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Review Article

Role of Dietary Omega-3 Fatty Acids in Hypertension

Marguerite M. Engler*

Department of Physiological Nursing, University of California, USA

***Corresponding author**

Marguerite M. Engler, Department of Physiological Nursing, University of California, P.O. Box 34857, Bethesda, Maryland, 20827, USA, Tel: 650-346-6431; Email: marguerite.engler@nursing.ucsf.edu

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Abstract

Hypertension is a major risk factor for cardiovascular disease which increases with aging. Dietary and lifestyle interventions have been recommended to optimize blood pressure levels. Dietary omega-3 fatty acids, eicosapentaenoic (EPA) and docosahexaenoic acids (DHA), have an important role in cardiovascular health and disease. Convincing experimental and clinical evidence suggests that EPA and DHA provide vascular protection by improving endothelial function and lowering blood pressure. Potential mechanisms for these effects include fatty acid uptake and incorporation into endothelial cell membranes which modulate multiple important cell functions. The present review also addresses the vascular physiology, endothelial function and pathophysiology of hypertension, the potential mechanisms and metabolism of omega-3 fatty acids. In addition, guidelines for dietary Intake of omega-3 fatty acids and measurement of omega-3 fatty acid intake are presented.

ABBREVIATIONS

EPA: Eicosapentaenoic Acid; DHA: Docosahexaenoic Acid

INTRODUCTION

Hypertension is a world-wide health concern. Over the past two decades, it has risen from being fourth to the first risk factor for global disease burden [1]. Blood pressure control is suboptimal with only 40% of hypertensive patients reaching a blood pressure target goal of less than 140/90 mm Hg. Hypertension is also major risk factor for cardiovascular disease affecting nearly 80 million Americans with the highest prevalence in African Americans [2]. It is highly prevalent in aging, more than double than in younger individuals. Hypertension is the most important contributing risk factor for death and disability in the world and the prevalence is expected to increase world-wide over the next twenty years [3]. Hypertension is also known as the silent killer because of the absence of symptoms in hypertensive individuals.

Hypertension is defined as systolic blood pressure >/=140 mm Hg or diastolic blood pressure >/= 90 mm Hg, taking anti-hypertensive medication or being told twice by a physician or other professional that one has hypertension [2]. According to 2009-2012 NHANES data, 46% of individuals with hypertension do not have it controlled [2]. A recent review emphasized the benefits of blood pressure lowering for the prevention of cardiovascular disease [4]. Blood pressure lowering < 130 mmHg for systolic blood pressure decreases the risk of cardiovascular disease and death [4]. Several modifiable factors contributing to hypertension have been identified including tobacco use, psychological stressors, diet and sleep apnea [2].

Guidelines stress the importance of dietary and lifestyle interventions to optimize blood pressure levels [5]. Dietary therapies such as omega-3 fatty acids offer an easy, alternative approach for blood pressure management. The benefits of omega-3 fatty acids in preventing coronary heart disease have been well documented in many studies as well as the recent Pooling Project of 19 Cohort Studies [6] and a meta-analysis of randomized controlled trials and prospective cohort studies [7]. These studies showed that EPA and DHA are associated with reduced risk of coronary heart disease.

Long chain omega-3 polyunsaturated fatty acids obtained in the diet from fatty fish and fish oils, are cardioprotective nutrients with many beneficial features including anti-inflammatory, anti-thrombotic, anti-arrhythmic, anti-hypertensive and anti-hyperlipidemic [8]. Convincing evidence suggests a positive role for dietary omega-3 fatty acids in reducing systolic and diastolic blood pressure [9,10]. The purpose of this paper is to review the scientific and clinical evidence on the vasculoprotective role of omega-3 fatty acids in hypertension. The review also focuses on the metabolism of omega-3 fatty acids as well as the vascular physiology, pathophysiology associated with hypertension and potential mechanisms of action for long-chain omega-3 fatty acids, EPA and DHA in lowering blood pressure. The guidelines for dietary Intake of omega-3 fatty acids and measurement of omega-3 fatty acid intake are presented.

