DOI 10.26724/2079-8334-2022-3-81-76-82
UDC 616.36-003.826-06:616.12-008.331.1

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QUERCETIN EFFECTIVENESS IN THE COMPLEX HYPOLIPIDEMIC THERAPY OF PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE WITH METABOLIC SYNDROME

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86 patients with metabolic syndrome and comorbid nonalcoholic fatty liver disease were carried out general clinical and laboratory-instrumental examinations. After registration of the initial data, the patients were divided into 2 groups: 41 patients with the use of rosuvastatin were added quercetin 40 mg 3 times a day for 3 months to the basic therapy (group 1). The basic therapy with rosuvastatin only was carried out in 45 patients (group 2). After the treatment on the 90th day, positive changes in lipid metabolism were registered in all the patients. The group 2 patients had a decrease in the level of low-density lipoproteins by 21.2 % ($p<0.05$), an increase in high-density lipoproteins by 43.3 % ($p<0.05$). The liver transaminase activity was lower by 15.0 %, concentration of pro-inflammatory interleukin-6 and cytokeratin-18 – by 10.0 % ($p>0.05$). In patients of the group 1 the level of low-density lipoproteins decreased by 39.5 % ($p<0.05$), the triglycerides – twice, activity of transaminase – by 30.0 % ($p<0.05$). The high-density lipoproteins level increased by 72.0 % ($p<0.05$). Interleukins and cytokeratin-18 concentration reliably decreased by 23.0 % ($p<0.05$) ($p=0.001$). It was found that the comorbid course of the nonalcoholic fatty liver disease is accompanied by an increase in the oxidative stress intensity, which is determined by increased level in the blood of the end products of lipid peroxidation – malondialdehyde – on average 3.8 times ($p<0.05$). The use of quercetin in the complex therapy of the nonalcoholic fatty liver disease contributes to a reliable reduction in the oxidative stress intensity, an increase in the antioxidant protection activity (superoxide dismutase), the consequence of which is a significant reduction in the hepatocytes apoptosis process (decrease in cytokeratine-18 level 1.27 times as much).

Key words: metabolic syndrome, nonalcoholic fatty liver disease, hypolipidemic therapy, quercetin, inflammation.

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ЕФЕКТИВНІСТЬ ЗАСТОСУВАННЯ КВЕРЦЕТИНУ У КОМПЛЕКСНІЙ ГІПОЛІПІДЕМІЧНІЙ ТЕРАПІЇ ХВОРИХ НА НЕАЛКОГОЛЬНУ ЖИРОВУ ХВОРОБУ ПЕЧІНКИ ПРИ МЕТАБОЛІЧНОМУ СИНДРОМІ

Проведено загально клінічні та лабораторно-інструментальні обстеження 86 пацієнтів з метаболічним синдромом і коморбідним захворюванням на неалкогольну жирову хворобу печінки. Після реєстрації вихідних даних, хворих поділили на 2 групи: до базисної терапії 41 пацієнтам із застосуванням розувастатину додавали кверцетин 40 мг 3 рази на день протягом 3 місяців (1 група). Базисну терапію тільки розувастатином проводили у 45 хворих (2 група). Після лікування на 90-у добу у всіх пацієнтів були зареєстровані позитивні зміни в обміні ліпідів. У пацієнтів 2 групи було виявлено зменшення рівня ліпопротеїнів низької щільності на 21,2 % ($p<0,05$), підвищення ліпопротеїнів високої щільності на 43,3 % ($p<0,05$). Активність печінкових трансаміназ зменшувалась на 15 %, концентрація прозапального інтерлейкіну IL-6 та цитокератину-18 на 10,0 % ($p>0,05$). У пацієнтів першої групи рівень ліпопротеїнів низької щільності зменшився на 39,5 % ($p<0,05$), вміст тригліцеридів у 2 рази, активність трансаміназ на 30 % ($p<0,05$). Рівень ЛПВЩ підвищувався на 72,0 % ($p<0,05$). Концентрація інтерлейкінів і цитокератину-18 достовірно зменшилась на 23,0 % ($p<0,05$). Встановлено, що коморбідний перебіг неалкогольної жирової хвороби печінки супроводжується зростанням інтенсивності оксидативного стресу, який визначається підвищеним вмістом в крові кінцевих продуктів пероксидного окислення ліпідів – МДА в середньому у 3,8 рази ($p<0,05$). Застосування кверцетину у комплексній терапії неалкогольної жирової хвороби печінки сприяє вірогідному зниженню інтенсивності оксидативного стресу, підсиленню активності антиоксидантного захисту (супероксиддисмутази), наслідком чого є істотне зниження процесу апоптозу гепатоцитів (зниження вмісту цитокератину-18 у 1,27 рази).

