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A closer look at polyunsaturated fatty acids and hypertension

Bliższe spojrzenie na wielonienasycone kwasy tłuszczowe i nadciśnienie tętnicze

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Summary

Hypertension is the most common chronic cardiovascular disease in adults in all Western societies. Unfortunately, hypertension treatment is still often insufficient and in most countries the majority of patients still have inadequately controlled blood pressure. In recent years, dietary modifications and supplementations, including polyunsaturated fatty acids (PUFA), have attracted considerable interest as a potentially complementary therapy for the treatment of hypertension. The reduction of blood pressure due to PUFA supplementation may be a consequence of promoting nitric oxide-induced endothelial relaxation, a reduced vasoconstrictive response to catecholamines and angiotensin II, improved vasodilatory responses, arterial compliance and reduced oxidative stress. It has been clearly demonstrated that PUFA decreases blood pressure in experimental studies, animal models and clinical trials, especially in higher doses (more than 3g/day). Thus, PUFA consumption might be useful, particularly in the control of patients with 1st degree hypertension or as a complementary method in treating patients with antihypertensives. The consumption of fishes, the main source of PUFA, needs to be recommended for all the hypertensives to reduce cardiovascular risk. Because of the dose-dependent effect differences, the choice of a correct dose of PUFA may be difficult and controversial. Therefore, a qualified healthcare provider should be consulted prior to starting treatment with PUFA supplements.

Keywords: **hypertension • PUFA • fish oil**

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INTRODUCTION

Hypertension is the most common chronic cardiovascular disease in adults in all Western societies [28, 71]. According to the WHO, hypertension is the leading risk factor for death worldwide. In more than 95% of the cases, the etiology of essential hypertension remains still unknown. The pathogenesis of hypertension is known to involve endothelium dysfunction, renin-angiotensin-aldosterone (RAA) system, sympathetic system, oxidative stress; however, a complete understanding of the causes for hypertension and its high prevalence remains unclear.

Hypertension prevalence varies between countries [71]. The survey NATPOL 2011 reveals a high prevalence of hypertension of 32 %, and only in about 26% of all hypertensive patients' blood pressure is well controlled [76]. The PONS study revealed an even higher hypertension prevalence of 67% in the Polish population aged 45-64 years old in the Kielce province [65]. Generally, hypertension affects approximately 31 % adults aged ≥18 years and increases with age to 70% among persons aged ≥65 years [75].

Thus, hypertension is emerging as a major health problem both in Poland and in the other countries. However, increased blood pressure is one of the most preventable risk factors for cardiovascular diseases; it can be easily detected and it can be effectively treated. Despite huge progress in the science of hypertension, treatment is still often insufficient and in most countries majority of patients still have inadequately controlled blood pressure [16]. Reduced salt intake, moderation of alcohol consumption, body weight optimization and exercise have been shown to support antihypertensive medication therapy in controlling blood pressure.

In recent years, dietary modifications and supplementations have attracted considerable interest as a potential complementary therapy for the treatment of hypertension. Polyunsaturated fatty acids seem to be of particular importance. Omega-3 fatty acids are a group of biologically occurring Polyunsaturated Fatty Acids (PUFA). PUFA n-3 include alpha linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), while PUFA n-6 include linoleic acid (LA) and arachidonic acid (AA).

Linoleic acid (LA) and α-linolenic acid (ALA) cannot be synthesized by mammals and thus must be obtained from the diet. LA is present in soybean, palm, corn, canola oils, margarine and shortenings, and is by far the most abundant PUFA in today's Western diet [21]. ALA is found in green plants, nuts and botanical oils, such as flax seed oil [5]. LA can be converted in humans to arachidonic acid and then via cyclooxygenase and lipoxygenase pathways into prostaglandins, thromboxanes and leukotrienes. Eicosanoids have been shown to promote inflammation in numerous diseases including cardiovascular disease, asthma, and arthritis [63]. Long chain omega-3 polyunsaturated fatty acids (n-3 PUFA) have anti-inflammatory properties, with health benefits ascribed mainly to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA and EPA are two long chain omega-3 fatty acids that function as precursors to eicosanoids prostaglandins, thromboxanes, and leukotrienes. DHA and DPA are synthesized from alpha-linoleic acid (ALA). The rate of this biosynthesis mechanism is very low; therefore, it is recommended to obtain EPA and DHA from additional sources. Sources of animal omega-3 EPA and DHA fatty acids include fish oil, egg oil, squid oil, and krill oil. The health benefits of high oily fish consumption were first recognized in the Greenland Inuit, in whom n-3 PUFA consumption was correlated with a lower cardiovascular risk (CVD) mortality rate. PUFA, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), possess cardiovascular protective effects. Therefore, a diet that includes two to three servings of oily fish per week has been recommended. The American Heart Association recommended that a human diet should include high levels of n-6 PUFA that comprise at least 5%-10% of the energy intake [20]. Meta-analysis shows that omega-3 have beneficial effect on vascular function and significantly decrease blood pressure [6]. Other randomized controlled trials show that 0.7g daily amount of EPA and DHA can decrease blood pressure in patients with isolated systolic hypertension. The authors found the result as a clinically significant [41].