Guidelines for dietary intake of omega-3 fatty acids

Reportedly 30 million Americans consume fish oil to improve their health [11]. Despite the prevalent use of fish oil, < 25% are directed by health care providers [12]. For cardiovascular health, consumption of two servings of fish per week (equivalent to

approximately 1 gram of EPA and DHA daily) is recommended for individuals with no prior history of coronary heart disease and at least one serving of fish daily for those with known coronary heart disease [13]. Based on the current evidence, a U.S. federal report suggests that even 200-300 mg/day of EPA and DHA is cardioprotective [14].

Many cardiovascular clinical trials have utilized higher doses of 3 grams of EPA and DHA or more daily [10]. Fish oil supplements are also recommended because they are more highly concentrated, purified and easier to consume. Four to ten capsules can provide 3 grams of EPA and DHA or more daily. Additional studies have shown that DHA supplementation alone may be a more effective alternative with cardiovascular benefits [15-18]. For blood pressure lowering, clinical trials with omega-3 fatty acid doses in the range of 2-4 grams/day have decreased systolic and diastolic blood pressure by 4 and 2 mmHg, respectively [19].

Rich dietary sources of omega-3 fatty acids include cold-water seafood such as salmon, herring and krill as well as plants and algae. It is important to note that the levels of omega-3 fatty acids are higher in wild-caught fish compared to farm-raised fish.

No clinically significant adverse effects of fish oil have been reported at doses up to 4 grams/day [8]. Minimal side effects at high doses may include mild gastrointestinal discomfort or fishy belching [20]. Freezing of the capsules reportedly eliminates the later effect. No adverse interactions have been reported with medications such as lipid-lowering drugs or anti-hypertensive medications [8]. However, caution is recommended if high doses of EPA and DHA (>3 grams/day) are used if combined with aspirin or blood thinners (ex. warfarin) due to the risk of increased bleeding [21].

Measurement of omega-3 fatty acid intake

A marker for cardiovascular risk based on the measurement of blood concentrations of omega-3 fatty acids is the Omega-3 Index [22,23]. The index is reflective of the omega-3 fatty acid content of EPA and DHA in the red blood cell membranes (% of total fatty acids). The fatty acid composition of red blood cell membranes represents long-term exposure to circulating fats [24] so it may be a robust, useful biomarker to assess patients with hypertension. The Omega-3 Index in the United States ranges from 4- 6 % compared to Japan where fish consumption is increased and the index is approximately 9% [25]. The greatest cardioprotection is associated with an Omega-3 index of ≥8% while an index of ≤ 4% is the least cardioprotective or associated with increased risk of coronary heart disease death [22,23,26] (Figure 1).

The Omega-3 Index can be modified by increasing intake of omega-3 fatty acids. One study reported that supplementation with 1.8 grams/day of EPA and DHA for 5 months resulted in an Omega-3 Index increase to 9.5%, well above the cardioprotective range [27]. The Omega-3 Index is also correlated with omega-3 fatty acid content in the heart [28]. It offers several advantages over other blood tests for omega-3 fatty acid intake and has been studied extensively for the past 10 years [29]. The Omega-3 Index has been shown to have low biological variability of

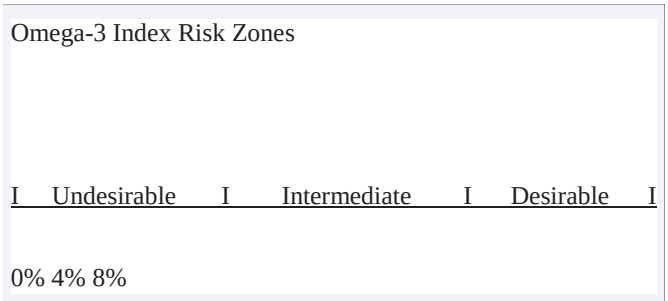

Figure 1 The Omega-3 Index is reflective of the EPA and DHA content in red blood cell membranes. The estimated target levels for cardioprotection are in the desirable range at 8% or greater, intermediate range between 4 and 8%, and <4% is considered undesirable or associated with increased risk of coronary heart disease risk. Adapted from Harris W.S. 2007 [23].

EPA and DHA compared to whole blood, plasma, and plasma phospholipids [29]. Further research is needed to validate the use of the Omega-3 Index in hypertensive patients. However, given the existing evidence for the blood pressure lowering effect of omega-3 fatty acids, the Omega-3 Index offers great promise to assess hypertensive patient's response to dietary omega-3 supplementation.

