Pleiotropic effects of omega-3 polyunsaturated fatty acids in complex treatment of patients with comorbidity of chronic pancreatitis and stable coronary artery disease

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Key words: chronic pancreatitis, stable coronary artery disease, omega-3 polyunsaturated fatty acids, comorbidity, treatment

INTRODUCTION

Chronic pancreatitis (CP) is one of the most common, rapidly progressing diseases of the pancreas (AD) (up to 70 %) with a high incidence of temporary disability and primary disability (up to 15.0%). CP is characterized by progressive flow with an increase in functional non-adequacy of software, development of disorders in lipid metabolism, prooxidant antioxidant and calicreatin-kinin (CCS) systems [2, 12]. These epidemiological data due largely preserving the importance of the main etiological factors XII, alcohol abuse, presence of liver and biliary tract diseases, stomach and duodenal ulcers, hyperlipidemia, a component of atherosclerosis, as well as increased exposure to adverse environmental factors [3, 4, 9].

It is known about the negative effect of CP on the cardiovascular system. Found that in 15.5% of patients with gastroenterological diseases, including s from pancreatitis, occurs stable coronary heart disease (SIHS) — angina or atherosclerosis or claim ostinfarktnyy infarction [1, 4]. To date, very relevant, while a poorly understood cause of CP, C and coronary artery disease, hyperlipidemia is, rather,dyslipidemia, which l ezhyt the basis of atherosclerosis [7, 15, 16]. The violation of lipid metabolism is often associated with the so-called lipid triad: increased levels of very low density lipoprotein (LDL) or triglycerides (TG), low density atherogenic lipoprotein (LDL), and low density lipoprotein (HDL). This triad is at the heart of the pathogenesis of atherosclerosis, CIHS and other diseases in general [8, 14, 20].

It is known that CP in combination with CICS is accompanied by a lipid metabolism disorder (hyperthyroidism and dyslipidemia), the most important of which is hypertriglyceridemia. Preparations of basic therapy (statins) inhibit the synthesis of cholesterol, directly reducing the amount of LDL cholesterol. On the fraction of triglycerides statins act only through a certain cascade of biochemicaltransfusion, that is, indirectly [10]. A drug was chosen that could enhance the lipid-lowering effect of statins and directly affect hypertriglyceridemia. Our choice has stopped on the preparation of omega-3polyunsaturated fatty acids (PUFA) — Omakor, certified by F DA. Each capsule of Omacoru (1000 mg) contains 460 mg eicosapentaeno, 380 mg of okozahexaenoic acid and 160 mg mg of auxiliary substances: alpha-tocopherol, gelatin, glycerol. Unlike other drugs of this group, in Omakor, omega-3 PUFAs are contained in biochemically active compounds, ethyl esters. Hypolipidemic action of Omacor is due to the ability of eicosapentaenoic and docosahexaenoic acids to inhibit the activity of enzymes responsible for the synthesis of triglycerides in liver cells [18, 19]. Also, omega-3 PUFAs haveanticoagulation, anti-aggregate, anti-inflammatory, antioxidant and immunomodulatory effects.

It has been proved that in patients with comorbid flow of CP and CICS activation of lipid peroxidation (LPO) occurs while the antioxidant system (AOS) deficiency develops. Thus, the

imbalance in the POL-AOS system is a damaging link in the metabolic control chain, which affects the formation and progression of CP. Also, the presence and depth of violations in the LPO-AOS largely determine the severity of the course of the disease. In oxidative stress, free radicals block the metabolism of acinar cells, melt lysosomal granules and zymogen granules, oxidize lipids of cell membranes, resulting in an inflammatory reaction with mast cell cytotoxic degeneration, platelet activation and complement, which in turn activates pancreatic progenes [5, 13, 17].

It is also known that when the inflammatory process in the body activates CCS. The largest amount of calicreatin (CK) is found in the glandular structures, in particular in the software. Therefore, in the case of damaged pancreatic cysts, changes in CCS such as increased QC and plasma proteolytic activity (PPA) and a decrease in α_1 -inhibitor proteases (α_1 -IP) and kininase-II are observed. It is also known that till now mechanisms of realization of inflammatory process influence in software for the development and progression of SICs have not yet been studied [11]. The combination of CP and CICC leads to a number of structural and metabolic changes that affect the course of both diseases, and necessitates the development of a systematic approach to the study of these violations in this group of patients [6]. The uncertainty of these mechanisms leaves open questions of medical therapy for such a contingent of patients, which in general reduces the effectiveness of treatment for patients with SIRS. Therefore, the search for effective treatment regimens in this area is relevant to modern medicine.

