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Omega-3 Polyunsaturated Fatty Acids in Blood Pressure Control and Essential Hypertension

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Abstract

Hypertension is a worldwide problem that affects up to 22% of adults and contributes to the global burden of disability due to cardiovascular disease. Several factors influence blood pressure and participate to the development of hypertension. Among these factors, polyunsaturated fatty acids of the omega-3 family (omega-3 PUFA) are effective hypotensive agents. Through their anti-inflammatory and antioxidant properties, omega-3 PUFA can improve cardiac hemodynamics and vascular function and potentially reduce arterial stiffness and atherosclerotic damage. However, despite this promising evidence many meta-analyses on the cardiovascular effect of omega-3 PUFA were inconclusive. The choice of the omega-3 PUFA sources, baseline tissue content of these fatty acids, and individual compliance to their intake can be reasons for such a discrepancy between studies. Basic and clinical research on these fatty acids documents interesting mechanisms through which these molecules could be useful in the treatment of hypertension and its related organ damage. The role of the maternal dietary habit during pregnancy and the quality of prenatal growth on the effect of omega-3 PUFA in cardiovascular system need further investigations. This chapter summarizes the literature of the past 30 years on the antihypertensive effects of this family of essential fatty acids.

Keywords: Omega-3 fatty acids, Cardiovascular disease, Atherosclerosis, Vascular function, Oxidative stress

1. Introduction

Worldwide, hypertension affects more than one billion people and about 22% of individuals older than 18 years suffer from this disease. Untreated hypertension increases the risk and mortality for myocardial infarction and stroke, as well as it is responsible for chronic invalidating disorders such as coronary and peripheral vascular diseases, heart and renal failure, and visual impairment, all problems that heavily impact the individual's quality of life [1]. Although a descending trend of blood pressure levels has been observed in the past decades [2], hypertension remains the most underdiagnosed, undertreated, and uncontrolled problem [3] among the noncommunicable diseases. For these reasons, the prevention of hypertension is one of the main goals of the global healthcare system.

Primary or essential hypertension is diagnosed when secondary causes of high blood pressure are excluded [4]. Therefore defined, essential hypertension is a modifiable cardiovascular risk factor often associated with several inappropriate conditions related to lifestyle habits, such as overweight/obesity, excess of alcohol consumption, and high salt intake. Lifestyle changes have proven to reduce blood pressure and are highly recommended as the first step to treat hypertensive disease in all affected patients [4]. Among these changes, dietary habits have a primary role because food quantity affects directly body weight and food quality can modulate some minerals and nutrients associated with blood pressure regulation. For example, low salt and low alcohol intake, and increased consumption of polyunsaturated fatty acids of the omega-3 family (omega-3 PUFA) have shown to reduce blood pressure levels and in some cases to reduce the cardiovascular risk [5]. In this chapter, we present evidence of the beneficial effects of omega-3 PUFA on blood pressure and hypertension-related organ complications.

2. Biochemistry and physiology of the omega-3 PUFA

Long-chain PUFA are present in all tissues of mammals; though mammals cannot directly synthesize these fatty acids because they lack enzymes to make double bonds at some position in the fatty acid chain. Therefore, long-chain PUFA need to be consumed with diet and for that reason they are “essential” fatty acids. Essential PUFA are those of the omega-6 and omega-3 families, whereas nonessential are those of the omega-7 and omega-9. Nonessential PUFA families can be synthesized directly from endogenous saturated fatty acids. The “omega” letter indicates the last methyl carbon opposed to the carboxyl group of the acyl chain and the expression of “minus 6” or “minus 3” indicates the position of the first double bond from the last methyl group. Fatty acids are abbreviated with the C letter standing for “carbon” followed by the number of carbons in the molecule, the number of double bonds separated by colon, and the PUFA family name [6].

Linoleic acid (C18:2, LA) is the precursor of long-chain omega-6 PUFA that is abundant in vegetable oils such as those derived from soybean, corn, and rapeseed and in some species of insects. The omega-6 arachidonic acid (C20:4, AA) derives from LA through elongation and desaturation of the acyl chain (**Figure 1**) and it is involved in important cellular processes

including eicosanoids and endocannabinoids production, inflammation, and hemostasis. The content of AA in vegetables is poor and its main source is animal-derived food. Alpha linolenic acid (C18:3, ALA), an analog of LA with one more double bond, is the precursor of long-chain omega-3 PUFA. By elongation and desaturation of its acyl chain, it is converted into the two principal long-chain omega-3 PUFA, the eicosapentaenoic acid (C20:5, EPA) and the docosahexaenoic acid (C22:6, DHA). ALA is from plant origin where it is abundant in seeds and vegetable oils, whereas EPA and DHA are mainly from marine source. In particular, fish directly synthesize EPA and DHA by ingesting phytoplankton enzymes. Since in humans the rate of conversion of ALA in EPA and DHA is relatively slow, the main source of omega-3 PUFA is seafood (**Table 1**). Enrichment in omega-3 PUFA content of cell membranes can be reached by omega-3 consumption for a relatively short time (days or weeks) [7].

