmethionine (600 mg Agepta) by sublingual administration for 90 days. Patients with NASH with a comorbid flow of obesity and CKD of I-II degree group 2B (32 patients), except S-adenosylmethionine (600 mg Agepta, sublingual), received meldonium (500 mg vasonate) enterally for 90 days. The examinations were carried out prior to treatment and on the 90th day of treatment.

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 [11]. 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 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.

Results of the research and their discussion. 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, $p < 0.05$).

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 [5, 7, 8, 11]. The content of homocysteine in the blood increased significantly in patients of both groups, respec-

Table 3

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

Indicators, units measurement	Groups of patients surveyed			
	PHP	Group 2A before treatment	Group 2A after treatment	Group 2B before treatment
FibroTest, c.u.	0,18±0,01	0,46±0,02*	0,28±0,01 */**	0,45±0,01 *
PBOP, μmol/l	41,48±3,72	84,52±3,38*	56,25±2,27 */**	83,50±3,73 *
FOP, μmol/l	12,39±0,34	17,35±0,57 *	14,31±0,48 */**	17,38±0,54 *
HA, mmol/l	1,92±0,02	2,83±0,02 *	2,24±0,03 */**	2,85±0,02 *
SC, mmol/l	0,84±0,01	0,92±0,02 *	0,86±0,02	0,93±0,02 *
fibronectin, μg/ml	334,94±12,04	525,30±22,19 *	395,48±8,56 **	527,42±20,31*
FGF, nmol/l	17,92±1,07	53,30±2,23 *	33,27±2,15 */**	53,23±2,29 *
lysis AA, E440/ ml×hour	2,41±0,02	3,99±0,02 *	3,34±0,02 */**	3,99±0,02 *
α2-MG, mmol/l	2,35±0,12	6,34±0,12 *	4,23±0,11 */**	6,35±0,14 *
H2S, μmol/l	74,21±3,15	23,52±1,76 *	63,75±1,38 */**	23,51±1,73 *
Homocysteine, μmol/l	9,9±0,52	62,8±1,97 *	27,3±0,64 */**	62,4±1,93 *
NO, μmol/l	17,62±1,43	7,12±0,38 *	9,23±0,45 */**	7,13±0,35 *
ET-1, pmol/l	6,01±0,94	15,25±0,76 *	12,17±0,62 */**	15,25±0,76 *

Notes: * - changes are probable in comparison with the index in PHP (P <0,05);
** - changes are probable when comparing indicators in patients before treatment (P <0.05);
# - changes are possible when comparing indicators after treatment in patients with group 2A (P <0.05).

tively, 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). The obtained data indicate that in patients with NASH, which arose on the background of obesity, a significant increase in the synthesis of collagen and glycoproteins was observed in the comorbidity with CKD, which was accompanied by an ineffective resorption of newly formed collagen due to insufficient activation of collagenolysis and proteolysis, a significant imbalance in the metabolism system of the connective tissue, which leads to progressive fibrosis of the liver and kidneys and the violation of their functions. This contributed to the violation of homeostasis H2S, confirming the data of the correlation analysis (table 2). 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 [2, 8].

All of the above factors are likely risk factors and direct links in the pathogenesis of the progression of NASH and the CKD [2-7], which need to be influenced by adequate medication support [2].

The administration of the drug ademetionin in the complex therapy showed the effect presence of this drug on a significant correction of the revealed disorders of H2S homeostasis and components of extracellular matrix (table 3). Thus, the average index of fibrotest in patients with NASH in group 2A after treatment decreased by 1.6 times (p <0.05), in the group 2B — 2.3 times (p <0.05).