Ключові слова: метаболічний синдром, неалкогольна жирова хвороба печінки, гіполіпідемічна терапія, кверцетин, запалення.

The study is a fragment of the research project "Comorbid conditions in patients with metabolic syndrome: familial hypercholesterolemia, fatty hepatosis, periodontopathies (pathogenesis, diagnosis, correction)", state registration number 0121U00263

The prevalence of the metabolic syndrome (MS), which is associated with a subclinical damage to vital organs, is increasing. Defects in lipid and carbohydrate metabolism are extremely widespread components of the MS pathogenesis, which cause disorders in the cells, tissues, and organs. The liver plays a key role in lipid and carbohydrate metabolism disorder. It was established that insulin resistance against the MS background induces the accumulation of lipids in hepatocytes, increasing the liver susceptibility. Systemic inflammation taking place against the background of lipids accumulation in the liver tissues with MS causes its damage, inflammation, and fibrosis [6, 8]. The frequent incidence of the nonalcoholic fatty liver disease (NAFLD) in patients with MS with the development of inflammation in the liver tissue, which occurs under the oxidative stress influence, substantiates a necessity of using antioxidant drugs that would

affect the main pathogenetic components of the disease development. So, a special attention in the management of patients with NAFLD against the MS background is drawn to a possibility of using plant antioxidants capable of correcting indicators of oxidative stress, inflammation, in particular, compounds from the flavonoids series, such as quercetin.

The purpose of the study was to improve the efficacy of therapy in patients with nonalcoholic fatty liver disease and metabolic syndrome.

Material and methods. 86 patients (average age 46+8 years) with metabolic syndrome were examined. The metabolic syndrome was diagnosed according to the Metabolic Syndrome Consensus [5].

All the examined patients underwent a general clinical examination, which included the anamnestic data collection, physical examination, laboratory (clinical blood and urine analysis, biochemical tests of the blood serum: liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGTP), lipid profile (total cholesterol (TC), very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides (TG), LPO indicators, AOS [3] enzyme immunoassay with determination of IL-6 and CK-18 concentration [2].

The level of malondialdehyde (MDA) was determined by the reaction with thiobarbituric acid, which at high temperature in an acidic environment proceeds with the formation of a dyed trimethyl complex. The activity of superoxide dismutase (SOD) was determined by the level of inhibition by the nitrotetrazolium blue reduction enzyme with the participation of reduced nicotinamide-adenine dinucleotide (NAD) and phenazine methosulfate [3].

The liver ultrasound, liver elastography, and ECG were carried out.

The diagnosis “Nonalcoholic fatty liver disease” was established according to the current guideline “Nonalcoholic fatty liver disease” (2014), the recommendations “Diagnosis and treatment of nonalcoholic fatty liver disease: a practical guide of the American Association for the Study of Liver Diseases, College of Gastroenterology and the American Gastroenterological Association (2012) and EASL – EASD – EASO Clinical Practice Guidelines for the management of nonalcoholic fatty liver disease (2016) [4, 7].

For the diagnosis of nonalcoholic steatosis, ultrasound was used, which allows not only to assess the state of the liver (both the morphological component and acoustic properties), but also to detect the gallbladder and liver vessels abnormalities. The presence of steatohepatitis was diagnosed when ultrasound signs of fatty liver dystrophy were combined with increased level of liver transaminases.

The patients were divided into 4 groups by “simple randomization”: the first group – 41 patients with NAFLD with MS, who received a standard hypolipidemic therapy, HMG-CoA reductase inhibitor rosuvastatin “Rosuvastatin IS” (“Interchim”, Ukraine) per os 20 mg/day and the quercetin preparation ("Quertin" chewable tablets produced by the Borshchahivka Chemical Plant) by 40 mg three times a day for a long time, for 3 months; the group 2 – 45 patients with NAFLD with MS used the same term (90 days), the rosuvastatin course consisted of 20 mg/day; the group 3 included 20 patients with MS without liver complications, who were not subject to hypolipidemic therapy; the group 4 (the control group) consisted of 14 practically healthy people.

After registration of initial data, the basic therapy and quercetin were prescribed to all the patients of the studied groups.

The comprehensive laboratory-instrumental examination was carried out at the beginning of treatment, on the 40th and 90th day of treatment.

The mathematical computer processing of the research results was carried out using the software package “Statistica 8.0” – (Stat Soft Inc, USA). The differences were considered reliable at the level of statistical significance $p<0.05$.

