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The Individual Contribution of Fatty Acids to the Development of Cardiovascular Diseases

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ABSTRACT

Impaired fatty acid (FA) metabolism may be an important factor that increases the development and progression of atherosclerosis and related cardiovascular diseases (CVD). However, most of the research focuses on studying the influence of classification groups of FA. Therefore, the aim of this lecture was to present both pro- and anti-atherogenic functions of each FA. This paper considers up-to-date information about the effects of saturated (myristic (C 14:0), palmitic (C 16:0), stearic (C 18:0)), monounsaturated (palmitoleic (C 16:1), oleic (C 18:1)), and polyunsaturated (linoleic (C 18:2 omega-6), alpha-linolenic (C 18:3, omega-3), dihomo-gamma-linolenic (C 20:3, omega-6), arachidonic (C 20:4, omega-6), eicosapentaenoic (C 20:5 omega-3), docosahexaenoic (C 22:6 omega-3)*)* FAs on CVD. The accumulated data expand the understanding of the role of FAs in metabolic processes, which will allow us to move from fundamental research to practical aspects of the use of these substances in the treatment of CVD. In the future, these results can be used in the interpretation and prediction of changes in lipid metabolism disorders in CVD.

Keywords: fatty acids, lipids, cardiovascular diseases, blood, risk factors

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Вклад жирных кислот в развитие сердечно-сосудистых заболеваний

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РЕЗЮМЕ

Нарушение обмена жирных кислот (ЖК) может являться значимым фактором, потенциирующим развитие и прогрессирование атеросклероза и связанных с ним сердечно-сосудистых заболеваний (ССЗ). Тем не менее большинство исследований сосредоточены на изучении влияния классификационных групп ЖК. Поэтому цель настоящей лекции – представить как про-, так и антиатерогенные функции каждой жирной кислоты.

В настоящей работе рассмотрены современные сведения о влиянии насыщенных (миристиновой (С 14:0),

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пальмитиновой (С 16:0), стеариновой (С 18:0)), мононенасыщенных (пальмитолеиновой (С 16:1), олеиновой (С 18:1)) и полиненасыщенных (линолевой (С 18:2, омега-6), альфа-линоленовой (С 18:3, омега-3), дигомо-гамма-линоленовой (С 20:3, омега-6), арахидоновой (С 20:4, омега-6), эйкозапентаеновой (С 20:5, омега-3), докозагексаеновой (С 22:6, омега-3)) жирных кислот на ССЗ. Накопленные данные расширяют представления о роли ЖК в метаболических процессах, что позволит перейти от фундаментально-поисковых работ к практическим аспектам применения данных веществ в лечении ССЗ. В перспективе эти результаты могут быть использованы при интерпретации и прогнозировании изменений метаболических нарушений липидов при ССЗ.

Ключевые слова: жирные кислоты, липиды, сердечно-сосудистые заболевания, кровь, факторы риска

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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INTRODUCTION

The growing prevalence of chronic non-communicable diseases, primarily cardiovascular diseases (CVDs), is a huge problem for the health care system [1]. Coronary heart disease (CHD) caused by atherosclerotic lesions of the coronary arteries is the main and most common nosology among CVDs [2]. For a long time, atherosclerosis can be asymptomatic, which is associated with a latent stage of the disease, in which morphological changes in the coronary arteries are already present [3]. However, following the growth of the atherosclerotic plaque, gradual stenosis of the coronary and other arteries occurs, leading to complications, such as myocardial infarction (MI), stroke, angina pectoris, cerebrovascular insufficiency, sudden cardiac death, etc. [4, 5]. At the same time, the rate of atherosclerosis progression is strictly individual, which necessitates preventive measures at the population and individual levels aimed at eliminating or minimizing the incidence of CVD and the associated loss of working capacity.