The content of fibronectin in the blood decreased —

correspondingly in 1,3 and 1,6 times (p <0,05). We have established the significant effect of ademetionin on the content of FGF in the blood, respectively, in the group 2A after treatment in 1.6 times, in the group 2B — in 2.5 times (p <0.05). The content of SC in the blood of patients after treatment decreased by 1.3 and 1.4 times (p <0.05), respectively, however, normative indicators reached only in the group 2B. Indicators of the intensity of degradation of fucoglycoproteins decreased in both groups, respectively, in 1,4 and 1,8 times (p <0,05) with normalization of the indicator only in patients in group 2B. Thus, we have established a significant corrective effect of ademetionin on the extracellular matrix metabolic rate of liver connective tissue for comorbidity with CKD, which proved to be a decrease in the index of liver fibrosis by 1.6-2.3 times (p <0.05).

Another factor that has recently been recognized as a regulator of connective tissue metabolism, which is actively opposed to organ fibrosis by the inflammatory process, is the H2S molecule [10]. Under the influence of treatment with ademetionin in patients with NASH and CKD, we found a significant increase in H2S content in the blood compared with the indicator before treatment: in group 2A — 2.7 times (p <0.05). In patients in group 2B, the growth was 3.1 with a normalization of the index (p <0.05), indicating a higher efficiency of the ademetionin complex with meltedon for restoring the regulatory role of H2S with the inhibition of fibrotic processes.

It is known that vasoconstriction and hypoxia are the leading factors in fibrogenesis, so it is possible that reduced NO production promotes fibrosis in the liver and kidney tissue. The use of the complex of ademetionin and meltedonium contributed to a possible restoration of the synthesis and liberation of the endothelial cells of the endothelium with the elimination of the manifestations of endothelial dysfunction: an increase of 2.4 times with the normalization of the index — compared with 1.3 times in the treatment with ademetionin alone (p <0.05).

It is known that the deficiency of H2S in a strong interdependence correlates with the excess of homocysteine, which acts vasoconstrictor effect due to the blocking of acetylcholine-dependent vessel relaxation, inhibiting the transport of arginine and inhibiting NO synthesis [6,8]. Pathogenetic explanation for the data obtained may be provided by the results of a study of the homocysteine content in the blood in the dynamics of treatment with ademetioninum and meltedonium (2B) compared with baseline treatment in combination with ademetionum (2A). According to the data obtained, the increase in the content of homocysteine in the treatment of patients in the group 2A decreased to 2.3 times, and in patients in group 2B — 3.9 times (p <0.05) (Table 3). At the same time, the index of ET-1 in the blood in group 2A patients after treatment decreased by 1.3 times, and in patients in group 2B — by 2.1 times (p <0.05) with normalization of the indicator (p> 0, 05) and the difference with the indicator after treatment in group 2A (p <0,05).

In our opinion, the proposed complex therapy with the inclusion of antioxidant, antihypoxant, detoxification, membrane stabilizing, active metabolic and energotonic action [2] contributed to the stabilization of the extracellular components of liver, the normalization of the collagenolysis activity and the restoration of the collagen homeostasis balance in the body of patients with obesity and CKD.

Conclusions

1.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 with CKD 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).

2.Treatment using ademetionina in combination with meldonium for 3 months helped to balance the homeostasis of liver extracellular matrix components by stabilizing the membranes of hepatocytes, inhibition of the inhibitors of collagenolysis and proteolysis activity, reduce degradation of fucoglycoproteins, secretion of fibroblast growth factor and homocysteine restoring pool of hydrogen sulfide and monoxide nitrogen, which contributed a significant decrease in the index of liver fibrosis and warned the progression of comorbid diseases.

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Відомості про авторів

Хухліна О. С.— доктор медичних наук, професор, завідувач кафедри внутрішньої медицини, клінічної фармакології та професійних хвороб Вищого державного навчального закладу України «Буковинський державний медичний університет», м. Чернівці, Україна.

Антонів А. А.— кандидат медичних наук, асистент кафедри внутрішньої медицини, клінічної фармакології та професійних хвороб, Вищого державного навчального закладу України «Буковинський державний медичний університет», м. Чернівці, Україна.

Мандрик О. Є.— кандидат медичних наук, ассистент кафедри внутрішньої медицини, клінічної фармакології та професійних хвороб, Вищого державного навчального закладу України «Буковинський державний медичний університет», м. Чернівці, Україна.