Results of the study and their discussion. At the beginning of the study, the patients with NAFLD and MS complained of rapid fatigue, general weakness, heaviness in the right hypochondrium, lack of appetite, flatulence, and a tendency to constipation. During the objective examination, moderate enlargement of the liver was noted, sometimes pain during palpation. The liver enlargement was confirmed by ultrasound data, an uneven increase in the echogenicity of the liver tissue was observed. The patients of the group 1 complained of heaviness and discomfort in the right hypochondrium – 37 (90.2 %) patients, 34 (82.9 %) patients had decreased appetite. The patients of the group 2 had heaviness and discomfort in the right hypochondrium – 40 (88.8 %) patients, 37 (82 %) patients had decreased appetite, fatigue took place in 98.6 % patients. In the group 1, according to ultrasound, the 2nd degree liver steatosis (mostly diffused) was detected in 25 (60.9 %) patients, and 37 (90.2 %) patients had the diaphragmatic margin U-sound attenuation, according to elastography, liver density up to 5.8 kPa was in 32 (78 %) patients. In the group 2, 26 (57.7 %) patients had the 2nd level of fatty infiltration (diffused), 38 (84.4 %) patients had U-sound attenuation, and 35 (77.7 %) patients had the liver density up to 5.8 kPa according to the results of elastography.

Biochemical parameters of the blood serum compared to patients of the control group were elevated: liver enzymes ALT, AST, triglycerides, total cholesterol, LDL, MDA level, concentration of IL-6, CK-18 with a decrease in the SOD activity and the level of HDL. GGTP indicators in all groups ranged within the reference values (Table 1).

Table 1

The studied serum blood indicators in patients with metabolic syndrome and NAFLD before the treatment

Indices	Groups							
			Group 1			Group 2		
	Control group, n=14	MS n=20	NAFLD n=11	Steatosis n=22	NASH n=8	NAFLD n=12	Steatosis n=23	NASH n=10
TG, mmol/l,	1.15±0.07	1.90±0.07	1.96±0.08	2.08±0.08	2.26±0.09	1.9±0.09	2.10±0.08	2.32±0.09
p		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
p_1			>0.05	>0.05	<0.05	>0.05	>0.05	<0.05
VLDL, mmol/l,	0.38±0.12	0.68±0.11	0.72±0.10	0.76±0.13	0.80±0.14	0.74±0.12	0.78±0.13	0.82±0.16
p		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
p_1			>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
LDL, mmol/l	2.78±0.11	4.40±0.20	5.18±0.18	5.20±0.20	5.22±0.19	5.15±0.16	5.18±0.19	5.20±0.22
p		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
p_1			<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
HDL, mmol/l	1.25±0.08	1.10±0.09	1.10±0.09	1.30±0.08	1.10±0.07	1.00±0.07	1.20±0.09	1.18±0.09
p		>0.05	>0.05	>0.05	>0.05	<0.05	>0.05	>0.05
p_1			>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
TC, mmol/l	4.25±0.06	8.00±0.60	8.28±0.54	8.34±0.60	8.40±0.64	8.16±0.58	8.26±0.60	8.30±0.58
p		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
p_1			>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
ALT, units/l	24.20±2.2	105.80±7.60	102.60±5.8	106.80±6.4	107.4±6.2	106.80±5.8	108.00±6.50	107.60±6.68
p		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
p_1			>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
AST, units/l	27.10±1.60	94.00±8.20	92.50±6.80	93.00±7.00	94.00±8.00	94.00±7.60	93.80±8.00	94.00±8.20
p		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
p_1			>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
MDA, mmol/l	2.10±1.04	8.04±1.10	7.98±0.90	8.14±1.08	8.00±1.06	7.84±1.20	8.08±1.12	8.16±0.98
p		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
p_1			>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
SOD, units/l	26.60±3.80	12.08±4.20	11.98±3.60	12.20±4.00	10.84±2.80	12.24±3.60	11.46±2.80	10.96±2.40
p		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
p_1			>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
GGTP units/l	48.34±1.80	51.4±3.00	47.20±2.8	46.80±3.00	48.40±4.20	48.60±3.80	48.00±4.20	52.60±4.80
p		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
p_1			>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
IL-6	1.18±0.20	5.00±0.18	4.86±0.22	4.92±0.23	4.95±0.22	4.95±0.22	4.98±0.23	5.00±0.23
p		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
p_1			>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
CK-18	40.60±6.80	365.80±14.00	356.60±14.0	360.00±15.0	364.00±16.0	366.80±16.0	371.40±14.8	368.00±16.0
p		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
p_1			>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

Notes: 1. p – the difference reliability relative to the control group indices. 2. p_1 – the difference reliability relative to indices of the group with metabolic syndrome.