Metabolism of omega-3 fatty acids

Omega-3 polyunsaturated fatty acids are long chains of 18-22 carbon atoms with two or more double bonds. A double bond at the third bond position from the methyl end of the fatty acid molecule signifies an "omega-3" fatty acid. These fatty acids can be obtained in the diet from many sources or by supplementation as fish oil. The primary omega-3 fatty acids are α-linolenic acid (ALA; 18:3n3), EPA (20:5n-3) and DHA (22:6n3). (Figure 2) ALA is considered essential because it cannot be synthesized by the body. ALA is obtained from flaxseed, soybean, linseed and canola oils, walnuts and green leafy vegetables [30]. EPA and DHA are found in fish and fish oil. DHA can also be harvested from marine algae and taken alone in supplement form. Both long chain fatty acids EPA and DHA can be synthesized from ALA through a series of enzymatic steps of carbon chain elongation and desaturation but it is a slow, inefficient process.

Dietary intake of omega-3 fatty acids from fatty fish or fish oil supplements provides EPA and DHA directly and much more efficiently preformed, thereby bypassing the synthesis steps from ALA. Following consumption, omega-3 fatty acids are digested in the small intestines which facilitate absorption and transportation in the blood. EPA and DHA are transported in the circulation via lipoproteins or with albumin and stored in various organs and tissues in the body. They are also constituents of all cell membranes in the phospholipids where they maintain structural integrity and important functions throughout the body [29]. In human and animal studies, the EPA and DHA content in plasma, organs and tissues can be increased by dietary omega-3 fatty acid supplementation [31,32].

EPA and DHA are precursors to prostaglandins, thromboxanes and leukotrienes, collectively called eicosanoids. These lipid mediators are cardioprotective with anti-inflammatory, anti-

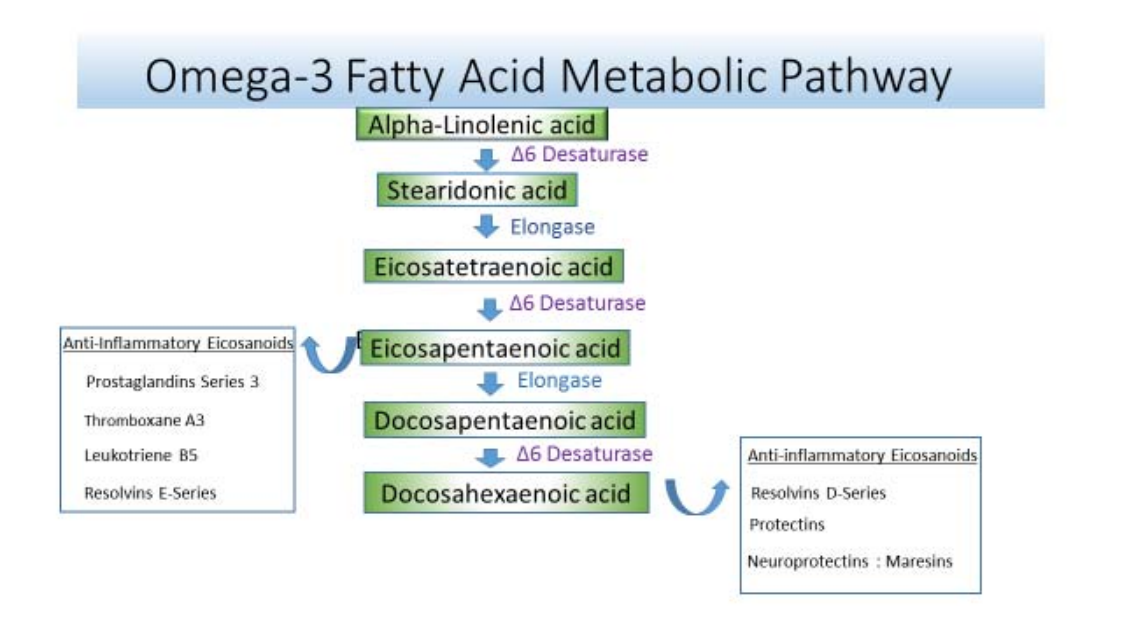

Figure 2 The diagram illustrates the metabolic pathway of omega-3 fatty acids and the conversion to longer chain polyunsaturated fatty acids (eicosapentaenoic acid: EPA and doscosahexaenoic acid: DHA). The parent omega-3 fatty acid is alpha-linolenic acid derived from nuts, seeds, oils and green leafy vegetables. Alpha-linolenic acid is converted to long chain EPA and DHA in the body through a series of elongation and desaturation steps. EPA and DHA derived from seafood and fish oil, are precursors of bioactive eicosanoids including prostaglandins, thromboxanes, leukotrienes and resolvins. DHA can also be retroconverted to form EPA [99]. Adapted from Harris WS 2008 [100].