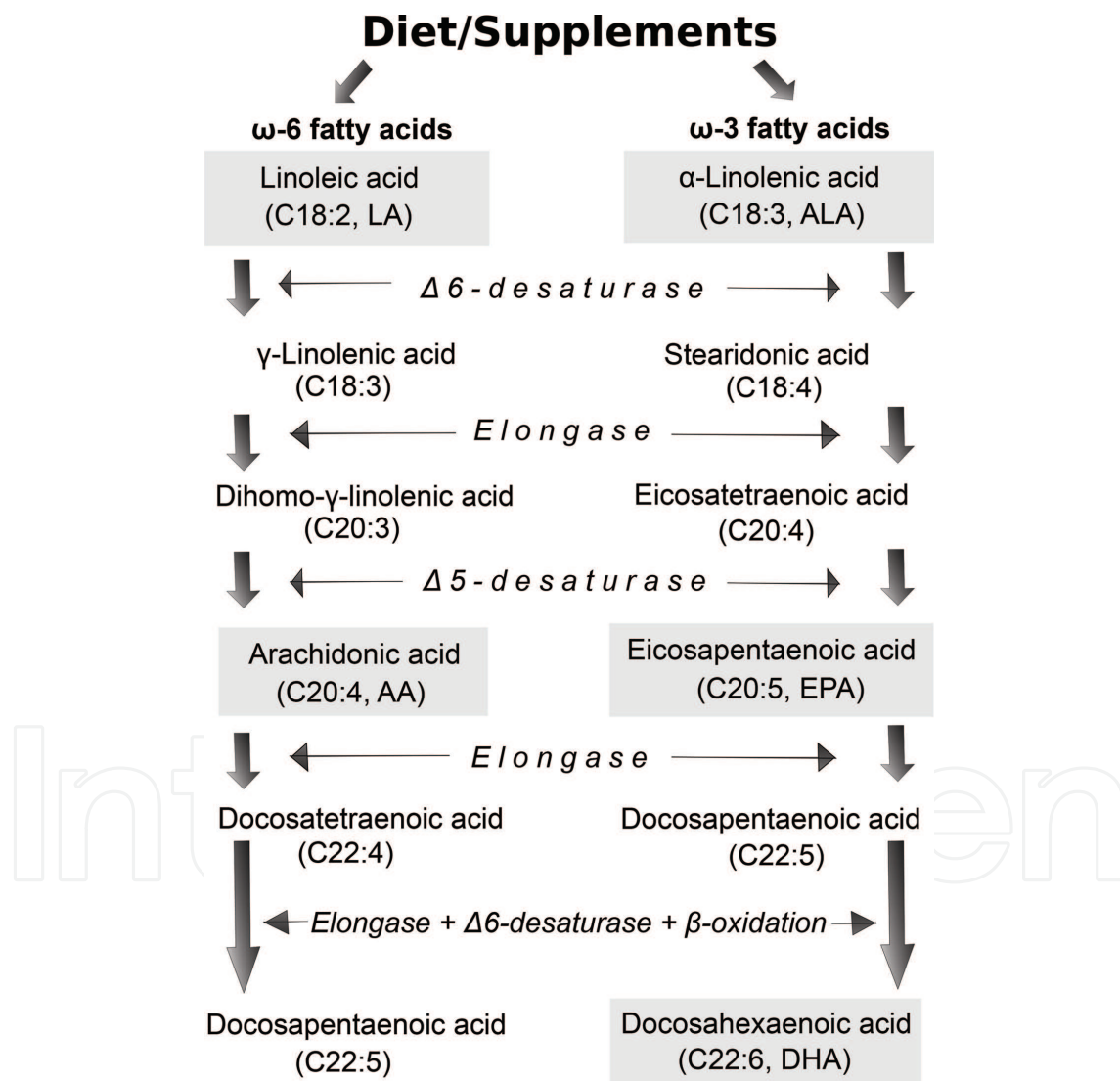


Figure 1. Biosynthesis of long-chain omega-6 and omega-3 polyunsaturated fatty acids from precursor essential fatty acids. The same elongase and desaturase enzymes act on linoleic and alpha-linolenic acids to produce omega-6 arachidonic acid and omega-3 eicosapentaenoic and docosahexaenoic acids, respectively. Only the last step of the biosynthetic pathway is located in peroxisomes where the beta-oxidation of 24-carbon long-chain fatty acids produce the final 22-carbon chains.