After 40 days of treatment, a tendency to decrease in the liver enzyme activity and lipidogram indicators was determined in all the patients, but there was no statistical reliability between the groups.

After 90 days of the hypolipidemic therapy with rosuvastatin alone, the patients experienced a decrease in complaints: 33 (73.3 %) patients felt heaviness and discomfort, 29 (64.4 %) patients had a decrease in appetite, 15 (33.3 %) patients had flatulence. Physical examination revealed a swollen abdomen in 8 (17.7 %) patients, and an enlarged liver in 32 (71.1 %). 23 (51.1 %) patients had 2nd-degree hepatic steatosis, and 32 (71.1 %) patients had U-sound attenuation.

On the 90th day, the patients of group 2 had a significant decrease in the LDL level – by 21.2 % ($p<0.001$) compared to the beginning of treatment, but the LDL level did not reach the values of the control group – it was higher by 47.4 %. The HDL level exceeded the values before treatment by 43.3 % ($p<0.001$). TG decreased by 19.1 %. The activity of the liver enzymes, in particular ALT, decreased by an average 15 %, AST – by 7.5 % compared to before treatment, while their values did not reach a statistically significant difference. HGTP activity was noted at the level of the initial data. The IL-6 level on the 90th day was lower by an average 10 % and the CK-18 level – by 8.2 % without statistical reliability of the indices.

During the rosuvastatin treatment, changes in lipid peroxidation (LPO) and the antioxidant system condition were determined in the blood serum of MS patients with NAFLD. A decrease in the level of the end product of free radical oxidation – MDA by 35 % ($p<0.05$) was revealed compared to before treatment. The activity of the key antioxidant enzyme – SOD increased by an average of 27.3 % ($p>0.05$).

A comparative analysis of the clinical data of the group 1 patients, who were administered quercetin together with rosuvastatin, determined a more pronounced tendency to reduced complaints, in particular, heaviness and discomfort in the right hypochondrium – 17 (41.4 %), decreased appetite – 12 (29.2 %), flatulence – 10 (24.3 %) patients. Physical examination revealed abdominal distension in 3 (7.3 %) patients, the liver enlargement in 21 (51.2 %). According to ultrasound, 18 (43.9 %) patients had the 2nd degree steatosis, and U-sound attenuation – in 27 (65.8 %) patients.

The blood serum analysis of these patients on the 90th day of treatment revealed a significant decrease in the LDL level – by 39.5 % ($p<0.05$) compared to before treatment, and was significantly lower – by 22 % compared to the group 2 ($p<0,01$). The TG level was determined reliably ($p<0.05$) 2 times lower compared to before treatment, being on average (1.06±0.08) mmol/l, also reliably 1.6 times lower than the indicator in the group 2. The HDL level was significantly higher on average by 72 % ($p<0.05$) compared to before treatment, by 12 % higher than on average at the group 2. AST activity was significantly lower – by 27 % ($p<0.001$) compared to before treatment and by 16 % compared to the second group. The GGTP activity ranged within the limits of the reference values. A significant decrease in IL-6 concentration on average by 23 % ($p<0.05$) and CK-18 level by 22 % ($p<0.001$) compared to before treatment was noted.

In the patients of the group 1, the MDA dynamics was more pronounced: the decrease occurred on average by 62 % compared to the indices before treatment ($p<0.05$), and it was almost twice as significant as in the patients of the group 2. An increase in SOD activity was noted on average 2.25 times compared to before treatment. Activation of the antioxidant enzyme was 66.4 % higher in patients of this group than in patients of the basic therapy only.

So, the main complaints of MS patients with NAFLD were heaviness in the right hypochondrium. When assessing the objective status, the liver enlargement by 2–3 cm below the level of the costal arch was revealed. An increase in the echogenicity of the liver, mainly diffused, was found in all patients during ultrasound. When evaluating the biochemical parameters of blood in patients with MS and NAFLD, an increase in the transaminases activity was found in 42 % of cases and GGTP – in 32 % of the examined with a probable difference from the control group, which indicates the presence of the cytolysis and cholestasis laboratory syndromes in patients, which confirm the development of steatohepatitis and can be compared with literature data.

Studies of the lipid metabolism indices showed an increase in the TC level in 80 % of patients compared to the control group. An increase in the LDL level was noted in 68 % of patients and reliably differed from the healthy group. However, the LDL level was reduced in 72 % of patients. The TG level was determined to be 1.8 times higher in 76 % of patients compared to the control group. The TG/HDL ratio can be used to indirectly assess the insulin resistance, which underlies the MS development. In our studies, the TG/HDL ratio was on average 0.92±0.14 in healthy people, while in the NAFLD patients with MS it was 1.78±0.22, which indicated the presence of the insulin resistance (IR).