thrombotic, anti-arrhythmic, and vasodilatory effects. They are synthesized from 20-carbon fatty acids in response to inflammatory signals. The eicosanoids formed from EPA are typically anti-inflammatory or inactive. Pro-resolving mediators derived from omega- 3 fatty acids include resolvins, protectins and maresins [33,34].

Vascular physiology, endothelial function and the pathophysiology of hypertension

The endothelium is comprised of a "cobble-stone" like pathway of endothelial cells lining the arterial lumen and serves as a barrier between the blood and interstitial space [35]. It plays an integral role in maintaining the structure and function of the cardiovascular system. Its functions are regulated by endocrine, paracrine and autocrine signals [36]. The endothelium is a key regulator of vascular health and maintains homeostasis by continually releasing vasoactive substances. Potent vasoactive factors including nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF), and prostacyclin (PGI_2) are produced by the endothelial cells. A balance in the production of these vasodilatory and vasoconstrictor factors contributes to vascular homeostasis. The endothelial cells also express adhesion molecules such as ICAM and VCAM that mediate the inflammatory process associated with atherosclerosis. The omega-3 fatty acids inhibit inflammation by altering the endothelial cell membranes, producing anti-inflammatory eicosanoids and suppressing expression of adhesion molecules [37,38,30].

Endothelial function is assessed by flow-mediated dilation, a non-invasive measure obtained by high resolution ultrasound of the brachial artery following reactive hyperemia. The vasodilatory response is dependent on release of nitric oxide from the endothelium [39]. Nitric oxide produced by the vascular endothelium is an important factor regulating blood pressure [40]. Nitric oxide is formed in the endothelium from the amino acid L-arginine via the enzyme nitric oxide synthase. Impairment in the synthesis pathway has been associated with essential hypertension [41] Nitric oxide mediates the dilation of vascular smooth muscle cells by increasing production of cyclic-guanosine monophosphate (cGMP) which results in activation of cGMP-dependent protein kinase [40].

Nitric oxide protects the endothelium by inhibiting platelet aggregation and adhesion, leukocyte adhesion to the vessel wall and proliferation of vascular smooth muscle cells [42]. Changes in endothelial function such as a loss of nitric oxide in the endothelium predisposes the vasculature to inflammation, oxidative stress, thrombosis and atherosclerosis. Endothelial dysfunction indicates abnormalities in vasodilatory capacity and is characterized by reduced nitric oxide bioavailability [36]. Endothelial dysfunction is also the initiating event in atherosclerotic coronary artery disease and subclinical target organ damage in essential hypertension [43].

Previous investigations have shown that patients with essential hypertension have impaired nitric oxide-mediated vasodilation in the coronary arteries [44,45]. In addition, a clinical investigation demonstrated that endothelial dysfunction in hypertension measured by forearm blood flow is an independent predictor of future cardiovascular events [46]. Specific drugs such as angiotensin-converting enzyme inhibitors (ACEs) and angiotensin receptor blockers (ARBs) reportedly improve endothelial function [47]. However, studies also suggest that

omega-3 fatty acids enhance the production of nitric oxide from the endothelial cells [48,49] and improve endothelial function [15,16]. This produces a cascade of beneficial physiological effects that increase flow-mediated dilation and inhibit the development of atherosclerosis (Figure 3).

Endothelial function is measured invasively by quantitative angiography of the coronary arteries. The first non-invasive test to measure endothelial function was described by Celermajer in 1992 [50]. Early investigations demonstrated endothelial dysfunction in hypertensive patients [44,45,51]. Numerous investigations assessing endothelial function in health and disease have since been conducted to increase our understanding of the clinical significance.

High resolution ultrasound of the brachial artery following reactive hyperemia is used to assess flow-mediated dilation, a noninvasive surrogate for endothelial function. Flow-mediated dilation in the brachial artery correlates with endothelial dysfunction in the coronary arteries [52]. This vascular measurement provides prognostic information about the presence of coronary artery disease or status of the arteries in the heart. It is widely used in clinical research and predictive of coronary artery disease.