Source	Total PUFA (g/100g)	LA (g/100g)	AA (g/ 100g)	ALA (g/100g)	EPA (g/100g)	DHA (g/100g)	Amount (g) to provide about 1 g of omega-3 PUFA	Cholesterol (mg/100g)
Salmon oil	40.324	1.543	0.675	1.061	13.023	18.232	3	485
Menhaden oil	34.197	2.154	1.169	1.490	13.168	8.562	5	521
Sardine oil	31.867	2.014	1.756	1.327	10.137	10.656	5	710
Cod liver oil	22.541	0.935	0.935	0.935	6.898	10.968	6	570
Herring oil	15.604	1.149	0.289	0.763	6.273	4.206	7	766
Flaxseed oil	67.849	14.327	0	53.368	0	0	2	0
Mackerel, Atlantic, cooked, dry heat	4.300	0.147	0.051	0.113	0.504	0.699	83	75
Herring, Atlantic, cooked, dry heat	2.735	0.167	0.077	0.132	0.909	1.105	50	77
Salmon, Atlantic, farmed, cooked, dry heat	4.553	0.666	1.273	0.113	0.690	1.457	47	63
Tuna, fresh, bluefin, cooked, dry heat	1.844	0.068	0.055	-	0.363	1.141	66	49
Tuna, fresh, yellowfin, cooked, dry heat	0.175	0.023	0.018	0.002	0.015	0.105	833	47
Trout, mixed species, cooked, dry heat	1.922	0.224	0.242	0.199	0.259	0.677	107	63
Halibut, Atlantic and Pacific, cooked, dry heat	0.352	0.041	0.017	0.013	0.080	0.155	425	60
Cod, Atlantic, cooked, dry heat	0.292	0.006	0.028	0.001	0.004	0.154	633	55
Flaxseeds	28.730	5.903	0	22.813	0	0	4	0

Data from the National Nutrient Database for Standard Reference 28 (2015). United States Department of Agriculture.

PUFA, polyunsaturated fatty acids; LA, linolenic acid; AA, arachidonic acid; ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; and DHA, docosahexaenoic acid.

Table 1. Polyunsaturated fatty acids and cholesterol composition of the major edible sources of omega-3 polyunsaturated fatty acids.

Fatty acids are quickly incorporated in phospholipids of plasma, platelets, neutrophil, and red blood cells, whereas enrichment of other tissues takes longer time. Omega-3 PUFA accumulate especially in cerebral cortex, retina, testes, muscle, and liver; omega-6 are ubiquitous in all tissues. The process of elongation and desaturation of precursors of PUFA is competitive because the synthesis of omega-6 and omega-3 PUFA utilizes the same enzymatic pathway. Despite that, ALA is a more affine substrate for desaturases and conversion of ALA into long-chain omega-3 PUFA is more efficient than that of LA into AA. Therefore, increased ALA availability reduces AA formation and the balance between omega-6 and omega-3 PUFA content in cell membranes can be modulated by changing the dietary habit. Accordingly, it has been shown that populations that live in regions with higher seafood consumption have lower omega-6 to omega-3 PUFA ratio than populations that live in farming-prevalent regions with a lower omega-3 PUFA consumption. Interestingly, the former populations are those with the lowest risk for cardiovascular mortality [8].

Deficiency of PUFA is rare in humans, because normal diet contains an adequate amount of omega-6 and omega-3 PUFA. However, signs of severe PUFA deficiency have been documented in premature infants with limited lipid stores or when these infants were fed with low lipid formulas; such signs were severe skin rash, loss of hair, and irritability. Several clinical conditions may also be associated with PUFA deficiency [9]. Clinical manifestations associated with PUFA deficiency consist of dermatitis, increased skin-water permeability, susceptibility to infection, higher sensitivity to radiation damage, impaired wound healing, hematological abnormalities, and fatty liver disease. Biochemically, PUFA deficiency is associated with an increased eicosatrienoic acid (C20:3 omega-9) to AA ratio (Holman index) because mammals can use oleic acid (C18:1 omega-9) as a precursor of long-chain PUFA only in the absence of the other families [10].

3. Effects of omega-3 PUFA on blood pressure regulation

Arterial blood pressure is the product of cardiac output and peripheral vascular resistance to blood flow. Cardiac output results from the stroke volume times the heart rate, whereas the vascular resistance to blood flow depends on the vascular function. Regulation of arterial blood pressure derives from a complex interaction between cardiovascular cell components with autocrine, paracrine, and endocrine factors and the involvement of the nervous and immune systems. Many physiologic systems are involved in blood pressure regulation such as that of baroreceptor signals, natriuretic peptides, renin-angiotensin-aldosterone, kinin-kallikrein, and catecholamine. In addition, several genetic, anthropometric, and dietetic factors can influence blood pressure, such as family history, age, gender, body mass index, and consumption of salt. Classically, hypertension is a multifactorial complex disease mainly related to an initial abnormality in the kidney that leads to inappropriate tubular sodium retention, intravascular volume expansion, cardiac overload, vascular dysfunction, and sustained high blood pressure levels [11].