IR is considered to be the main connecting link of all components of MS and liver damage [10, 11]. The initial effect of IR is the accumulation of free fatty acids in hepatocytes, which lead to liver steatosis. Against the background of steatosis and the formation of reactive oxygen species due to complex interactions between cytokines, endotoxins, macrophages, hepatocytes, lipolysis in adipose tissue increases, fatty dystrophy of hepatocytes occurs [12, 15]. At the same time, the oxidative stress develops with the formation of the inflammatory reaction and its transformation into steatohepatitis and further into nonalcoholic cirrhosis of the liver. Free fatty acids released into the portal circulation, enter the liver, become a source of LDL formation, which serve as transport forms of cholesterol [1,9]. NAFLD often leads to the development of highly atherogenic dyslipidemia with high titers of triglycerides, LDL, low HDL, maintaining the subclinical inflammation condition due to an increase in the concentration of pro-inflammatory cytokines, leukocytes, C-reactive protein (CRP), LPO processes enhancement [6, 11].

In our research, in patients with MS and NAFLD, LPO activation was determined, which manifested itself by a reliable 3.8 times increase in MDA level compared to the control group. During the antioxidant protection study according to the SOD activity in the blood serum, a reliable 2.2 times decrease was found compared to healthy people. The obtained results indicate a decrease in the functional capacity of the antioxidant system in NAFLD against the MS background. Suppression of the antioxidant system activity is one of the reasons for the oxidative stress development in MS patients, because in this case SOD is responsible for the removal of the primary active forms of oxygen – the superoxide anion radical. Our results are confirmed by the data of researchers [1, 8], who found the direct and reliable relationships between MDA and ALT, LDL, indicating the parallelism of LPO activation and the severity of cytolysis syndrome, dyslipidemia, and an increase in adipose tissue in the liver during MS. The SOD activity demonstrates reliable inverse relationships with transaminases [1].

Table 2

Changes in blood serum indicators in patients with nonalcoholic fatty liver disease on the background metabolic syndrome after treatment

Indices	Groups						
	Group 1				Group 2		
	Control group, n=14	NAFLD n=11	Steatosis n=22	NASH n=8	NAFLD n=12	Steatosis n=23	NASH n=10
TG, mmol/l, p p_1	1.15±0.07	1.00±0.06 >0.05	1.08±0.08 >0.05	1.12±0.10 >0.05	1.58±0.08 <0.05 <0.05	1.64±0.10 <0.05 <0.05	1.80±0.08 <0.05 <0.05
VLDL, mmol/l, p p_1	0.38±0.12	0.60±0.11 <0.05	0.68±0.10 <0.05	0.70±0.11 <0.05	0.72±0.12 <0.05 >0.05	0.78±0.10 <0.05 >0.05	0.80±0.08 <0.05 >0.05
LDL, mmol/l p p_1	2.78±0.11	3.10±0.13 >0.05	3.19±0.15 <0.05	3.24±0.14 <0.05	4.10±0.12 <0.05 <0.05	4.10±0.13 <0.05 <0.05	4.28±0.15 <0.05 <0.05
HDL, mmol/l p p_1	1.25±0.08	1.96±0.15 <0.05	1.92±0.12 <0.05	1.94±0.20 <0.05	1.68±0.12 <0.05 >0.05	1.72±0.13 <0.05 >0.05	1.76±0.15 <0.05 >0.05
TC, mmol/l p p_1	4.25±0.06	6.46±0.56 <0.05	6.50±0.62 <0.05	6.55±0.58 <0.05	7.48±0.48 <0.05 <0.05	7.64±0.54 <0.05 >0.05	7.86±0.50 <0.05 >0.05
ALT, units/l p p_1	24.20±2.2	76.10±6.70 <0.05	79.00±7.20 <0.05	78.00±6.40 <0.05	92.50±7.10 <0.05 >0.05	90.40±6.70 <0.05 >0.05	92.30±5.80 <0.05 >0.05
AST, units/l p p_1	27.10±1.60	66.40±4.20 <0.05	69.80±4.00 <0.05	70.80±3.60 <0.05	78.40±3.80 <0.05 >0.05	82.60±5.00 <0.05 >0.05	85.90±3.60 <0.05 <0.05
MDA, mmol/l p p_1	2.10±1.04	2.80±0.80 >0.05	3.20±0.52 >0.05	3.00±0.60 >0.05	5.80±0.65 <0.05 <0.05	4.80±0.80 <0.05 >0.05	5.20±0.75 <0.05 <0.05
SOD, units/l p p_1	26.60±6.75	24.80±4.60 >0.05	25.60±3.60 >0.05	28.40±5.20 >0.05	16.20±3.60 >0.05 >0.05	15.90±4.40 >0.05 >0.05	12.20±4.00 >0.05 >0.05
GGTP, units/l p p_1	48.34±1.80	41.40±3.80 >0.05	42.40±4.20 >0.05	41.80±4.30 >0.05 >0.05	58.00±5.20 >0.05 >0.05	56.40±5.00 >0.05 >0.05	55.60±5.12 >0.05 >0.05
IL-6 p p_1	1.18±0.20	3.75±0.22 <0.05	3.80±0.20 <0.05	3.85±0.28 <0.05	4.54±0.30 <0.05 >0.05	4.42±0.36 <0.05 >0.05	4.38±0.80 <0.05 >0.05
CK-18 p p_1	40.60±6.80	280.00±20.00 <0.05	286.00±22.00 <0.05	288.00±22.00 <0.05	340.00±20.00 <0.05 <0.05	339.00±21.00 <0.05 >0.05	335.00±22.00 <0.05 >0.05