Potential mechanisms by which omega-3 fatty acids may reduce risk for cardiovascular disease are complex and include the following: alteration of the physicochemical properties of cell and organelle-membrane structure and function, direct interaction with and modulation of membrane channels and proteins, regulation of gene expression through nuclear receptors and transcription factors, changes in arachidonic acid-derived eicosanoid profile and conversion of n-3 PUFA to bioactive metabolites [73], reduction of the heart susceptibility to ventricular arrhythmia, antithrombogenic, hypotriglyceridemic (fasting and postprandial) effect, growth retardation of atherosclerotic plaque, reduction of adhesion molecules expression, reduction of platelet-derived growth factor, anti-inflammatory effect [7]. Beneficial physiologic effects of n-3 PUFA include also inhibition of prostacyclin, thromboxane and cytokine production to reduce inflammation, reduction of endothelial adhesion molecule expression, reduction of blood viscosity, decreased levels of platelet-activating factor and platelet-derived growth factor, decreased oxygen free-radical generation and at last, but not least mildly hypotensive effect [54]. The reduction of blood pressure may be a consequence of promoting nitric oxide-induced endothelial relaxation, which increases nitric oxide production, a reduced vasoconstrictive response to catecholamines and angiotensin II, improved vasodilatory responses, arterial compliance [50] and reduced oxidative stress.

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ENDOTHELIUM AND PUFA

Endothelial dysfunction (ED) is a major contributor to the pathogenesis of cardiovascular disease [27, 74]. An association between hypertension and inflammation or endothelial dysfunction has now been clearly demonstrated. In recent years, PUFA has been considered as anti-inflammatory agent, improving vascular endothelial function. In some studies, n-3 PUFA consumption decreased markers of endothelial dysfunction [61]. DHA and proEPA are a metabolized by lipoxygenase enzymes to anti-inflammatory and pro-resolving mediators, resolvin E1 and resolvin D1 [31, 67]. A diet rich in polyunsaturated fatty acids (PUFA) improves endothelium-dependent relaxations in porcine coronary arteries [33]. Dlugosowa demonstrated that the consumption of omega-3 fatty acids led to the up-regulation of phosphorylated isoform of Cx43 in the aorta of SHR, which was accompanied with reduced blood pressure and the stimulation of nitric oxide synthase activity [10]. An improvement in endothelial function was found in healthy volunteers, in obese adolescents and in patients with chronic heart failure [8, 11, 29, 43, 68]. Part of the clinically relevant benefit n-3 PUFA supplementation is thought to be due to an improvement in and the reduction in inflammation. The acute phase protein, C-reactive protein (CRP), is involved in immune responses and has roles that include activating the complement system and enhancing phagocytosis [46]. A definite reduction in inflammation measured by C-reactive protein (CRP) was observed in healthy male smokers [40, 51, 52], obese adolescents [8], and in patients with coronary artery diseases [12]. Moreover, in addition to decreasing blood pressure, omega-3 PUFA can reduce systemic vascular resistance, heart rate independently of vagal activation, and left ventricular hypertrophy and improve diastolic function [19].