A growing body of evidence suggests that fatty acids (FAs) and their metabolites play an important role in atherogenesis [6]. In addition to their structural and/or energy functions, FAs are associated with the regulation of hemodynamics, inflammation, endothelial dysfunction, antioxidant defense, and other important biological processes [7, 8]. This is due to their chemical structure, showing differences for both saturated (SFA) and unsaturated FA (UNFA) [6]. Therefore, the aim of this lecture was to study the role of each FA on the risk of developing CVD. It should be noted that FAs are divided into short-chain, medium-chain, and long-chain FAs based on the number of carbon atoms in their hydrocarbon chain. In addition, according to the presence and number of double bonds in their carbon chain, they can be classified into SFAs (contain no double bonds); monounsaturated FAs (MUFA) (contain one double bond), and polyunsaturated FAs (PUFA), whose structure contains two or more double bonds [9, 10].

SATURATED FATTY ACIDS

As important energy sources, long-chain SFAs can be incorporated into lipoproteins, circulate in the blood, be stored in fat depots, and be used to synthesize other lipid compounds in the body [11]. Currently, the relationship between tissue SFA levels and the risk of atherosclerotic CVD is widely studied, mainly because SFAs can increase low-density lipoprotein cholesterol (LDL-C) concentrations [12]. Nevertheless, there is growing evidence that individual SFAs generally have different biological functions [13].

The most common SFA in the human body is palmitic acid (C16:0), which is an important component of membrane, secretory, and transport lipids, so both deficiency and excess of this SFA are harmful [14–16]. It can enter the body with food or be formed by endogenous synthesis (i.e., *de novo* lipogenesis) as a result of excess energy intake from carbohydrates and/or proteins [17]. To date, the relationship between high levels of palmitic acid in the blood and the risk of developing CVD is beyond doubt. The clinical and observational data indicate that C16:0 may be

associated with adverse cardiovascular events, as well as with overall mortality [18–20]. A population-based study by C.L. Chei et al., which was an additional study to the CIRCS (Circulatory Risk in Communities Study, Japan) [21], revealed that the average level of palmitic SFA was higher in patients with CAD than in the control group. Another population-based study, the LURIC (The Ludwigshafen Risk and Cardiovascular Health study, Germany) [19], showed a direct association with an increased risk of CVD mortality only for C16:0. Moreover, high palmitic acid intake (≈50% of total SFA intake) has been shown to elevate LDL-C [22] and interleukin-6 [18] levels and increase the risk of CHD [23, 24].

Stearic acid (C18:0) is also one of the main SFAs included in triglycerides. It can be obtained from a wide range of foods, including meat, fish, dairy products, etc. Meanwhile, under the action of palmitoyl elongase, cells can elongate C16:0 palmitic SFA to C18:0 stearic SFA [17]. Unlike palmitic FA, data on the effect of stearic SFA on lipid metabolism and, therefore, on the risk of CVD remain controversial. In the Mendelian Randomization Study [25], it was shown that a genetic predisposition to higher levels of stearic SFA in plasma was positively associated with CVD, such as stroke and venous thromboembolism. The EPIC-Norfolk study (European Prospective Investigation into Cancer, UK) [26] found that the concentration of stearic SFA in plasma was positively associated with an increased risk of CHD. At the same time, the CHS study (Cardiovascular Health Study, USA) [27] reported an inverse relationship between high C18:0 levels and all-cause mortality among elderly individuals (over 65 years of age). When studying the effect of stearic SFA, it was found that intake of C18:0 could reduce the level of total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and apolipoprotein A1 in the blood serum, compared to palmitic SFA [28].

However, no significant effect on LDL-C and HDL-C levels has been found in previous studies [22]. The Nurses' Health Study, which included data from the Health Professionals Follow-up Study [24], showed that higher intake of stearic SFA was associated with an increased risk of developing CHD over 24–28 years of follow-up. On the contrary, in the EPIC-NL study (European Prospective Investigation into Cancer and Nutrition–Netherlands Cohort, Netherlands) [29], no significant contribution of stearic acid to the development and course of CHD was found. Thus, the effect of stearic SFA on lipid metabolism, inflammation, and/or endothelial function is not uniform, and additional research in this area is certainly needed.