Notes: 1. p – the difference reliability relative to the indicators of the control group. 2. p_1 – the difference reliability in indicators between the group 1 and group 2.

The analysis of the effect of treatment on lipid peroxidation and the state of antioxidant status showed that the group of patients with NAFLD and MS who received quercetin in addition to the basic therapy, had a significant decrease in the level of the secondary product of free radical oxidation – MDA in the blood plasma compared to the group receiving the basic therapy only. At the same time, an increase in the SOD activity was noted, which indicates the activation of the organism antioxidant protection. This can be connected with the fact that quercetin is one of the most common flavonoids with a multimodal effect due to antioxidant activity, anti-inflammatory, anti-hypoxic, membrane-stabilizing, immunomodulating properties, the adding of which to the hypolipidemic therapy has a positive effect on both the oxidant and the antioxidant system, manifested in the LPO inhibition and the compensatory processes activation, which provides the maintenance of free radicals at the level necessary for the normal course of metabolic processes in the cell [13, 14].

The research data indicate that the development of chronic subclinical inflammation in MS patients with NAFLD is characterized by an increase in the concentration of markers of systemic inflammation – proinflammatory cytokines IL-6, which were determined to be four times higher than the indicators of the control group, which is probably caused by the metabolic disorders severity and was compared with changes in liver ultrasound and elastography data. The patients with rosuvastatin monotherapy had decreased concentration of IL-6 and CK-18, however, patients who were prescribed quercetin in addition to rosuvastatin had more pronounced anti-inflammatory and hypolipidemic effects and significantly lower levels of IL-6 and CK-18 [2, 12].

Therefore, the combined hypolipidemic therapy with quercetin, corrects metabolic processes in the liver tissues cells, the organism, reduces chronic systemic inflammation realizing an additional pathogenetically necessary effect on lipid metabolism (decrease of LDL, TG, TC, increase of HDL), on structural and functional state of the liver (ALT, AST, CK-18).

The results obtained in the course of the study open up new perspectives for the correction of metabolic shifts, elimination of the oxidative stress in patients with NAFLD with MS by administration of the complex hypolipidemic therapy with quercetin, which significantly reduces the risk of the metabolic syndrome complications and improves their treatment.

Conclusions

1. MS patients have a high risk of developing NAFLD (72.8 % according to ultrasound data) with corresponding shifts of clinical and laboratory parameters compared to healthy patients. The relationship between laboratory indicators (hypercholesterolemia, hypertriglyceridemia, cytolysis of hepatocytes, systemic inflammation) and clinical characteristics, results of instrumental research methods, which indicate the liver damage severity in MS, was revealed.

2. Hypolipidemic therapy with rosuvastatin in patients with NAFLD for 3 months led to a decrease in the TG level by 21.1 % ($p<0.05$), LDL – by 21.2 % ($p<0.05$), CK – by 9 % ($p>0.05$). A decrease in IL-6 by 10.0 % and CK-18 – by 8.2 % was found, but these data did not have a statistic significance. The liver enzymes activity and the liver ultrasound results did not change significantly after treatment.

3. Against the background of the combined therapy with rosuvastatin and quercetin, a clear regression of clinical manifestations of the disease was observed in patients with NAFLD and MS than in patients with rosuvastatin only: there were almost 2 times less complaints, namely, periodic pain in the right subcostal region, symptoms of asthenovegetative and dyspeptic syndromes. The positive dynamics of clinical symptoms was accompanied by a decrease in the activity of the inflammatory process in the liver tissue: the level of serum transaminases, markers of POL and lipid metabolism, concentration of IL-6 and CK-18. The obtained biochemical and immunological indicators corresponded to the changes according to the elastography data: a decrease in the degree of liver steatosis (n=9; 23.8 %), a decrease in the size of the liver (n=8; 18.6 %), the U-sound attenuation to the diaphragmatic margin (n= 6; 15.6 %).

