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Hypolipidemic effect of ω_3-polyunsaturated fatty acids in coronary heart disease and carotid atherosclerosis

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The aim of the study was to evaluate the efficacy of hypolipidemic action of ω_3-polyunsaturated fatty acids in patients suffering from coronary heart disease (CHD) with postinfarction cardiosclerosis (PICS) and atherosclerotic lesions of carotid arteries up to 40%.

Methods. The study included 90 participants with CHD, PICS, atherosclerotic stenosis <40%, and laboratory-confirmed dyslipidemia. Patients of the main group were prescribed ω_3-polyunsaturated fatty acids (ω_3-PUFA) in addition to the baseline therapy. The study was conducted at the Kursk City Clinical Emergency Hospital from December 2022 to May 2023. Laboratory and instrumental diagnostics were performed at 4-week intervals, including ECG, duplex scanning of the brachiocephalic arteries, complete blood count, urinalysis, biochemical blood analysis with the determination of the patient's lipid profile. Before and after the start of therapy, patients were surveyed using the SF-36 questionnaire. Data were statistically processed by calculating Student's criterion with Bonferroni correction for independent and dependent variables.

Results. At the end of the 24th week of the study, the target hypolipidemic effect was registered in 26.6% of patients with type IV hyperlipidemia (HL) and 35.3% — with type IIB HL, optimal values of high-density lipoprotein cholesterol (HDL–C) (>1.0 mmol/l) were achieved in 17.5% of patients with type IV HL and in 21.3% — with type IIB HL. According to the SF-36 questionnaire, 57.2% of those studied showed positive changes in physical health after being treated with ω_3-PUFA.

Conclusion. As a result of the study, it was found that ω_3-PUFAs have a hypolipidemic effect in patients with

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CHD (PICS, dyslipidemia and carotid atherosclerosis) and improve the quality of life of the patients.

Keywords: coronary heart disease, carotid atherosclerosis, ω_3 polyunsaturated fatty acids, postinfarction cardiosclerosis, hyperlipidemia.

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Introduction

Cardiovascular diseases (CVD) remain the leading cause of mortality and disability in the adult population in all countries [1, 2]. In the Russian Federation, cerebral vascular pathology ranks second in the structure of mortality from cardiovascular diseases [3]. The search for new approaches to the therapy of cardiological patients is a key aspect in reducing cardiovascular mortality and improving the quality of life.

Lipid metabolism disorders are considered to be the main link in the development and progression of arterial atherosclerosis, increasing the risk of cardiovascular events [4, 5]. In the Russian Federation, there is a high prevalence of atherogenic dyslipidemia, according to data from the ESSE-RF epidemiological study [2]. Carotid artery stenosis is a consequence of arterial lesions with atherosclerotic plaque. Carotid artery stenosis >50 % is associated with up to 36 % probability of ischemic stroke. If the stenosis is < 50 %, additional evaluation to determine the morphologic appearance of the atherosclerotic plaque is indicated because unstable atheroma is the leading cause of embolic stroke [6].

Hypolipidemic therapy is aimed at preventing cardiovascular complications and further progression of atherosclerosis. Drugs with pleiotropic effects are of some interest, as they reliably increase the life expectancy of patients. Preparations from the group of ω_3-polyunsaturated fatty acids (ω_3-PUFA) have not only hypolipidemic action, but also reduce platelet aggregation, have anti-inflammatory effect [5], potentiate antioxidant effect of high-density lipoproteins (HDL–C) [7], which can be used to correct dyslipidemia in patients with carotid atherosclerosis and prevent the development of organic brain lesions.

The aim of the study was to evaluate the the hypolipidemic effect of Omacor in CHD patients with postinfarction cardiosclerosis (PICS) and atherosclerotic stenosis < 40 %.

Methods

The study included 90 men aged 51 to 59 years (M = 54.5 years) with a diagnosis of CHD (PICS) with hyperlipidemia (HL) type IIB (combined HL) and type IV (hereditary triglyceridemia) according to Fredrickson and instrumentally confirmed atherosclerotic stenosis of the carotid arteries up to 40 %. General, laboratory and instrumental examinations of the patients were performed before and every 4 weeks during the study, including medical history, anthropometry, and the measurement of blood pressure (BP). Complete blood count and urine analysis, blood biochemistry with determination of lipid fractions (total cholesterol (TC), low-density lipoprotein (LDL–C) and high-density lipoprotein (HDL–C), triglycerides (TG), atherogenic index (AI) and glucose level), Holter monitoring, ultrasound duplex scanning of brachiocephalic arteries (BCAUS) were also performed, as well as the consultation with a neurologist. Patients' quality of life was assessed before pharmacological intervention and after four months of therapy using the SF-36 questionnaire.