One of the less common SFAs is myristic acid (C14:0). At relatively low concentrations in the human body, it is also an important component of cell membranes and can systematically influence lipoprotein metabolism [30]. The amount of endogenously biosynthesized myristic FA from lauric acid (C12:0) following elongation or from palmitic SFA following peroxisomal β-oxidation is much smaller than the amount supplied by dietary sources [31]. Within the Ventimiglia di Sicilia Heart Study [32], it was found that the levels of myristic SFA in plasma were inversely correlated with HDL-C levels. The Verona Heart Study reported a strong positive relationship between myristic acid and plasma apolipoprotein CIII concentrations [30]. The study by S.O. Ebbesson et al. [33] showed positive associations between high plasma C14:0 levels and CVD risk factors: increased levels of triglycerides, LDL-C, blood pressure (BP), body mass index (BMI), plasma glucose, as well as an inverse relationship with HDL-C. In an additional study to CIRCS [21], it was noted that high serum levels of myristic SFA were associated with an increased risk of CHD.

Nevertheless, a few data suggest that morbidity and mortality from CVD depend not so much on the total amount of SFA consumed, but on their ratio to UNFA [34].

MONOUNSATURATED FATTY ACIDS

The interest in the role of MUFA is steadily growing. In addition to exogenous intake, MUFAs can be endogenously synthesized in the liver and adipose tissue using microsomal stearoyl-CoA desaturase-1 from precursors – SFA [35]. MUFAs can promote a healthy blood lipid profile, improve blood pressure, glycemic control, etc. [36]. However, the effect of MUFAs on inflammation has not been sufficiently studied. However, there is increasing evidence indicating a close relationship between MUFAs and anti-inflammatory conditions [37]. Some of the key MUFAs, from the standpoint of their functional role in the body, are considered to be omega-7 palmitoleic (C16:1) and omega-9 oleic (C18:1) acids.

Recently, palmitoleic MUFA has been considered as a lipid hormone (or lipokine) derived from adipocytes, which allows adipose tissue to regulate systemic metabolism, indicating its physiological significance [38]. It has been established that C16:1

can be detected as a cis- or trans-isomer and is also associated with cholesterol metabolism, insulin sensitivity, and hemostasis [39–41]. At the same time, its effect on the body, in particular on the cardiovascular system, is still controversial among researchers. The EPIC-Norfolk Study [26], which involved 25,639 people, found no relationship between the content of palmitoleic MUFA in plasma and CHD.

In another prospective study – CIRCS [21], involving 12,840 individuals, positive associations of serum palmitoleic MUFA levels with a higher risk of developing CHD were registered in both men and women. In a population-based study of 1,828 patients with MI and 1,828 controls [42], it was found that C16:1 in adipose tissue had an inverse relationship with acute MI. Most likely, the opposite conclusions are due to different patient samples and/or the biomaterial used. At the same time, a significant number of researchers are inclined to believe that palmitoleic MUFA can have an anti-inflammatory effect [43] and even reduce harmful effects of SFA. In particular, C16:1 promotes differentiation of primary macrophages into the anti-inflammatory M2 phenotype, protecting against the pro-inflammatory effects of palmitic acid [44]. In addition, C16:1 can reduce the levels of pro-inflammatory cytokines produced by lipopolysaccharide-stimulated macrophages (interleukin-6/-8, tumor necrosis factor α) [45].

Oleic acid accounts for approximately 80% of MUFAs in plasma phospholipids. In the PREDIMED study (PREvención con DIeta MEDiterránea, Spain) [46], researchers wanted to demonstrate that consumption of a Mediterranean diet enriched with olive oil (as a key component and source of plant oleic MUFA) was inversely correlated with CVD. However, it was shown that dietary oleic FA intake did not affect its plasma levels, since the concentrations of oleic MUFA in the blood are regulated by other factors, including *de novo* synthesis from stearic MUFA [47].