During the measurement, blood flow is interrupted by an inflated cuff and this produces ischemia. When the cuff is deflated, blood flow and shear stress increases, which stimulate release of nitric oxide and produces vasodilation. The change in diameter of the brachial artery is measured from the ultrasound arterial images and flow-mediated dilation is quantified. This is related to nitric oxide bioavailability and endothelial function is determined [53]. This rigorous methodology for measurement of endothelial function is easy to repeat in patients but arterial image acquisition requires a trained, experienced vascular sonographer with the procedure conducted under specific controlled conditions. The patient needs to fast overnight before the measurement, the room needs to be temperature controlled and the patient is supine for the testing [54]. The measurement of endothelial function with high resolution ultrasound is accurate, reproducible, predictive of coronary artery disease and low risk for the patient [55].

The mechanism for endothelial dysfunction in hypertension

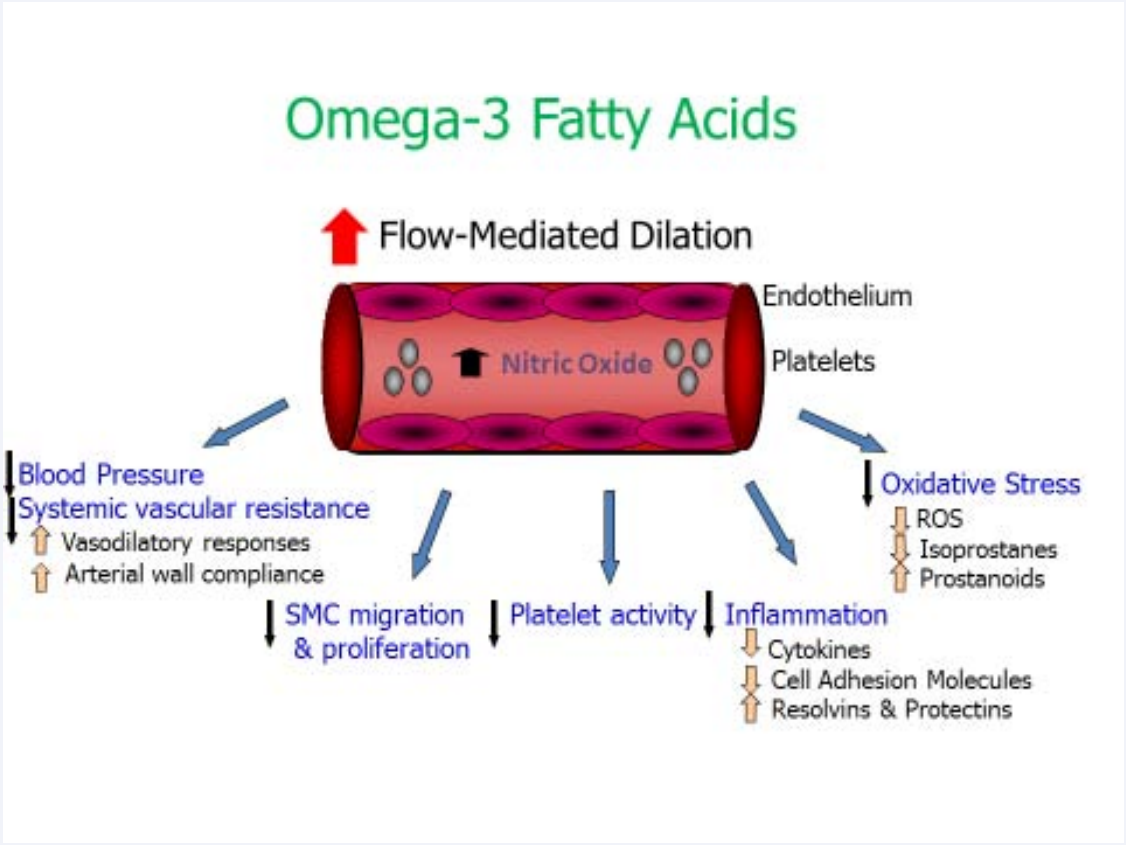

Figure 3 The diagram depicts the potential mechanisms for the cardioprotective effects of omega-3 fatty acids. Incorporation of these fatty acids into the vasculature increases flow-mediated dilation, lowers blood pressure and systemic vascular resistance. Other effects include changes in vascular wall permeability by decreasing smooth muscle cell (SMC) migration and proliferation, a reduction in platelet activity, prevention of inflammation by inhibiting cell adhesion and decreasing synthesis of pro-inflammatory cytokines. Resolvins and protectins are formed from omega-3 fatty acids and have potent anti-inflammatory properties. Omega-3 fatty acids also decrease oxidative stress by reducing formation of reactive oxygen species (ROS) and isoprostanes which leads to increased nitric oxide bioavailability and vasodilation. Prostacyclin, a vasodilatory prostanoid, is also synthesized in the endothelial cells and vascular SMCs. Hypertension occurs when there is an imbalance in the production of endothelial-derived relaxing and contracting +factors [35].

has been attributed to an increase in superoxide production and reduced nitric oxide bioavailability [56,57]. Without nitric oxide, the endothelium loses its ability to protect the vasculature against inflammation, thrombosis, oxidative stress and atherosclerosis. Another mechanism for endothelial dysfunction in hypertension includes angiotensin-converting enzyme (ACE) which converts angiotensin I to vasoconstrictor angiotensin II in the endothelium. Angiotensin II plays an important role in endothelial dysfunction in hypertension by enhancing production of another vasoconstrictor, endothelin, which collectively presents as endothelial dysfunction [58]. Angiotensin II also causes the production of superoxide and by-product peroxynitrite. Oxidation of arachidonic acid induced by peroxynitrite leads to the synthesis of isoprostane, another vasoconstrictor [59]. The release of these vasoconstrictors shifts the balance and disturbs vascular homeostasis.