Inclusion criteria: male sex, age of patients from 51 to 59 years, confirmed diagnosis of CHD: stable angina, functional class II–III (FC), PICS, instrumentally confirmed atherosclerotic stenosis of carotid arteries up to 40 %, proven dyslipidemia (TG>1.77 mmol/L, TC>5.0 mmol/L, LDL–C>3.0 mmol/L), absence of contraindications to the prescription of ω_3-PUFA. Informed and voluntary consent was obtained from all patients to participate in the study. The study was conducted at the Kursk City Clinical Emergency Hospital from December 2022 to May 2023.

Cardiac patients were excluded from the study based on the following criteria: contraindications to ω_3-PUFA prescription, unstable angina pectoris, stable angina pectoris FC IV, valvular disease, II–III degree atrioventricular block, carotid stenosis > 40 %, circulatory insufficiency above stage IIA, history

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of stroke, diabetes mellitus (DM), thyroid disease, symptomatic AH, side effects of treatment, refusal of observation.

All study participants were prescribed baseline therapy (β-adrenoblockers, statins, antiplateletes, angiotensin-converting enzyme inhibitors) with individual selection of drug dosages according to clinical guidelines for the treatment of CHD [8]. Patients in the control group (20 patients) were prescribed baseline therapy only. The main group (70 patients) was prescribed Omacor (PATHEON SOFTGELS, B.V., The Netherlands) at a dosage of 1 g per day instead of statins in addition to basic pharmacotherapy. To evaluate the effect on TG levels, the dosage was increased according to the drug's instructions (4 g/day). Hypolipidemic therapy was carried out for 24 weeks.

Data were statistically processed using the STATISTICA 12.0 (StatSoft Inc.). Student's criterion with Bonferroni correction was calculated for dependent and independent variables. Differences were considered statistically significant at $p<0.05$.

Results

Baseline lipid metabolism values were comparable in all randomized groups taking into account the phenotype of dyslipidemia: mean values of TC — 7.53±0.59 mmol/l (type IIB) and 4.98±0.31 mmol/l (type IV), TG in patients with type IIB HL — 3.36±0.9 mmol/l, with type IV — 4.2±0.98 mmol/l. At the 8th week of the study in patients with type IIB HL, who were included in the control group, there was a decrease in TC by 23.5% and LDL–C by 22.4%; there was an increase in HDL–C by 18.6% ($p<0.05$). Among patients with type IV dyslipidemia who took only baseline therapy, there was a significant decrease in TC by 22.7%, LDL–C by 30.3%, TG by 31.7% ($p<0.05$), an increase in HDL–C by 18.6% ($p<0.01$), which contributed to a significant decrease in AI by 32.1%. Pharmacologic intervention was continued. By week 16, optimal lipid profile values were achieved in 13.4% of patients with type IV dyslipidemia and in 39.4% of patients with combined HL. The optimal values of the lipid profile were taken as the indicators presented in the national guidelines for the diagnosis of correction of lipid metabolism disorders: TC<5.0 mmol/l, TG<1.7 mmol/l, LDL–C <1.4 mmol/l, HDL–C>1.0 mmol/l [9]. Further lipid profile values did not change significantly. The overall lipid-lowering effect of baseline therapy is presented in Figure 1.

In patients with CHD, PICS, atherosclerotic stenosis of carotid arteries < 40% and type IIB HL who underwent 8-week treatment with ω_3-PUFA the following changes in lipid metabolism parameters were observed: the level of TC decreased by 18.2%; also the level of LDL–C — by 19.2% and TG — by 35.5%. At the same time, HDL–C increased by 20.8% ($p<0.01$) and AI decreased by 36.5% ($p<0.05$). In patients with type IV HL, the following changes were observed af-