The results of the MESA (The Multi-Ethnic Study of Atherosclerosis, USA) study [47] show that elevated levels of oleic MUFA in plasma phospholipids may be a risk factor for the development of CVD and all-cause mortality. In the Aldo-DHF (Aldosterone in Diastolic Heart Failure, Germany) study [48], positive correlations were observed between the level of oleic MUFA and established cardiovascular risk factors, such as atherogenic dyslipidemia, dysglycemia, and obesity. In the population-based FINRISK study (Finland) [49], it was determined that high levels of MUFA in the blood, including oleic FA, were associated with a higher risk of CVD. Similar results were obtained with respect to arterial hypertension [50] and inflammation [51]. Despite the relevance of studying the role/influence of MUFAs in the development of CVD and their risk factors, additional studies are needed on the influence of non-dietary factors, such as genetics or younger populations.

POLYUNSATURATED FATTY ACIDS

Recently, special attention has been paid to the role and importance of nutrients, especially long-chain omega-3 and omega-6 PUFAs. It has been shown that omega-3 PUFAs may be beneficial in various diseases and conditions, such as atherosclerosis [52], obesity [53], and inflammation [54]. However, the cardioprotective properties of omega-3 PUFAs are considered to be the most studied. The biological effects of omega-6 PUFAs are still poorly understood and are the subject of active debate [55]. Although most studies report that some omega-6 PUFAs are associated with a lower risk of CVD [56], they have powerful vasodilatory, antiplatelet, and antiarrhythmic effects [57].

The alpha-linolenic acid (C18:3, omega-3) is the most common omega-3 PUFA that can be obtained only from food (mainly from plant sources: flaxseed oil, walnuts, soy, etc.) [58]. One of the large meta-analyses of the Cochrane Database [59], which included 86 randomized controlled trials lasting at least 12 months, assessed the effect of increased omega-3 FA intake on overall mortality, CVD, obesity, and lipid profile. The results showed that an increase in alpha-linolenic PUFA slightly reduced the risk of cardiovascular events. A subsequent meta-analysis [60] including the results of 47 studies confirmed that increasing alpha-linolenic PUFA intake by 1 g / day was associated with reductions in triglycerides, total cholesterol, and LDL-C, thereby preventing CVD.

In a meta-analysis of 27 observational studies [61], data on the association of alpha-linolenic PUFA and the risk of developing CVD were summarized. Observations show that total exposure to C18:3 omega-3 PUFA is associated with a moderately lower risk of CVD. Within the PREDIMED study [62], it was found that in people with high cardiovascular risk, but without previous CVD, the alpha- PUFA intake was inversely correlated with all-cause mortality. The Alpha – Omega study [63] revealed a trend toward

a reduction in the risk of CVD with alpha-linolenic PUFA consumption in patients receiving modern cardiac treatment.

In a study of the relationship between the levels of alpha-linolenic PUFA in plasma and the risk of acute coronary syndrome, T.A. Zelniker et al. [64] found significant inverse associations of C18:3 omega-3 with a lower risk of sudden cardiac death, independent of traditional risk factors and lipid levels. And in a study on mice, it was shown that a diet rich in C18:3 omega-3 can protect against endothelial dysfunction and prevent the development of atherosclerosis by suppressing the inflammatory response and the formation of foam cells [65].

Eicosapentaenoic acid (C20:5, omega-3) is considered to be an essential omega-3 PUFA. It is found primarily in fish and other seafood but can be biosynthesized in small amounts from its main precursor, alpha-linolenic PUFA [66]. There is strong evidence that eicosapentaenoic PUFA has beneficial effects on endothelial function and increases the synthesis of eicosanoids (which dilate blood vessels and reduce thrombus formation and inflammation) [67]. In addition, its potential therapeutic effects on the atherosclerotic plaque include anti-inflammatory and antioxidant activity, reduction of macrophage and foam cell accumulation in lipid spots, reduction of monocyte adhesion, and increase in the thickness of the fibrous cap of the plaque [67–70].