4. A comparative analysis of the comprehensive examination of patients with NAFLD with MS determined quercetin effectiveness during a long-term combined hypolipidemic therapy and a necessity of preventing the development and progression of metabolic disorders associated with the disease.

The further studies will be aimed at studying indicators of the systemic inflammation, metabolic shifts of lipid and carbohydrate metabolis in patients with comorbid conditions of MS in order to assess the applied therapy and the duration of its effects, with the determination of the remote treatment results.

References

1. Bulatova IA, Shchekotova AP, Karlysheva KN. Osobennosti okislitelnogo stressa pri metabolicheskom sindrome s zhirovym porazheniiem pecheni. Sovremennyie problem nauki i obrazovaniia. 2014;2:41–47 [in Russian]

2. Dynnyk NV Zastosuvannya neinvazyvnykh biomarkeriv i mistse tsytokeratynu-18 u diahnostytsi patsiientiv z nealkolnoyu zhyrovoyu khvoroboiu pechinky. Ukrayinskyy naukovo-medychnyy molodizhnyy zhurnal 2016;2(95):12–18 [in Ukrainian]

3. Goryachkovskiy AM. Klinicheskaya biokhimiya v laboratornoy diagnosis. Odessa, 2005. 616 p. [in Russian]

4. Lishchyna OM, Khobzei MK, Kharchenko NV. Unifikovanyy klinichnyy protokol "Nealkoholnyy steatohepatyt "Nakaz MOZ Ukrainy No. 826 vid 06.11.2014. URL: http://mtd.December_gov.ua/images/dodatki/2014.826Gepatyty/2014_826_UKRMD_NSTPT.pdf. [in Ukrainian]

5. Mychka VB, Vertkin AL, Vardayev LI, Druzhilov MA, Ipatkin RV, Kalinkin AL et.al. Konsensus ekspertov po mezhdistsiplinarnomu podkhodu k vedeniyu, diagnostike i lecheniyu bolnykh s metabolicheskim sindromom. Kardiovascularnaia terapiia i profilaktika. 2013;12(6):41–81. DOI: 10/15829/1728-8800-2013-6-78-82 [in Russian]

6. Chorna VV, Khlyestova SS, Humenyuk NI, Makhnyuk VM. Pokaznyky zakhvoryuvanosti i poshyrenosti ta suchasni pohliady na prophylaktyku khvorob. Visnyk Vinnytskoho natsionalnoho medychnoho universytetu 2020:24(1):158–164. DOI 10.31393/reports-vinmedical-2020-24(1)-31 [in Ukrainian]

7. 2016 ESC/EAS Guidelines for the management of dyslipidemias/Developed with the special contribution of the European Association for Cardiovascular Prevention Rehabilitation (EACPR). Russ. J. Cardiol. 2017;5(145):7–77.

8. Bilovol OM, Kniazkova II, Kuzminova NV, Kiriienko OM, Abramova LP, Gavrylyuk AO. Therapeutic efficacy of quercetin in patients with arterial hypertension and metabolic syndrome. World of medicine and biology. 2021;1(75):18–22. DOI: 10.26724/2079-8334-2021-1-75-18-22

9. Bischoff SC, Bernal W, Dasarathy S, Merli M, Plank LD, Schuútz T et al. The European Society for Clinical Nutrition and Metabolism practical guideline: Clinical nutrition in liver disease. Modern Gastroenterology. 2021;2(118):28–40. DOI: 10.30978/MG-2021-2-28

10. Finck BN. Fargeting Metabolism, Insulin Resistance and Diabetes to treat Nonalcoholic steatohepatitis. Diabetes. 2018;67(12):2485–2493. DOI: 0.2337/dbi18-0024.

11. Hernandez–Baixauli J., Quesada–Vazquez S., Marine Casado R. Cardoso KG Caimari A, delBas JM et al. Detection of early disease risk factors associated with metabolic syndrome: a new era with the NMR metabolomics assessment. Nutrients. 2020;12(3):806. DOI: 10.3390/nu 12030806.

12. Kang YE, Kim JM, Joung KH, Lee JH, You BR, Choi MJ et al. The Roles of Adipokines, Proinflammatory Cytokines, and Adipose Tissue Macrophages in Obesity – Associated Insulin Resistance in Modest Obesity and Early Metabolic Dysfunction. PloS One. 2016;11(4):e0154003. DOI: 10.1371/journal.pone.0154003.