Endothelial function is reportedly improved with diets rich in monounsaturated or polyunsaturated fatty acids [60,61]. Previous studies assessing flow-mediated dilation of the brachial artery have shown that patients supplemented with fish oil have improved endothelial function [62]. We have previously shown that supplementation with algal-derived DHA (1.2 grams/day) for 6 weeks increases flow-mediated dilation and improves endothelial function in hyperlipidemic children at risk for early heart disease [15]. Increased DHA content in red blood cells is also associated with improved endothelial function [63].

Potential mechanisms of action for omega-3 fatty acids

Fatty acids are integral components of cell membranes which influence the physical properties and several cell functions such as ion transport, receptor interactions, cell signaling and gene expression [64,23, 65-68]. The fatty acids can also be converted to bioactive eicosanoids with anti-inflammatory, anti-thrombotic and vasodilatory properties. By increasing intake of omega-3 fatty acids, the fatty acid composition can be modified to include higher levels of EPA and DHA at the expense of omega-6 fatty acids particularly arachidonic acid [31,32,69]. The resulting decrease in arachidonic-acid derived eicosanoids such as PGE_2 and LTB_4 produces an anti-inflammatory effect. Eicosanoids derived from EPA like PGE_3 and LTB_5 are less biologically active than arachidonic-acid derived eicosanoids and they have anti-inflammatory properties.

Changesin the fatty acid composition of vascular cell membranes may affect endothelial function in hypertension. Omega-3 fatty acids incorporated into vascular endothelial and smooth muscle cells have a direct effect on vascular function. We have demonstrated that both EPA and DHA exert vasorelaxant effects in isolated arteries [70-74]. This has been demonstrated in experimental models of hypertension, hypercholesterolemia, aging [75-77] and in systemic arteries in hypercholesterolemic adults [78,79,62]. A meta-analysis of 16 randomized controlled trials also showed that supplementation with omega-3 fatty acids significantly improves endothelial function [80].

Interestingly, human studies have shown that patients supplemented with omega-3 fatty acids have higher content of EPA in carotid plaque phospholipids which is associated with decreased plaque inflammation and more stable atherosclerotic plaques [81]. This is clinically significant since plaque vulnerability to rupture is a major factor in acute cardiovascular events.

The favorable effects of EPA and DHA on blood pressure may be attributed to several potential mechanisms (Figure 3). Increased production or release of nitric oxide from the endothelial cells [82,48,49] induces vasodilation. Blood pressure and systemic vascular resistance are decreased as a result. Arachidonic acid – mediated inflammatory pathways may also be inhibited by the replacement of arachidonic acid with ω-3 fatty acids in cell membrane phospholipids [83]. Increased biosynthesis of lipid mediators such as eicosanoids, resolvins, protectins, and maresins derived from ω-3 fatty acids may vasodilate arteries and inhibit inflammatory processes [33]. They may also protect tissue from damage in ischemic episodes.