The JELIS (Japan Eicosapentaenoic acid Lipid Intervention Study, Japan) study [71] showed that the introduction of eicosapentaenoic PUFA at a dose of 1.8 g / day led to a decrease in CVD by 19% in patients receiving statins and a decrease in LDL-C concentration in the blood by 25% after treatment. The results of the multicenter, randomized REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial, USA) study [72] indicate that in patients with elevated triglyceride levels who received icosapent ethyl 4 g / day, the risk of major ischemic events, including sudden cardiac death, was significantly lower.

The OCEAN (Omacor Carotid Endarterectomy Intervention, UK) study [73] noted that higher levels of eicosapentaenoic PUFA in atherosclerotic plaques were associated with a decrease in the number of foam and T cells, less pronounced inflammation, and increased stability. Accordingly, the use of C20:5 omega-3 in individuals with a high risk of developing CVD as additional drug therapy helps reduce this risk [74].

Docosahexaenoic acid (C22:6, omega-3) is a very long-chain omega-3 PUFA found in high concentrations in fish, fish oil, and some algae [75]. Clinical studies using dietary supplements with high levels of docosahexaenoic PUFA have shown stable anti-inflammatory, antioxidant, antiatherogenic, and antiproliferative effects [76, 77]. In a double-blind, multigroup, placebo-controlled, randomized study [78], it was shown that C 22:6 omega-3 was more effective than C 20:5 omega-3 in reducing blood triglyceride levels, partly due to differential regulation of liver enzymes associated with lipogenesis. However, consumption of docosahexaenoic PUFA at a dose of ~3 g/day for 10 weeks may be more effective in reducing inflammatory markers, such as interleukin-18, tumor necrosis factor α, and C-reactive protein [79]. There is also evidence that consumption of docosahexaenoic PUFA increases not only C22:6 omega-3 in blood and tissues, but also C20:5 omega-3 eicosapentaenoic PUFA [80]. Moreover, the increase in the omega-3 FA index is significantly higher after supplementation with docosahexaenoic PUFA (2.7 g/day)[81]. Finally, a number of authors have found that docosahexaenoic PUFA causes a greater decrease in blood pressure, heart rate, and total peripheral resistance compared to eicosapentaenoic PUFA [82–84]. Thus, relatively high levels of free omega-3 PUFA may not always be associated with protection of the acutely damaged heart, but nevertheless have a beneficial effect on the body as a whole.

Linoleic acid (C18:2, omega-6) is the main dietary source of other omega-6 PUFAs, such as gamma-linolenic acid, dihomo-gamma-linolenic acid, and arachidonic acid. Linoleic acid is mainly obtained from vegetable oils [85]. There is increasing evidence that high linoleic acid levels are significantly associated with a reduction in the risk of development and mortality from CVD [86, 87]. According to the results of the Cochrane Database meta-analysis [88], which included 19 randomized controlled trials, higher intake of linoleic PUFA instead of SFA or carbohydrates reduced the risk of developing MI and total serum cholesterol by 6%. According to a meta-analysis of 30 prospective studies from 13 countries [56], higher levels of linoleic PUFA *in vivo* were associated with a lower risk of CVD, in particular, mortality from stroke.

In a meta-analysis of observational studies [86], high serum/dietary omega-6 C18:2 levels were inversely proportional to the risk of hypertension. In addition, the results of the International Study of

Macro-Micronutrients and Blood Pressure Study (INTERMAP) [89] show that dietary linoleic PUFA intake may contribute to the prevention and control of unfavorable blood pressure levels in the general population. In a study aimed at investigating the risks of CVD in communities (CIRCS) [21], it was found that serum levels of omega-6 linoleic PUFA were inversely associated with the risk of CHD.