THE OXIDATIVE STRESS AND PUFA

Oxidative stress plays an essential role in the pathogenesis of the diseases of cardiovascular system, including hypertension. It results from an imbalance between free radicals and their detoxification by endogenous and exogenous scavengers, including polyunsaturated fatty acids. The administration of antioxidants results in improved status in both hypertensive patients and animal model. However, the impact of consuming oxidized n-3 PUFA on metabolic oxidative stress and inflammation is poorly described. Matesanz et al. has shown that n-3 polyunsaturated fatty acids (n-3 PUFA), the essential constituents of oily fish, can modulate the nitroso-redox balance by increasing vasculoprotective NO and decreasing superoxide anion (O_2^-) production in endothelial cells [38]. n-3 PUFA diminish platelet superoxide production in hypertensive and diabetic patients in vivo, which suggests a therapeutic role of these agents in reducing the vascular-derived oxidative stress associated with diabetes [39]. Lluis has described that supplementation with fish oil derived omega-3 PUFA increased SOD (superoxide dismutase), GPX (glutathione peroxidase) in erythrocytes and plasma antioxidant capacity (ORAC) in rats [36]. Other studies have also shown that a diet supplemented with fish oils does not increase cellular oxidative damage, but may even exert an antioxidant effect [17, 60]. Wales demonstrated that the supplementation of ApoE-/- mice with a diet high in n-3 PUFA content protected the mice against pro-inflammatory and oxidative stress responses following short-term infusion with angiotensin II [70]. Other research with spontaneously hypertensive obese (SHROB) rats proved that EPA and DHA supplementation decreases oxidative stress by increasing activity of antioxidant enzymes in abdominal fat, kidneys and erythrocytes [42].

However, PUFA are highly prone to oxidation, producing potentially deleterious 4-hydroxy-2-alkenals. Tanito et al. described possible harmful effects of high levels of n-3 PUFA on retinal membrane degeneration [66]. Peroxidation of dietary LC n-3 PUFA may decrease their nutritional value, causes loss of nutritional quality and further leads to the generation of genotoxic and cytotoxic compounds, such as the 4-hydroxy-2-alkenals [18]. The major end-products derived from n-3 and n-6 PUFA peroxidation are 4-Hydroxy-2-hexenal (4-HHE) and 4-hydroxy-2-nonenal, which can act as genotoxic and cytotoxic agent. Urinary concentrations of 8-oxo-7,8-dihydroguanine (8-oxoGua), a good indicator of systemic oxidative DNA damage was lower after fish-oil supplementation but higher after n–3 PUFA or DHA supplementation [22, 30, 69].

FISH AND FISH OIL IN HYPERTENSION TREATMENT

Fish is the major food source of long-chain n-3 PUFA, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and, in smaller amounts, docosapentaenoic acid (DPA). It was demonstrated that the consumption of freshwater fish (300-600 g daily) is associated with raised plasma concentrations of n-3 polyunsaturated fatty acids, lower blood pressure, and lower plasma lipid concentrations [55]. Blood pressure was decreased –5.5/–3.5 mm Hg in trials of untreated hypertensives given >3 g/d of omega-3 fatty acids [2]. However, DHA seems to be more effective than EPA in lowering blood pressure [44]. A meta-analysis of the effect of n-3 PUFA in fish oil on blood pressure concluded that greater consumption of n-3 PUFA was associated with a greater reduction in blood pressure, particularly in omega-3 fatty acids have a dose-dependent, hypotensive effect, the extent of which seems to be dependent on the degree of hypertension [24]. Another meta-analysis demonstrated a significant reduction in the blood pressure of –3.4/–2.0 mm Hg in studies with hypertensive subjects who consumed 5.6 g/d of omega-3 fatty acids. The greater consumption of n-3 PUFA was associated with a greater reduction in blood pressure, particularly in hypertensive subjects and those with lipids disorders and atherosclerosis [45].

Geleijnse showed in a meta-regression analysis of 90 randomized trials of fish oil and BP that high intake of fish oil may lower BP, especially in older and hypertensive subjects [15]. Meta-analyses of randomized controlled trials in humans revealed that fish oil reduces HR, particularly in those with higher baseline HR or longer treatment duration [47]. Interestingly, Armitage et al. found that increased blood pressure later in life may be associated with perinatal n-3 fatty acid deficiency in rats [3], which may indicate the importance of PUFA supplementation in utero. However, not all data on the impact of PUFA on blood pressure has been coherent [1].

