KAPITEL 1 / *CHAPTER 1* [1]
THE EFFECT OF OMEGA-3 POLYUNSATURATED FATTY ACIDS ON THE CARDIOVASCULAR SYSTEM

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Introduction.

Cardiovascular disease (CVD) remains the leading cause of death in the world, despite significant progress in pharmacotherapy and interventional cardiology. One of the key approaches to reducing cardiovascular risk is lifestyle modification, including changes in dietary habits, increased physical activity, weight control, quitting bad habits and psycho-emotional regulation. Abdominal obesity and hypertriglyceridemia have a close pathogenetic relationship and significantly increase the risk of cardiovascular disease. The main mechanisms of their interaction are insulin resistance, systemic inflammation and lipid metabolism disorders.

Effective correction of these conditions requires a comprehensive approach, including lifestyle changes and, if necessary, drug therapy. Insulin resistance is a common pathogenetic mechanism that causes both the accumulation of visceral fat and elevated TG levels. The presence of abdominal obesity increases the risk of hypertriglyceridemia by 3-5 times, which significantly increases the overall cardiometabolic risk.

The following factors contribute to the development of cardiovascular disease [1]: age over 45 years for men and over 55 years for women; high blood pressure; high cholesterol and/or triglycerides; smoking, excessive alcohol consumption, diabetes mellitus, carbohydrate metabolism disorders, overweight, unhealthy diet, low physical activity (physical inactivity), early menopause in women, high stress levels, depression, and night snoring.

Of particular interest is the possibility of non-drug control of modifiable risk factors for the primary and secondary prevention of cardiovascular disease [2]. Non-drug methods of risk factor correction are extremely effective in the primary and

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secondary prevention of CVD. They have an evidence base and should be used as an integral part of treatment. Despite this, patient compliance remains low, which requires active involvement of doctors in educating and motivating patients.

The main risk factors and their non-drug correction:

1. Nutrition and diet therapy. Poor nutrition contributes to the development of atherosclerosis, hypertension and metabolic syndrome. The most effective dietary approaches are:

Mediterranean diet: proven to reduce the risk of cardiovascular events by 30% due to its high content of unsaturated fats, antioxidants and fibre.

- DASH diet: helps to reduce blood pressure and improve lipid profile.

- Reduced consumption of saturated fats, trans fats, refined carbohydrates and salt.

2. Physical activity. Regular physical activity is associated with a 20-35% reduction in cardiovascular mortality.

- Aerobic exercises (walking, running, swimming, cycling) - reduce blood pressure, improve insulin sensitivity and increase high-density lipoprotein levels.

- Strength training - helps reduce visceral fat and improves metabolic parameters.

3. Controlling body weight. Obesity is an independent risk factor for CVD. Even a 5-10% reduction in body weight significantly reduces blood pressure, glucose and atherogenic lipids.

- Body mass index (BMI) <25 kg/m² and waist circumference <94 cm in men and <80 cm in women are associated with a lower risk of CVD.

4. Quitting smoking and alcohol.

- Smoking cessation after 1 year reduces the risk of coronary heart disease (CHD) by 50%, and after 15 years this risk approaches the level of non-smokers.

- Alcohol consumption increases the risk of arrhythmias, hypertension and cardiomyopathy.

5. Psycho-emotional state and stress management. Chronic stress and depression are independent risk factors for CVD.

- Relaxation techniques (meditation, yoga, cognitive behavioural therapy) help to reduce cortisol levels, improve heart rate variability and lower blood pressure.

- Social support and quality sleep (>7 hours/day) have a cardioprotective effect.

The effect of ω-3 polyunsaturated fatty acids (ω-3 PUFAs) on the blood lipid spectrum is well known [5]. Clinical reduction of triglyceride (TG) levels on the background of ω-3 PUFA therapy is associated with both an increase in the rate of conversion of very low-density lipoprotein to low-density lipoprotein and a direct inhibition of TG synthesis, possibly due to increased β-oxidation of fatty acids [5]. In clinical practice, dietary correction and statin therapy alone cannot normalise elevated TG levels.