Кузьмінська О. Б.— лікар-гастроентеролог ОКУ «Лікарня швидкої медичної допомоги» м. Чернівці, Україна; здобувач каф. внутрішньої медицини, клінічної фармакології та професійних хвороб Вищого державного навчального закладу України «Буковинський державний медичний університет», м. Чернівці, Україна.

Дудка І. В.— кандидат медичних наук, доцент кафедри внутрішньої медицини, клінічної фармакології та професійних хвороб Вищого державного навчального закладу України «Буковинський державний медичний університет», м. Чернівці, Україна.

Дудка Т. В.— кандидат медичних наук, ассистент кафедри внутрішньої медицини, клінічної фармакології та професійних хвороб Вищого державного навчального закладу України «Буковинський державний медичний університет», м. Чернівці, Україна.

Сведения об авторах:

Хухлина О. С.— доктор медицинских наук, профессор, заведующая кафедрой внутренней медицины, клинической фармакологии и профессиональных болезней Высшего государственного учебного заведения Украины «Буковинский государственный медицинский университет», г. Черновцы, Украина

Антонив А. А. — кандидат медицинских наук, ассистент кафедры внутренней медицины, клинической фармакологии и профессиональных болезней Высшего государственного учебного заведения Украины «Буковинский государственный медицинский университет», г. Черновцы, Украина. Ел. почта: antonivalona@ukr.net.

Мандрик О. Е.— кандидат медицинских наук, ассистент кафедры внутренней медицины, клинической фармакологии и профессиональных болезней Высшего государственного учебного заведения Украины «Буковинский государственный медицинский университет», Черновцы, Украина

Кузминская О. Б.— врач-гастроэнтеролог ОКУ «Больница скорой медицинской помощи» г. Черновцы, Украина; соискатель каф. внутренней медицины, клинической фармакологии и профессиональных болезней Высшего государственного учебного заведения Украины «Буковинский государственный медицинский университет», г. Черновцы, Украина

Дудка И. В.— кандидат медицинских наук, доцент кафедры внутренней медицины, клинической фармакологии и профессиональных болезней Высшего государственного учебного заведения Украины «Буковинский государственный медицинский университет», Черновцы, Украина.

Дудка Т. В.— кандидат медицинских наук, ассистент кафедры внутренней медицины, клинической фармакологии и профессиональных болезней Высшего государственного учебного заведения Украины «Буковинский государственный медицинский университет», Черновцы, Украина.

Information about the authors:
Khukhlina O. S.— Dr. of med. sc., professor, head of the department of Internal Medicine, Clinical Pharmacology and Occupational Diseases at Higher Educational Institution of Ukraine «Bukovinian State Medical University», Chernivtsi, Ukraine.
Antoniv A. A.— PhD, assistant professor of the department of Internal Medicine, Clinical Pharmacology and Occupational Diseases, Higher Educational Institution of Ukraine «Bukovinian State Medical University», Chernivtsi, Ukraine.
Mandryk O. Ie.— PhD, assistant professor of the department of Internal Medicine, Clinical Pharmacology and Occupational Diseases, Higher Educational Institution of Ukraine «Bukovinian State Medical University», Chernivtsi, Ukraine.
Kuzminska O. B.— Gastroenterologist, Chernivtsi Emergency Medicine Hospital, Applicant of the Department of Internal Medicine, Clinical Pharmacology and Occupational Diseases, Higher Educational Institution of Ukraine «Bukovinian State Medical University», Chernivtsi, Ukraine.
Dudka I. V.— PhD, associate professor of the department of Internal Medicine, Clinical Pharmacology and Occupational Diseases, Higher Educational Institution of Ukraine «Bukovinian State Medical University», Chernivtsi, Ukraine.
Dudka T. V.— PhD, assistant professor of the department of Internal Medicine, Clinical Pharmacology and Occupational Diseases, Higher Educational Institution of Ukraine «Bukovinian State Medical University», Chernivtsi, Ukraine.

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