Thus, it is well documented that n-3 PUFA consumption reduces systolic and diastolic blood pressure. However, there has been a discussion if fish consumption or fish oil supplementation should be preferred. There are several limitations in using fish oil as a source of supply of these essential fatty acids. The teratogen, carcinogen, and mutagen contaminants including DDT (dichlorodiphenyltrichloroethane) and dioxin-like polychlorinated biphenyls; methyl mercury, heavy metals (Pb, Cr, Hg, Cd, and As), and antibiotics [14, 34, 57, 62] are the most serious limitations. Moreover, fish oil has undesirable odors and flavors. It is worth noting that toxins accumulated in seafood may be harmful to the growing fetus [14, 53]. The concern regarding the possible risk from intake of excessive mercury or other contaminants is offset by the neurobehavioral benefits of an adequate DHA intake and can be minimized by avoiding the intake of predatory fish (e.g., pike, marlin, mackerel, tile fish, swordfish). Moreover, there are alternative sources of EPA and DHEA: egg oil, squid oil, and krill oil. Recently, Laidlaw et al. demonstrated that for the general population, the form and dose of omega-3 supplements may be immaterial. However, risk reduction in several elements of cardiovascular disease was achieved to a greater extent by the concentrated fish oil than by any other supplement [32]. The form and dose may be important for those interested in reducing their risk of cardiovascular disease, and fish oil should be preferred from among other supplements.

DOSES OF PUFA IN HYPERTENSION

Mozzafarian et al. showed that different doses of PUFA have different effects. The antiplatelet, anti-inflammatory, and triglyceride-lowering effects of omega-3 PUFAs require relatively higher doses of DHA and EPA (e.g., 3 to 4 g/day), whereas some of the antiarrhythmic effects, improvement in heart failure can be achieved at lower doses (500 to 1000 mg/day) [48]. Although the median intake of EPA and DHA is less than 150 mg/day in USA, most trials examining antihypertensive effects have tested the efficacy of 3 grams or more per day [32, 48, 64]. Such high doses ω-3 PUFA (≥ 3 g/day) produces a small but significant decrease in blood pressure, especially systolic blood pressure, in older and hypertensive subjects [4, 26]. Eating fatty fish twice a week provides - approximately 1 gram of EPA and DHA per day [35]. However, omega-3 fatty acids in high doses (≥ 3 g/day) are not recommended for treatment of hypertension, because and at this dose level, may result in a moderate increase in bleeding times that are generally lower than those seen with ASA therapy [23]. Moreover, higher dose supplementation frequently causes fishy belching [35].

Thus, much lower doses are recommended. The WHO recommend PUFA intake 1/2% of energy/day for the general population [26]. Most Authoritative Bodies, Expert Scientific Organization and Health Organization recommend no more than 500 mg per day (EPA+DHA) for cardiovascular disease risk reduction [13, 25]. 3-5 servings of fish per week should be consumed due to Gastroenterology Word Organization in general adult population [58, 72]. According to National Heart Foundation of Australia 500 mg EPA + DHA per day, obtained through fish, fish oil capsules, or enriched foods & drinks should be con-

Table 1. The recommendation for PUFA intake in Europe for adult population

Organization	Recommendation	Target population
Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice [56]	>two servings of fish weekly, one of which should be oily	general adult population for cardiovascular risk reduction
Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) [58]	2-3 serving of fish weekly	general adult population for cardiovascular risk reduction
	1 g/day n-3 unsaturated fats, from natural food sources, nutraceutical and/or pharmacological supplements	secondary prevention of CVD

sumed to lower the risk of coronary artery disease, 1000 mg for patient suffer with CHD and 1200 mg to 4000 mg for patient with hypertriglicerydemia [49]. Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society recommends two or three portion of fish per week for cardiovascular risk reduction. For secondary prevention of CHD 1 g/day n-3 unsaturated fats are indicated, which is not easy to derive exclusively from natural food sources, and the use of nutraceutical and/or pharmacological supplements may be considered [58]. Expert Workshop of the European Academy of Nutritional Sciences recommends obtaining 200 mg EPA + DHA from other sources for people who do not eat fish [9]. Due to Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts), to prevent cardiovascular events fish should be consumed at least twice a week, including that one should be oily fish (Table 1) [37, 56, 59].

CONCLUSION

It has been clearly demonstrated that PUFA produces a decrease in blood pressure in experimental studies, animal models and clinical trials. Prospective cohort studies indicate that PUFA or fish intakes are associated with a lowered risk of cardiovascular disease mortality, whereas evidence from randomized controlled trials is less conclusive [37, 59]. However, ω-3 polyunsaturated fatty acids consumption might be useful, particularly in the control of patients with 1degree hypertension or as a complementary method for patients treated with antihypertensives. The consumption of fishes needs to be recommended for all hypertensives as a way to reduce cardiovascular risk. Because of differences in the effect of doses, the choice of a correct dose of PUFA may be difficult and controversial. Therefore, a qualified healthcare provider should be consulted to start treatment with PUFA supplements.

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