Consequently, the use of the drug Omega-3 PUFA in standard baseline therapy with comorbidity of CP and CIC is the most appropriate and pathogenetically grounded.

The aim of the study was to investigate the effectiveness of a course of treatment with omega-3 polyunsaturated fatty acids (Omakor) for correction of lipid, etc. at oksydatno anti-oxidant violationsand dyslabansu a kallikrein-kinin system in patients with comorbid interruptions g m o CP and SIHS.

MATERIALS AND METHODS

To achieve this goal, 90 patients with CF with concomitant CIHS (angina pectoris I- II functional class) were selected, who were treated in day hospital of Ternopil city clinical hospital № 2. Among them was 4 6 (5 1, 2%) male Kiv age (49,9 ± 8,7) years and 44 women (48, 8 %) age (52.65 ± 6.2) years. The study did not include patients with acute IHD in anne amnesia, insulin dependent diabetes mellitus, unstable angina pectoris, severe arterial hypertension, severe heart rhythm disorders, and severe concomitant diseases.

Depending on the treatment program, the females were divided into two groups: I group (4 5 patients) received standard protocol treatment with SF (enzyme inhibitors, proton pump inhibitors, antispasmodics, prokinetics, nitrates, beta blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, calcium antagonists, statins, antiplatelet agents); The second group (45 patients) than C SW additionally received the drug omega-3 PUFAs (Omacor) for 2 tablets (2000 mg) 1 time per day for one month. The control group was made up of 20 practically healthy persons aged 19 to 46 years, the average age was 32.2 ± 1.8, years Among them there were 11 (5 5 %) men and 9 (45 %) women.

The diagnosis of CV was verified according to generally accepted criteria in the clinic. The diagnosis of CICS was established in accordance with the recommendations of the International Classification of Diseases of the 10th Revision, according to the classification approved by the Ministry of Health Ukraine no 152 dated 02.03.2016. The functional class of

angina pectoris is based on the classification of the angina of the Canadian Association of Cardiologists (1976) and bells and endometrs.

Indicators of lipid exchange in blood serum of patients under study were determined using Lachema kits on the analyzer using the following methods: total cholesterol (CHS) — by the reaction of cholesterol esters after oxidation to hydrogen peroxide with phenol and 4- amino-antipyrine, TG — by reaction with methyl acetone and ammonium ions After bathing with potassium hydroxide, common lipids — in reaction with phosphonate reagent after hydrolysis of sulfuric acid.

The Freudwald formula calculated the level of LDL cholesterol:

Cholesterol LDLC = HCV — HDL HDL — (0.2 × LPDNC) (1.1)

LPDNCH = TG/2,2 (1.2)

CA = (HDL — HDL)/HDL (1.3)

The trial of PAH and AOP before and after treatment was judged by levels of malonic aldehyde (MA), superoxide dismutase (SOD), SH-groups, catalase and ceruloplasmin (CP) of blood.

SOD activity was determined based on its ability to compete with nitrotetrazolium blue for superoxide anions formed as a result of the aerobic interaction of the reduced form of $NADH_2$ andphenazine methasulphate. The number of enzymes was determined by spectrometric method. The norm is considered (62,15 ± 2,82) mind. unit

The level of catalase activity was determined by the ability of hydrogen peroxide to form a stable colored complex with ammonium molybdate, the intensity of which depends on the activity of catalase in the sample. The norm of catalase activity in the blood is (17,48 ± 0,87) %.

The levels of SH groups, CPUs and MAs were determined by Boyer, H.D. Ravina and VN Orechovich with thiobarbituric acid, respectively. The norm of SH-blood groups — (60.5 ± 2.13) m mol/l,MA — (2,810 ± 0,085) m to mol/l, and the amount of CPU in the norm should not exceed 300 mg/l

Determination of indicators of CCS was carried out using the following methods:

- Proteolytic activity of the plasma (PPA) was determined by hydrolysis of protamine sulfate. The basis of the developed method is the determination of the amount of arginine that is cleaved from protamine sulfate by the action of plasma proteases [18];
- The activity of calicreatin (CC) was investigated using a method based on the determination of the amount of para-nitroaniline, which is cleaved by the action of calicreatin from the synthetic substrate of the chromosome of the RK [18];
- Prekalikrein (PAC) was determined using the Veremeenko method, which is based on coalin activation, protamine sulfate incubation, reaction with trichloroacetic acid and determination of PAC by arginine level [13];
- -inhibitora activity α_1 protease (α_1 -IP) and α_2 -makrohlobulinu (α_2 -MH) determined uniform spectrophotometric method for the inhibition of the hydrolysis of N-bezolles-L-arginine ethyl ester;
- determination of the activity of kininase-II was carried out by spectrophotometric Folk method by cleavage of hippuryl-β-arginine [13].