Hypertriglyceridaemia is a characteristic feature of dyslipidaemia in hypertension (HT) in individuals with concomitant abdominal obesity (AO). These individuals are at increased risk of developing cardiovascular complications, so maximal optimisation of treatment of this category of patients is a primary objective of preventive cardiology practice [1]. Visceral fat plays an active role in lipid and carbohydrate metabolism disorders, which leads to an increase in blood triglyceride (TG) levels and the development of atherogenic changes in blood vessels. Excessive visceral fat contributes to the development of insulin resistance, which increases lipolysis and the intake of free fatty acids (FFAs) in the liver.

Decreased levels of adiponectin and increased leptin lead to impaired appetite regulation and fat accumulation. Visceral fat adipocytes actively synthesise proinflammatory cytokines (TNF-α, IL-6, CRP), which contribute to atherogenesis. Oxidative stress worsens endothelial function, increases platelet aggregation and accelerates the progression of atherosclerosis. Fats entering the liver stimulate the synthesis of very low-density lipoproteins (VLDL), which are the main carriers of triglycerides. This increases blood TG levels and contributes to the formation of an atherogenic lipid profile.

Insulin resistance is a common pathogenetic mechanism that causes both the accumulation of visceral fat and elevated TG levels. The inflammatory state and oxidative stress caused by visceral fat stimulate VLDL hyperproduction and the development of atherogenic dyslipidaemia. The presence of abdominal obesity increases the risk of hypertriglyceridemia by 3-5

One of the most important mechanisms of action of ω-3 PUFAs is the improvement of vascular endothelial function, which is a key factor in the pathogenesis of atherosclerosis, hypertension and other cardiovascular diseases (CVD) [6]. ω-3 PUFAs change the composition of phospholipids in endothelial cell membranes, modulate the synthesis of eicosanoids (prostaglandins, thromboxanes, leukotrienes) and regulate the functional activity of the vascular endothelium [6]. Nitric oxide is the main vasodilator synthesised by endothelial cells via the enzyme endothelial NO synthase (eNOS) [6]. ω-3 PUFAs stimulate the expression of eNOS, which leads to increased NO synthesis and vasodilation. This reduces peripheral vascular resistance and helps to normalise blood pressure. ω-3 PUFAs reduce oxidative stress, which is an important factor in the development of endothelial dysfunction. They inhibit the formation of reactive oxygen species (ROS) and improve the balance between pro- and antioxidant mechanisms [6].

Chronic inflammation is the main cause of endothelial dysfunction and atherosclerosis. ω-3 PUFAs reduce the production of pro-inflammatory cytokines (TNF-α, IL-6, CRP) and promote the synthesis of anti-inflammatory mediators (resolvins, protectins, maresins). ω-3 PUFAs modulate the synthesis of eicosanoids, in particular, reduce the level of thromboxane A2 (a powerful vasoconstrictor and platelet aggregation factor) and increase the level of prostacyclin (a vasodilator and platelet aggregation inhibitor). This helps to reduce the risk of thrombosis [6].

Clinical trials confirm the positive effect of ω-3 PUFA on the vascular endothelium. In the JELIS (Japan EPA Lipid Intervention Study) study, taking 1.8 g of eicosapentaenoic acid per day significantly reduced the risk of cardiovascular complications in patients with dyslipidaemia [7]. In another GISSI-Prevenzione study, the use of ω-3 PUFAs in patients after myocardial infarction reduced mortality by 20% [8].

Thus, ω-3 PUFAs have a multifactorial positive effect on vascular endothelial function, which is realised through improved NO production, reduced inflammation, antioxidant effects, and reduced thrombosis [6]. The inclusion of omega-3s in the diet or their use as pharmacological therapy is an effective approach to the prevention and

treatment of cardiovascular diseases.

The aim of the study. To study the dynamics of the main indicators of the blood lipid spectrum and vascular endothelial function as a marker of atherosclerosis when ω-3 PUFAs are added to the standard combined antihypertensive and hypolipidemic therapy in patients with hypertension and arterial hypertension.