In a Mendelian randomization study [90], it was shown that higher serum omega-6 C18:2 levels were inversely associated with lower levels of lipids, including LDL-C, HDL-C, and total cholesterol. In general, it can be noted that enriching the diet with a moderate amount of linoleic acid-rich oil may reduce the risk of cardiometabolic diseases [91].

Dihomo-gamma-linolenic acid (C20:3, omega-6) is considered to be one of the key omega-6 PUFAs, which has antiatherogenic effects. It inhibits the formation of foam cells, reduces the proliferation of endothelial cells, improves mitochondrial function, etc. [92]. By means of enzymatic activity, gamma-linolenic acid (C18:3, omega-6) is very quickly converted into dihomo-gamma-linolenic PUFA. The latter, in turn, can be metabolized into the anti-inflammatory eicosanoid – prostaglandin E1, via the cyclooxygenase pathway [93]. In the body, it is found in lipids (primarily phospholipids) and most cells, and C20:3 omega-6 levels are consistently increased following C18:3 omega-6 supplementation [94]. In mice, dihomo-gamma-linolenic PUFA supplementation has been shown to reduce aortic lipid content, along with macrophage and smooth muscle cell levels and ICAM-1 and VCAM-1 expression [93].

Few studies have shown an association between low levels of dihomo-gamma-linolenic PUFA and the severity of CHD [95]. In the OMEMI study [96], low serum levels of dihomo-gamma-linolenic PUFA were associated with an increased risk of all-cause mortality in elderly patients who had recently experienced MI. Similar results were obtained by S. Ouchi et al. [97], where the authors concluded that low levels of dihomo-gamma-linolenic PUFA in serum may be a predictor of permanent CVD (acute coronary syndrome, MI). In the work by T. Nagai et al. [98], lower levels of omega-6 PUFA, in particular C20:3, were associated with higher incidence of adverse events (death from all causes and observation of heart failure) after acute decompensated heart failure.

Finally, arachidonic acid (C20:4, omega-6), also known as eicosatetraenoic PUFA of the omega-6 class, is worth noting. It can enter the human body as part of various foods (meat, eggs, salmon, vegetable oils, walnuts) or be formed by endogenous synthesis due to release from phospholipids in the cell membrane by cytosolic phospholipase A2 (PLA2) [99]. It is usually esterified as triglycerides or glycerophospholipids to maintain cell membrane structure and function. It is well known that arachidonic PUFA can compete with omega-3 eicosapentaenoic PUFA for cyclooxygenase and lipoxygenase *in vivo* [100]. The arachidonic PUFA and its metabolites play an important role in the functioning of the cardiovascular system. They act as vasodilators or vasoconstrictors and modulate vasodilation in pathological and physiological conditions [101].

Nevertheless, the results of studies on the associations of circulating or tissue levels of arachidonic PUFA with CVD are rather inconclusive. A meta-analysis of 30 prospective studies [56] did not support adverse cardiovascular effects of arachidonic PUFA. Moreover, the authors suggested that higher plasma C20:4 levels may be associated with a lower risk of developing CVD. In two population-based cohort studies conducted in the Netherlands [102], no association was found between arachidonic PUFA levels and the risk of developing CHD. In the analysis of data obtained from a retrospective registry of patients with acute hypertensive stroke [103], lower serum arachidonic PUFA levels were independently associated with poor functional outcome in acute intracerebral hemorrhage. According to the results of a study using genetic variants [104], positive associations of arachidonic PUFA with atherosclerotic CVD and venous thromboembolism were found. When studying the content of arachidonic PUFA in adipose tissue, a positive association with the risk of MI in the Danish Prospective Cohort Study (DCH) was established [105].

CONCLUSION

Thus, the study of the influence of FA on the development of CVD is a promising area of research. Data on the associations of different SFA, MUFA, and PUFA with lipid and lipoprotein parameters and inflammatory markers of CVD may be of interest for obtaining new data clarifying and supplementing the mechanisms of the effect of FA on the cardiovascular system.

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