Statistical processing of the obtained data was performed on a personal computer using standard software packages of Microsoft Excel and with the help of Statistica for Windows version 6.0 (Stat Soft inc., USA).

RESULTS AND THEIR DISCUSSION

By analyzing the lipid metabolism indices before and after treatment in patients of the two study groups, we determined a statistically significant improvement in the entire spectrum of lipidogram parameters (p <0.05). In patients of group II, the percentage changes in lipidogram rates were more significant than in patients of Group I, which proves the property of omega-3 PUFAs to enhance thehypopipidemic effect of statins (Fig. 1).

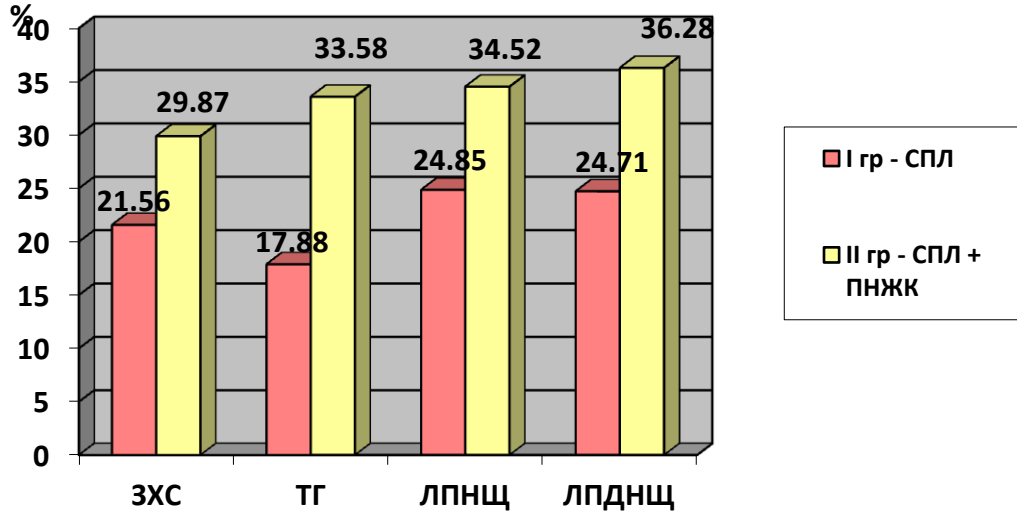

Fig. 1. Percentage reduction of lipidogram rates after treatment in patients with CP with concomitant CID in comparative groups.

In particular, under the influence of treatment proslidkovuvalos statistically significant reduction of TG in patients as a group, and in patients II group on such indicators to treatment, but patients II group, which further took the drug omega-3 PUFA, the level of TG was 15, 70 % lower than in patients with Group I (p <0.05). As a result of the treatment, a statistically significant decrease in the levels of LDL-HPV and LDL-C in the two treatment groups was observed compared with the pre-treatment (p <0.001). It should be noted that the level of LDL and LDL in patients of group II after treatment was statistically significantly lower than those of Group I (p <0.05), which proves a significant hypolipidemic effect of omega-3 PUFAs. The level of HCV after treatment was also statistically significantly lower in the two treatment groups compared to the post-treatment period, but in the second group, the decrease was more significant and statistically significant in these groups in the 1st group (p <0.05).

As for HDL, their concentration under the influence of treatment increased in all groups compared to baseline (p <0,05), but in the second group of patients, this increase was higher by 27.48% in comparison with patients and groups. CA after treatment was statistically significantly reduced in all groups as compared to the time before treatment (p <0.001). CA after treatment was also more statistically significantly decreased in patients of group II compared to patients in group I (p> 0.05), which again proves the direct influence of omega-3 PUFAs on lipid metabolism.