Evidence for EPA and DHA in Hypertension

The cardioprotective effects of omega-3 fatty acids, EPA and DHA, have been demonstrated in numerous clinical, experimental and epidemiological studies. Omega- 3 fatty acids have many beneficial physiological effects that may prevent or inhibit atherosclerotic heart disease. Over the last two decades, the evidence from randomized controlled intervention trials is compelling for the blood pressure lowering effects of fish oil rich in EPA and DHA [10,19,84,85]. Differing doses of omega-3 fatty acids between 2-4 grams/day have been evaluated in clinical trials of hypertension. Meta-analyses of controlled clinical trials with fish oil supplementation have demonstrated that the blood pressure reduction is dose (> 3 grams/day) and time dependent with significant blood pressure reductions (5.5 mmHg systolic and 3.5 mmHg diastolic) [10,84]. Overall, additional studies have reported improvements in blood pressure with reductions of 4 mm Hg in systolic and 2 mm Hg in diastolic blood pressure [19].

The results of meta-analyses of 36 randomized clinical trials showed that fish oil supplementation (3.7 grams/day of EPA and DHA) lowered systolic blood pressure by 2.1 mm Hg and diastolic blood pressure by 1.6 mm Hg, respectively [85]. A meta-analysis of 70 randomized controlled trials with provisions of EPA and DHA (mean 3.9 grams/day) demonstrated a reduction in blood pressure, 4.51 mmHg systolic and 3.05 mmHg diastolic. They also showed that this was as effective or more than other life-style interventions such as physical activity and restricting alcohol and sodium to lower blood pressure in hypertensive populations not taking anti-hypertensive medications [86]. A 4 mm Hg reduction in blood pressure is clinically meaningful since the risk of coronary artery plaque rupture and stroke is also reduced [87]. A recent study in adults with isolated systolic hypertension consuming low doses of fish oil with both EPA and DHA (1.8 grams/day) for 8 weeks demonstrated significant reductions in blood pressure [88]. Previous studies assessing flow-mediated dilation of the brachial artery have shown that patients supplemented with fish oil rich in EPA and DHA have improved endothelial function [62].

Evidence has also emerged that DHA alone is a potent anti-hypertensive nutrient [16]. Two clinical trials investigating supplementation with low dose DHA and EPA demonstrated that only DHA lowered blood pressure [17,18]. Even higher

doses of DHA (4grams/day) given to overweight adults for 6 weeks significantly reduced blood pressure [89]. We have previously reported that dietary supplementation with DHA for 6 weeks attenuated the development of hypertension by 34 mm Hg in young spontaneously hypertensive rats [31]. This anti-hypertensive response was associated with a marked increase in DHA at the expense of omega-6 fatty acids in systemic arteries as well as various organs including the heart, liver and kidneys [31].

In hypertension, the pathology of the artery changes with increased arterial wall thickness due to abnormal growth and hypertrophy of vascular smooth muscle cells [91]. In experimental hypertensive animal studies, we have shown that DHA supplementation has a direct effect on the vasculature leading to the attenuation of hypertension and vascular hypertrophy [91]. Hypertension- induced vascular wall thickness is reduced in both the coronary artery and aorta of the hypertensive rat supplemented with DHA [91]. Other potential mechanisms for the blood pressure lowering effect of DHA include blunting of the renin-angiotensin-aldosterone system by decreasing adrenal synthesis of aldosterone [90], changes in renal arachidonic acid metabolism [90], modulation of calcium release and influx in vascular smooth muscle cells, and activation of vascular ATP-sensitive potassium channels by vasodilatory prostanoids [70]. Additional mechanisms have been proposed including suppression of vasoconstrictor prostanoids, release of nitric oxide, reduced plasma noradrenaline, changes in calcium flux, antioxidant effects of omega-3 fatty acids and an increase in HDL cholesterol [92]. We have found that DHA supplementation (1.2 grams /day for 6 weeks) improved the lipoprotein subclass profile without significant changes in total cholesterol, LDL, HDL or triglyceride concentrations [93]. However, we found that the less atherogenic, large buoyant LDL subclass increased by 91% and the more atherogenic, small, dense LDL subclass decreased by 48% with DHA supplementation [93].