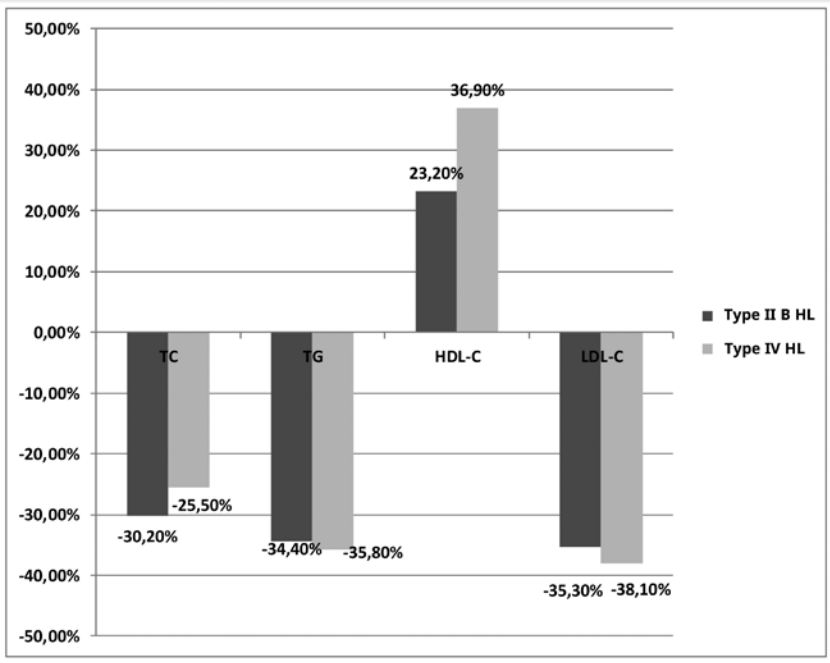

Fig. 1. Degree of decrease in lipid fractions of the control group by the end of the 24th week of the study

Table 1. **Changes in lipidogram by 24 weeks of treatment with Omacor (4 g/day) in CHD patients with type IIB and IV HL**

HL type	TC, mmol/L	TG, mmol/L	LDL–C, mmol/L	HDL–C, mmol/L	AI
Prior to pharmacologic intervention					
IIB type	8.25±1.2	3.3±0.98	5.16±1.16	0.77±0.19	8.82±2.84
IV type	4.98±0.52	4.0±1.25	1.97±0.5	1.03±0.29	3.9±2.4
8 weeks					
IIB type	6.75±1.1*	2.13±0.6*	4.17±1.08*	0.93±0.22*	5.6±2*
IV type	4.82±0.52	2.46±0.77*	1.96±0.48	1.21±0.3*	2.94±2
16 weeks					
IIB type	6.0±1.0*	2.1±0.5*	4.15±1.0**	0.94±0.24**	5.5±2*
IV type	4.8±0.53	2.42±0.75*	1.92±0.48*	1.28±0.32*	2.92±2.1*
24 weeks					
IIB type	5.8±0.9*	2.0±0.7*	4.1±1.0**	0.95±0.21**	5.3±2*
IV type	4.75±0.65*	2.33±0.88**	1.91±0.46*	1.31±0.54**	2.77±2.4*

Note. * — p<0,05, ** — p<0,01 compared to pre-treatment values.

ter 8 weeks of treatment with ω_3-PUFA: TG levels decreased significantly — by 38.5%, HDL–C increased by 17.5%. At the same time, AI decreased by 24.6%.

Thus, with ω_3-PUFA pharmacotherapy, lipid profile target values were achieved in 17.6% of type IV HL CHD patients with verified carotid atherosclerosis and in 23.5% — with type IIB HL (p<0.05), leading to continuation of pharmacological correction.

In patients with type IIB HL, a 36.4% reduction in TG levels was observed after 16 weeks of ω_3-PUFA treatment. LDL–C levels decreased by 19.6%. At the same time, HDL–C increased by 22.1% (p<0.01). After 16 weeks of therapy in comorbid patients with type IV HL, a significant decrease in TG levels was observed — by 39.5%, HDL–C increased by 24.3% (Table 1).

By the end of week 24 of the study, patients with type IV HL on ω_3-PUFA therapy had a 27.2% increase in HDL–C (p<0.01). In patients with type IIB HL, there was a decrease in TG by 39.4% (p<0.05), a decrease in LDL–C by 20.5% (p<0.01) and an increase in HDL–C by 23.4% (p<0.01). Optimal lipid profile values were achieved in 26.6% of patients with type IV HL and 35.3% of patients with type IIB HL (Figure 2). Thus, the addition of ω_3-PUFA to baseline therapy allows for a more pronounced hypotriglyceridemic effect.

Based on the SF-36 questionnaire, positive changes in physical health were observed in 57.2% of subjects when ω_3-PUFAs were added to baseine therapy. Social activity increased in 18.1% of patients (p<0.05). The majority of respondents noted a reduction in the impact of pain syndrome on the quality of life. The