In the study of the state of indicators of the syndrome P OL and AOS Before treatment in patients with CP in combination with CIC, it was found that the level of MA as a marker for the intensification of LPA was significantly higher in I and II study groups compared with the control and was accordingly (6.35 ± 0.07) m to mol/l and (6.39 ± 0.09) m to mol/l. After the treatment, the level of MA in group I and significantly decreased by 1.40 m to mol/l (22,05 %),

while in the second group this indicator has significantly decreased by 2,22 m to mol/l (34.75 %), indicating a more significant procoal suppression with idantic mechanisms under the influence of receiving the drug omega-3 PUFA (Omacor) compared to rezul tatamy conventional treatment (Fig. 2).

Also, prior to treatment, there was a significant decrease in the efficiency of AOS enzymes by the level of SOD (Group I — (39.22 ± 0.47) mind. vehicles; Group II — (39.52 ± 0.45) mind. unit) andSH-groups (Group I — (38.55 ± 0.47) m mol/l; Group II — (38.52 ± 0.45) m mol/l) in both groups compared to control. After treatment was observed a significant increase Honorable ovirne SOD activity(by 24.98%) and increase ting of SH-groups (15.81%) in the second group, while in the first group, these figures increased slightly and unreliable.

The level of catalase in blood plasma before treatment in the 1st and 2nd group of patients was significantly higher compared to control ((55.72 ± 1.12) % and (55.77 ± 1.03) % respectively). After treatment, this indicator significantly decreased by 16.22 % in group I and in 30.68 % in the second group, which demonstrated the regulatory capacity of the PUFA (Omacor) preparation for AOP. As for the blood pressure level in Groups I and II, this indicator was elevated compared to control; after treatment, the level of the CPU significantly decreased in the two study groups (13.18 % in I r and 23.48 %in the second group), which proved the anti-inflammatory and corrective properties of PUFAs in the studied combined pathology (Fig. 2).

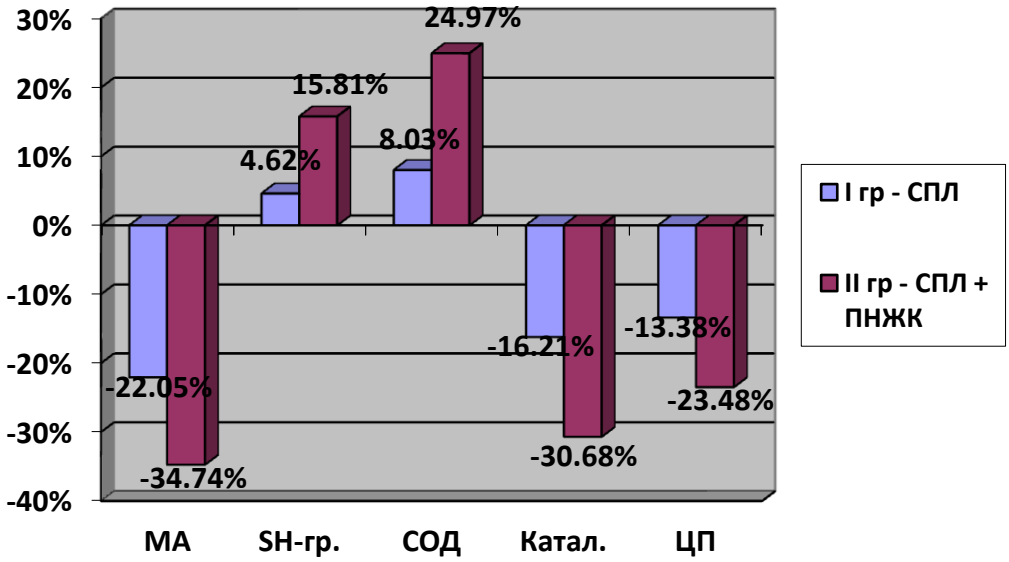

Fig. 2. Dynamics of indicators of the system of LPO-AOP after treatment in patients with COP with concomitant CICS in the comparative groups.

Based on the data presented in Table. 1, we can state the higher efficiency of the proposed treatment regimen, enhanced use of the drug omega-3 PUFA, compared with standard protocol treatment.Acne levels dropped by 11.94 % in group I and 17.63 % in group II, QC decreased by 7.52 % in group I and by 12.95 % in group II, the level of PKC increased by 9.56 % in group 1 and 16.62 % in group 2 (Table 1). 1). The levels of these indices after treatment in groups I and II were statistically significantly higher relative to those in the treatment ($p < 0.05$).