13. Miltonprabu S, Tomczyk M, Skalicka Wozniak K. Hepatoprotective effect of quercetin: From chemistry to medicine. Food Chem. Toxicol. 2017;108(Pt B):365–374. DOI:10.1016/j.fct2016.08.034.
14. Parkhomenko A, Kozhukhov S, Lutay Y. Multicenter randomized clinical trial of the efficacy and safety of intravenous quercetin in patients with ST-elevation acute myocardial infarction. European Heart journal. 2018;39(SI):431. DOI: 10.1093/eurheartj/ehy565.2152.
15. Sporea I, Popescu A, Dumitrascu D, Brise C, Nedelcu L, Trifan A, Braticevici CF. Nonalcoholic Fatty Liver Disease: Status Quo. Journal of Gastrointestinal and Liver Diseases. 2018;27(4):439–448. DOI: 10.15403/jgld.2014.1121.274.quo.

Стаття надійшла 15.08.2021 р.

DOI 10.26724/2079-8334-2022-3-81-82-88
UDC 616.12-008.33

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OXIDATIVE STATUS AND STATE OF ERYTHROCYTE MEMBRANES IN PATIENTS WITH CONTROLLED AND TRUE RESISTANT ARTERIAL HYPERTENSION

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Today, arterial hypertension is a global health problem in the whole world. The purpose of the study is to assess the oxidative status and the structural condition of erythrocyte membranes in patients with controlled and true resistant arterial hypertension. In patients, a deterioration in the oxidative status in the development of oxidative stress is observed as evidenced by a significant ($p<0.05$) increase in myeloperoxidase activity, accumulation of lipid and protein oxidation products, decreased antioxidant enzyme activity and reduced glutathione content. Structural and dynamic changes in the membranes of erythrocytes in these patients by the method of spin probes using the nitroxyl radical AdTEMPO and the damage to the structural organization of the lipid layer and proteins integrated in it as well as antioxidant system of erythrocytes were demonstrated. The obtained results may indicate an impairment of the structural organization of the lipid layer and its integrated proteins.

Key words: controlled and true resistant arterial hypertension, oxidative status, erythrocyte membranes, electron paramagnetic resonance.

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ОКСИДАТИВНИЙ СТАТУС І СТАН МЕМБРАН ЕРИТРОЦИТІВ У ПАЦІЄНТІВ ІЗ КОНТРОЛЬОВАНОЮ ТА РЕЗИСТЕНТНОЮ АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ

На сьогодні артеріальна гіпертензія є глобальною проблемою охорони здоров'я у всьому світі. Метою роботи є дослідження оксидативного статусу та структурного стану мембран еритроцитів у пацієнтів із контрольованою і резистентною артеріальною гіпертензією. У пацієнтів спостерігається порушення оксидативного статусу в бік розвитку оксидативного стресу, що підтверджується достовірним ($p<0,05$) зростанням активності мієлопероксидази, накопиченням продуктів окислення ліпідів та білків, зниженням активності антиоксидантних ферментів та вмісту відновленого глутатіону. Вперше досліджено структурно-динамічні зміни мембран еритроцитів у цих пацієнтів методом спінових зондів із застосуванням нітроксильного радикалу AdTEMPO та продемонстровано порушення структурної організації ліпідного шару та інтегрованих в ньому білків, а також антиоксидантної системи клітин еритроцитів. Отримані результати можуть свідчити про порушення структурної організації ліпідного бішару та інтегрованих в ньому білкових структур мембран еритроцитів.

Ключові слова: контрольована і резистентна артеріальна гіпертензія, оксидативний статус, мембрані еритроцитів, електронний парамагнітний резонанс.

The work is a fragment of the research project "Study of biochemical mechanisms in biological activity of physiologically active substances. Biochemical mechanisms for the development of pathological states and biologically active substances in these conditions", state registration No. 0119U100157.

Today, arterial hypertension (AH) is a global health problem in the whole world. In Ukraine, more than 40 % of the adult population has elevated arterial pressure [1]. AH is an important risk factor for the development of cardiovascular diseases first of all atherosclerosis, which leads to the dysfunction of many organs, including the heart, blood vessels, and kidneys [1]. The etiology of AH includes the interaction of genetic, environmental and pathophysiological factors that affect the regulatory systems of the body.

With this, the effect of many factors leads to the development of oxidative stress, which is characterized by a disrupted balance between the functioning of prooxidant and antioxidant systems. Excessive production of reactive oxygen species (ROS) against the background of reduced functional