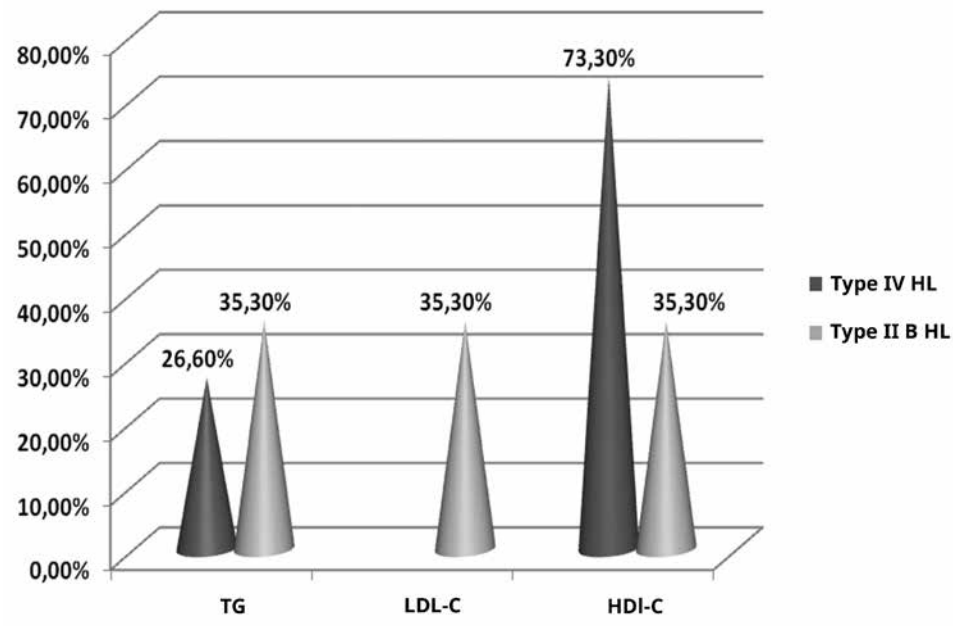

Fig. 2. Number of patients who achieved optimal lipid profile values by week 24 of ω_3-PUFA therapy

increase in vitality scale indices together with positive changes in psychological health confirms the improvement of life quality in patients with PICS, type IIB and IV HL, and atherosclerotic stenosis of carotid arteries <40 % when ω_3-PUFA were added.

Discussion

Under the activity of enzymes, ω_3-PUFAs are metabolized to prostaglandins, thromboxanes, leukotrienes, and nitro fatty acids, which have vasodilatory, anti-aggregatory, and anti-inflammatory effects [5]. In addition, ω_3-PUFAs improve vascular endothelial function [7] by stimulating endothelial nitric oxide synthase [10].

Special attention should be paid to the hypolipidemic effect of ω_3-PUFAs. The Framingham epidemiological study demonstrated that a TG level above 1.7 mmol/L significantly increases the risk of cardiovascular complications [1]. ω_3-PUFAs have mainly a triglyceride-lowering effect due to stimulation of beta-oxidation of free fatty acids and inhibition of TG synthesis in the liver, which decreases their concentration. It is known that in addition to lipid-lowering effects, the use of ω_3-PUFA leads to the stabilization of atherosclerotic plaque. Randomized studies have shown that the use of ω_3-PUFAs reduces macrophage infiltration of the atherosclerotic plaque coating in carotid arteries [5].

ω_3-PUFA supplements have been studied in a number of randomized, placebo-controlled clinical trials. The most convincing evidence base for the efficacy of this pharmacological group is represented by two studies: GISSI-prevenzion, which included people who had suffered a myocardial infarction, and GISSI-HF, which included patients with chronic heart failure. These studies show a significant reduction in cardiovascular mortality in these nosologies after administration of ω_3-PUFA [10]. The efficacy of ω_3-PUFAs in the prevention of cardiovascular complications was not proven in the ORIGIN trial, which included patients with type 2 DM [5]. However, the REDUCE-IT clinical trial, which was conducted in patients with a history of CVD or type 2 diabetes, showed a significant reduction in cardiovascular events and mortality in the groups taking ω_3-PUFA at a dose of 4 mg per day [1, 11].

The study by Skulas-Ray A.C. et al [12] showed that the hypotriglyceridemic effect of the combination of eicosapentaenoic and docosahexaenoic fatty acids (4 g per day) in patients with high baseline TG levels is effective both as monotherapy and in combination with other hypolipidemic drugs [13]. A meta-analysis by Khan S. U. et al. (38 studies, 149051 patients) showed that ω_3-PUFAs reduce cardiovascular mortality and improve patient prognosis [14].

The use of ω_3-PUFAs is associated with a lower risk of dementia [15], which may be due to the angioprotective effects of this pharmacological group on cerebral blood vessels [7].

Conclusion

Thus, the addition of ω_3-PUFA to the baseline therapy is reasonable for the correction of lipid metabolism disorders in patients with CHD, PICS combined with carotid atherosclerosis, as it allows to improve the quality of life of patients and achieve additional reduction of triglyceride levels.