Materials and methods. A 6-month treatment was performed in 44 male patients with stage II hypertension diagnosed in accordance with the recommendations of the Ukrainian Association of Cardiology, aged 60 to 85 years, on average (75±8.5) years with concomitant grade I AR. The abdominal type of obesity was established at a waist-to-hip ratio of ≥ 0.95 with a body mass index (BMI) of 30.0-34.9 kg/m². 22 patients received treatment according to the standard method (baseline therapy), namely antihypertensive therapy: lisinopril 10 mg once daily, amlodipine 5 mg once daily, and the lipid-lowering drug atorvastatin 10 mg once daily. 22 patients received ω-3 PUFAs at a dose of 1000 mg once daily as part of the baseline therapy. The lipid profile and vascular endothelial function were assessed before, 3 and 6 months after the start of therapy. The study of endothelial function was performed by Doppler ultrasonography of the brachial artery (BA) using an ultrasound diagnostic scanner 'LOGIQ 500' (General Electric, USA), using tests with reactive hyperemia (endothelium-dependent vasodilation, EDV) and nitroglycerin (endothelium-independent vasodilation, EIV). Dilatation of more than 10% of the initial diameter against the background of reactive hyperaemia is considered a normal reaction of the PA, while its smaller value or vasoconstriction are considered pathological.

Statistical processing of the data presented in the form of M+m was carried out by the methods of variation statistics using Student's t-test on a personal computer using Microsoft Excel statistical analysis software. The difference was considered significant at $p<0.05$.

Results of the study and their discussion. The baseline levels of total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL cholesterol) in both groups of patients did not differ and were 6.47+0.17, 2.64+0.14, 1.01+0.04 mmol/l in group I and 6.48+0.18, 2.59+0.13, 1.01+0.05 mmol/l in group II (M+m), $p>0.05$. Changes in blood

lipid transport function under the influence of various lipid-lowering therapy regimens were analysed after 6 months. The dynamics of the main lipid profile parameters is shown in the table.

Dynamics of lipidogram parameters in the use of different variants of lipid-lowering therapy against the background of combined antihypertensive therapy during 6 months of treatment (M+m)

Increase in the indicator, %.	lisinopril 10 mg/day + amlodipine 5 mg/day + atorvastatin 10 mg/day	lisinopril 10 mg/day + amlodipine 5 mg/day + atorvastatin 10 mg/day + ω-3 PUFA 1000 mg/day	p
	I group, n=22	II group , n=22	
TC	-25,1±2,6	-32,8±3,3	p<0,05
TG	-22,7±2,3	-40,8±2,1	p<0,001
HDL-C	28,7±2,6	38,6±2,5	p<0,05

Notes. Abbreviations: TG - total cholesterol, TG - triglycerides, HDL - high-density lipoprotein cholesterol, PUFA - polyunsaturated fatty acids, n - number of patients, p - reliability of the difference in the increase in indicators when using different variants of lipid-lowering therapy for the corresponding observation period by Student's exact t-test.

When analysing the results of treatment in the study groups of patients, the levels of LDL-C and TG were significantly lower when using antihypertensive and combined lipid-lowering therapy (group II). Also, in group II patients, the levels of the antiatherogenic fraction, HDL-C, were significantly higher after 6 months, which undoubtedly has a positive effect on the prevention of cardiovascular complications in this category of patients. Before treatment, the EZVD in both groups of patients did not differ and was significantly impaired (-2.1+0.29% of the initial diameter, p>0.05), and the EZVD in response to nitrates was preserved in both groups. After 6 months of

treatment, in the group of patients receiving standard therapy, EWVD improved, but remained far from normal values (6.8+0.23%, p<0.01). In the group of patients treated with ω-3 PUFAs, there was a statistically significant improvement in EWVD (9.86+0.28%, p<0.01) compared with the first group. Improvement of lipid profile and regression of endothelial dysfunction in patients with increased cardiovascular risk is of fundamental importance, since dyslipidaemia, by promoting deeper remodelling of the vessel walls and increasing the expression of adhesive molecules on the surface of endothelial cells, forms a vicious pathological circle that gives rise to atheroma formation [1]. Thus, the addition of ω-3 PUFAs to standard antihypertensive and lipid-lowering therapy contributes to more effective prevention of atherosclerosis in patients with hypertension and AD.