Table 1

The state of indicators of CCS in patients with CP with concomitant SIC before and after treatment in comparative groups

Indicator proteolysis	Comparison Group				
	CONTROL (n = 20)	1 group (n = 45)		Group 2 (n = 45)	
		before treatment	after treatment	before treatment	after treatment
PID, mmol/(h·l)	0.71 ± 31.83	55.68 ± 0.93 *	49.03 ± 0.63 * /#	55.52 ± 0.76 *	45.73 ± 0.48 * /# ** p <0.0 5
QC, μmol/(min·l)	52.15 ± 1.43	177.51 ± 1.62 *	164.16 ± 1.63 */ #	177.26 ± 1.59 *	154.31 ± 0.84 * /# ** p <0.0 5
PAC, μmol/(min·l)	72.57 ± 1.21	36.91 ± 0.67 *	40.44 ± 0.73 * /#	36.94 ± 0.67 *	43.08 ± 0.80 * /# ** p <0.05
α_1-IP, g/l	1.41 ± 0.02	1.98 ± 0.06 *	1.82 ± 0.01 */#	1.98 ± 0.02 *	1.71 ± 0.01 */# ** p <0.05
α_2-MG, g/l	1,50 ± 0,03	0.45 ± 0.02 *	0.56 ± 0.01 */#	0.45 ± 0.02 *	0.67 ± 0.01 */# ** p <0.0 5
Kininase-II, μmol/(min · l)	269.84 ± 1.74	152.97 ± 2.50 *	165.44 ± 1.16 */ #	152.84 ± 2.00 *	176.10 ± 2.12 * /# ** p <0.05

Notes: 1. * — statistical significance in relation to the control group (p <0,05);
2. # — statistical significance in relation to such indicators after treatment in their group (p <0,05);
3. ** — statistical significance for Group I after treatment.

The higher efficacy of the treatment regimen for patients with CP in combination with CICS, enhanced by the use of omega-3 PUFAs, can be judged by α_1-IP and α_2-MG levels. The level of α_1-IP significantly and statistically significantly decreased in the II group compared with the I group by 6.04 % (p <0.05). Concerning the level of α_2-MG and kininase-II, their importance in the group of patients who additionally took the drug omega-3 PUFAs, increased statistically significantly by 19.64 % and 6.44 %, respectively, in relation to the group of patients receiving only standard protocol treatment (p <0,05), which again emphasizes the effectiveness and expediency of the use of omega-3 PUFA in the treatment of patients from the gut of the poor by the flow of CP and CIC.

CONCLUSIONS

1. The addition to the complex therapy of patients with comorbid flow of CP and CIHS of the omega-3 PUFA resulted in a more significant increase in lipidogram (p <0.05) than in standard protocol treatment.
2. Use in treatment of patients with CP in combination with the drug SIHS omega-3 PUFAs (Omakor) spryya lo More reliable regression of at ksydantno-antioxidant disturbances compared with standard conventional therapy.

3. Adding to the complex therapy of patients with comorbid course of CP and SIHS drug omega-3 PUFA resulted in a higher level of performance improvement I studied parameters for CCR (p <0,05),than the standard basic therapy.

In the future, further studies are planned to examine the effect of omega-3 PUFAs on indicators of trophological status in patients with CP with concomitant SIC.

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Key words: chronic pancreatitis, stable coronary artery disease, omega-3 polyunsaturated fatty acids, comorbidity, treatment

Polyunsaturated fatty acids (PUFAs) of the class omega-3 are the substances that have a polytropic effect on different processes in the human body. The aim is to study the effectiveness of course treatment with omega-3 PUFAs for correction of lipid, prooxidative-antioxidant

disorders and imbalance in the kallikrein-kinin system (KKS) in patients with a comorbidity of chronic pancreatitis (CP) and stable coronary artery disease (SCAD). The study included 90 patients with CP combined with SCAD who were divided into two groups (depending on the treatment program): I group (45 patients) received standard protocol treatment (SPT); group II (45 patients) additionally to SPT received omega-3 PUMAs (Omacor) 2 capsules (2000 mg) during one month. It has been shown that the addition of omega-3 PUMAs to the treatment of patients with comorbidity of CP and SCAD is more conducive to improving the lipid and prooxidant-antioxidant states and KKS indices than the standard basic therapy.