The pleiotropic effect of ω_3-PUFA expands the possibilities of lipid-lowering therapy in comorbid patients. Numerous studies confirm the safety and efficacy of adding ω_3-PUFA supplements to the main therapy in patients with different levels of cardiovascular risk. The use of these drugs may become an effective way of secondary prevention of cardiovascular mortality in the Russian Federation.

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References

1. Kukharchuk V.V., Ezhov M.V., Sergienko I.V., et al. Eurasian association of cardiology (EAC); Russian national atherosclerosis society (RNAS, Russia) guidelines for the diagnosis and correction of dyslipidemia for the prevention and treatment of atherosclerosis (2020). Eurasian heart journal. 2020; 2: 6–29. Russian. DOI: 10.38109/2225-1685-2020-2-6-29
2. Mal G.S., Smakhtina A.M. Secondary hyperlipidemia: definition, phenotypes and inducing factors. International Journal of Heart and Vascular Diseases. 2021; 9(32): 43–51. Russian. DOI: 10.24412/2311-1623-2021-32-43-51
3. Krichman M.D., Travin N.O., Gazaryan G.G., Semitko S.P., Klimovsky S.D. Carotid stenting in the treatment of high perioperative risk patients. Bulletin of the National Medical and Surgical Center. N.I. Pirogov. 2022; 17(3): 101–108. Russian. DOI: 10.25881/20728255_2022_17_3_101

4. Borén J., Chapman M.J., Krauss R.M., Packard C.J. et. al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. European Heart Journal. 2020; 41 (24): 2313-2330. DOI: 10.1093/eurheartj/ehz962
5. Susekov A.V. ω_3 – Polyunsaturated Fatty Acids for the Treatment of Patients with Atherosclerosis and Lipid Metabolism Disorders. Medical business. 2020; 2: 32–45. Russian. DOI: 10.24411/2071-5315-2020-12209
6. Chernyavsky M.A., Irtyuga O.B., Yanishevsky S.N. et. al. Russian consensus statement on the diagnosis and treatment of patients with carotid stenosis. Russian Journal of Cardiology. 2022; 27 (11):76-86. Russian. DOI: 10.15829/1560-4071-2022-5284
7. Sergi D., Zauli E., Tisato V. et. al. Lipids at the nexus between cerebrovascular disease and vascular dementia: the impact of HDL-cholesterol and ceramides. International Journal of Molecular sciences. 2023; 24 (5): 4403–4422. DOI: 10.3390/ijms24054403
8. Clinical practice guidelines for Stable coronary artery disease. Russian Journal of Cardiology. 2020; 25 (11): 201–250. Russian. DOI: 10.15829/29/1560-4071-2020-4076
9. Ezhov M.V., Kukharchuk V.V., Sergienko I.V., et al. Disorders of lipid metabolism. Clinical Guidelines 2023. Russian Journal of Cardiology. 2023; 28 (5): 250–297. Russian. DOI: 10.15829/1560-4071-2023-5471
10. Elagizi A., Lavie C.J., O'Keefe E. et. al. An update on omega-3 Polyunsaturated fatty acids and cardiovascular health. Nutrients. 2021; 13 (1): 204–215. DOI: 10.3390/nu13010204
11. Deepak L.B., Steg P.G., Miller M. et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. New England Journal of Medicine. 2019; 380 (1): 11–22. DOI: 10.1056/NEJMoa1812792
12. Skulas-Ray A.C., Wilson P.W.F., Harris W.S. et al. Omega-3 fatty acids for the management of hypertriglyceridemia: A science advisory from the American Heart Association. Circulation. 2019; 140 (12): 673-691. DOI: 10.1161/CIR.0000000000000709
13. Kytikova O.Yu., Novgorodtseva T.P., Denisenko Yu.K. et al. Omega-3 Polyunsaturated fatty acids for the management of dyslipidemia and reduction of residual cardiovascular risk. Bulletin Physiology and Pathology of Respiration. 2023; 87:124-137. Russian. DOI: 10.36604/1998-5029-2023-87-124-137
14. Khan S.U., Lone A.N., Khan M.S. et al. Effect of omega-3 fatty acids on cardiovascular outcomes: a systematic review and meta-analysis. EClinicalMedicine. 2021; 38: 100997. DOI: 10.1016/j.eclinm.2021.100997
15. Ma H., Zhou T., Li X., Heianza Y. et al. Use of fish oil supplements is differently related to incidence of all-cause and vascular dementia among people with the distinct APOE ε4 dosage. Clinical Nutrition. 2022; 41 (3): 731–736. DOI: 10.1016/j.clnu.2022.01.019