In the diet of cardiac patients, it is important to limit the intake of saturated fats and at the same time ensure the intake of a sufficient amount of ω-3 PUFAs, which are a substrate for the synthesis of prostaglandins that have an antihypertensive effect [3]. The positive effects of ω-3 PUFAs are also associated with their ability to improve endothelial function, cause vascular dilatation and reduce the tendency to thrombosis. With the appearance of ω-3 PUFAs (eicosapentaenoic and docosahexaenoic) in the diet due to the inclusion of fish oil, flaxseed or rapeseed oil, blood rheological parameters improve, and blood pressure levels decrease [5]. To ensure the intake of ω-3 PUFAs, it is recommended to eat fatty sea fish found in the northern regions (trout, herring, salmon, sardines) at least 2-3 times a week. If it is not possible to include these types of fish in the diet, replace them with medications with ω-3 PUFAs. Flaxseed and olive oil, various nuts and seeds are good sources of PUFAs [2]. For patients with verified hypertension, the recommended level of ω-3 PUFA intake is significantly higher than for the general population (1000 mg per day - a combination of eicosapentaenoic and docosahexaenoic ω-3 PUFA) [5]. Compliance with dietary recommendations does not allow achieving a protective concentration of ω-3 PUFAs in cardiac rehabilitation in patients with hypertension. Therefore, drugs with a content of 1000 mg of ω-3 PUFAs have proven efficacy [5].

The results of numerous clinical studies show a positive effect of omega-3 on lipid

profile, blood pressure, inflammation and the risk of cardiovascular events. Mechanisms of cardioprotective action of ω-3 PUFA:

1. Effect on lipid profile. ω-3 PUFAs reduce blood TG levels, which is an important factor in the prevention of atherosclerosis and coronary heart disease (CHD). Eicosapentaenoic and docosahexaenoic PUFAs reduce the synthesis of triglycerides in the liver and increase their clearance. The REDUCE-IT study (2018) showed that a high dose of ω-3 PUFAs reduced the risk of cardiovascular events by 25% in patients with elevated TG levels and high cardiovascular risk [9].

2. Antihypertensive effect. ω-3 PUFAs contribute to a moderate reduction in blood pressure due to: vasodilation associated with increased bioavailability of nitric oxide (NO); reduction of arterial stiffness; inhibition of the renin-angiotensin system [6].

According to a meta-analysis of 70 studies (2014), consumption of 2-3 g of omega-3 per day reduced systolic blood pressure by 2.61 mm Hg and diastolic blood pressure by 1.64 mm Hg [6].

3. Antiarrhythmic effect. ω-3 PUFAs can reduce the risk of ventricular arrhythmias by slowing down cardiomyocyte depolarisation and stabilising cell membranes. The GISSI-Prevenzione study (1999) showed that taking omega-3 after myocardial infarction reduced the risk of sudden cardiac death by 45% [8].

4. Anti-inflammatory effect. ω-3 PUFAs reduce systemic inflammation, which plays an important role in the pathogenesis of atherosclerosis. ω-3 PUFAs inhibit the production of pro-inflammatory cytokines (IL-6, TNF-α). They promote the formation of resolvins and protectins, which accelerate the regression of inflammation in the vessels.

5. Influence on platelet aggregation and endothelial function. ω-3 PUFAs reduce platelet aggregation by inhibiting thromboxane A2. They improve endothelial function, which helps to dilate blood vessels and prevent thrombosis.

ω-3 PUFAs are generally safe, however:

- high doses (>4 g/day) may increase the risk of bleeding in patients taking anticoagulants;

- some supplements contain heavy metal impurities (mercury), so it is important to choose purified products;

- excessive consumption can cause gastrointestinal discomfort.

Conclusions.

1. The inclusion of ω-3 polyunsaturated fatty acids in the standard cardiac rehabilitation programme for patients with hypertension contributes to a significantly more effective reduction in total cholesterol and triglyceride levels and an increase in high-density lipoprotein cholesterol.

2. Patients with hypertension and abdominal obesity are characterised by significant endothelial dysfunction, and the addition of ω-3 polyunsaturated fatty acids to standard antihypertensive and lipid-lowering therapy leads to a significant improvement.