A recent investigation of the serum fatty acid profile in cases of newly diagnosed hypertension showed that the distinguishing fatty acid feature was a lower DHA content compared to match controls (Yang B 2016). This is supported by a meta-analysis of clinical studies that showed DHA had a better dose-response effect on blood pressure than EPA [84]. Another study demonstrated that DHA supplementation decreased blood pressure in hyperlipidemic adults compared to EPA [95]. Moreover, a clinical trial in overweight, young adults consuming fatty fish for 8 weeks showed that baseline red blood cell DHA content was associated with the greatest reduction in diastolic blood pressure [96]. Consistent with these findings, higher serum phospholipid levels of DHA were associated with lower clinic, resting, or 24-hour diastolic blood pressures [97].

The cardiovascular benefits of omega-3 fatty acids have even been demonstrated in cardiac surgery patients supplemented with omega-3 fatty acids prior to surgery. Length of hospital stay was reduced up to 2.4 days and attributed to the anti-inflammatory and anti-arrhythmic properties of omega-3 fatty acids [98].

CONCLUSION AND FUTURE DIRECTIONS

This review provides evidence from relevant clinical and experimental research investigations supporting the important role of dietary long chain omega-3 fatty acids in hypertension. In particular, we examined the effects of omega-3 fatty acids on physiological function as shown in Figure (1). EPA and DHA exert their cardioprotective effects through direct incorporation into cell membranes and by influencing important cell functions. Endothelial dysfunction is related to hypertension and target organ damage. Moreover, endothelial dysfunction in hypertension is predictive of future cardiovascular events. Various mechanisms associated with endothelial dysfunction were discussed. Omega-3 fatty acids improve endothelial function and lower blood pressure. Assessment of endothelial function may be useful in guiding therapy for hypertension. To optimize blood pressure levels in hypertension and for cardioprotection, the evidence indicates that fish oil doses of 4 grams/ day may be needed. Omega-3 fatty acids are also a safe therapy with no significant side effects reported after supplementation.

Future investigations are needed to determine appropriate dosages and duration for optimal blood pressure control. Important considerations in designing and optimizing future clinical trials with omega-3 fatty acids include assessment of omega-3 fatty acid status before and during treatment, adequate dosage of omega-3 fatty acids EPA and/or DHA, treatment duration, and increasing the number of subjects to maximize statistical power [29]. Moreover, the patient's health status, baseline fish consumption and concurrent medication therapy can also influence outcomes [30]. These are key factors that need to be considered in future investigations to determine the efficacy of omega-3 fatty acids in hypertension.

Determination of omega-3 fatty acid status also verifies compliance with the omega-3 fatty acid intervention. It may also prove to be useful in monitoring blood pressure responses to dietary omega-3 fatty acid intake. The omega-3 fatty acid status can be assessed by measuring circulating fatty acids such as whole blood, plasma or red blood cells. The Omega-3 Index which is the EPA and DHA content in red blood cell membranes has been studied extensively and has been shown to have low biological variability of EPA and DHA compared to whole blood, plasma and plasma phospholipids [29]. Moreover, studies which assess the Omega-3 index in hypertensive individuals are warranted. The Omega-3 Index could be determined at baseline in hypertensive patients and after dietary interventions to increase omega-3 intake while monitoring blood pressure. Current evidence also suggests that DHA alone may be more effective than EPA for hypertension. Further studies are needed to differentiate the appropriate omega-3 ratio for optimal blood pressure management. Personalized nutrition may evolve with specific recommendations for hypertensive individuals to reach and maintain optimal blood pressure levels based on the Omega-3 index.

A recent call to action to control hypertension identified several challenges to address the problem [99]. Key action items proposed for the prevention and treatment of hypertension include: 1. simplifying treatment options; 2. healthcare provider's failure to achieve target blood pressure goals, and, 3. poor patient education. This represents a significant opportunity for nurses and clinicians to empower patients with educational programs

and tools about high blood pressure. Another strategy includes assessing responsiveness to therapy in hypertensive patients by monitoring their progress. Technological advances such as mobile apps can also be used for self-assessment to monitor blood pressure at home.

Hopefully, this review will provide practical information for nurses and clinicians to guide discussions with patients in the use of omega-3 fatty acids for managing their hypertension.

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