Arterial hypertension is defined in adults when systolic (SBP) and diastolic (DBP) blood pressure levels persist over 140 or 90 mm Hg, respectively [4]. In fact, over these thresholds

lowering blood pressure is protective for the occurrence of organ damage and cardiovascular events. Reducing blood pressure by a few mm Hg in hypertensive patients can significantly decrease the incidence of stroke and coronary events [12] independently of the class of drug used [13]. Omega-3 PUFA intake has shown to reduce blood pressure especially in hypertensive patients by interacting with several mechanisms of blood pressure regulation (**Table 2**).

Mechanisms of blood pressure regulation
<ul style="list-style-type: none">• Reduction of stroke volume and heart rate• Improvement of left ventricle diastolic filling• Reduction of peripheral vascular resistances<ul style="list-style-type: none">◦ Improvement of endothelial-dependent and -independent vasodilation<ul style="list-style-type: none">■ Stimulation of nitric oxide production■ Reduction of the asymmetric di-methyl-arginine (ADMA)■ Reduction of endothelin-1■ Relaxation of vascular smooth muscle cells■ Metabolic effects on perivascular adipocytes■ Endothelial regeneration
Mechanisms of hypertension-related organ damage protection
<ul style="list-style-type: none">• Anti-inflammatory, antioxidant, and antithrombotic effects• Reduction of arterial stiffness• Experimental effects on left ventricular hypertrophy and abnormal gene expression• Effects on atherosclerotic plaque progression and stability

Table 2. Mechanisms by which omega-3 polyunsaturated fatty acids can modulate blood pressure levels and protect from the hypertension-related organ damage.

3.1. Effects of omega-3 PUFA on cardiac function and hemodynamics

Omega-3 PUFA can influence blood pressure by acting on the cardiac hemodynamics. In particular, the influence of omega-3 PUFA on the electrophysiological properties of cardiomyocytes can account for the reduced heart rate and the antiarrhythmic effect of these molecules [14]. Mozaffarian et al. [15] published a meta-analysis on the effects of omega-3 PUFA on resting heart rate demonstrating that fish oil treatment can reduce the heart rate by few beats per minute with respect to placebo. Omega-3 PUFA have shown also to improve heart rate variability, heart rate response during exercise, and heart rate post-exercise recovery by modulating the vagal tone [16, 17].

Influences of omega-3 PUFA on heart rate and peripheral vascular resistance may explain the effects of these fatty acids on the left ventricular function. Studies on nonhuman primates firstly showed that fish oil consumption can enhance left ventricular diastolic filling by improving left ventricular diastolic volume, stroke volume, and myocardial efficiency [18, 19]. In addition, other experimental studies demonstrated that omega-3 PUFA can blunt the hypertrophic response of the left ventricle to the pressure overload and prevent the abnormal gene expression of cardiomyocytes [20, 21]. Evidence for hemodynamic effects of omega-3 PUFA in humans was also reported. In a parallel double-blind randomized controlled trial (RCT) in 224 young-adult and middle-aged healthy men, 4 g/day of ethyl ester DHA reduced the heart rate of 2.2 bpm with respect to placebo without affecting blood pressure levels. In another study, a small group of about 50 men taking omega-3 PUFA improved left ventricular diastolic filling assessed by echocardiography when compared to controls [22]. In a cross-sectional study, an increased intake of non-fried fish (tuna or other broiled or backed fish) was associated with lower blood pressure, lower heart rate, lower systemic vascular resistances, greater stroke volume, and better ventricular diastolic function. Conversely, fried fish intake was associated with worse cardiac function [23].

3.2. Effects of omega-3 PUFA on vascular function

Vascular function results from a complex interaction between neurohormonal signaling, circulating cells, immune system, and different components of the vascular wall. These components consist of endothelial cells, vascular smooth muscle cells, extracellular matrix, and perivascular adipocytes. There is a clear relationship between inflammation, oxidation, thrombosis, and endothelial dysfunction, conditions continuously interacting in a vicious circle that promote high blood pressure and the atherosclerotic process. Omega-3 PUFA have shown to modulate vascular resistance and blood pressure by acting on several determinants of the vascular function.

3.2.1. Omega-3 PUFA in inflammation and thrombosis

Omega-3 PUFA affect several mechanisms of the inflammatory process [24]. The intake of omega-3 PUFA increases these fatty acids in phospholipids of cells involved in inflammation at the expenses of omega-6 PUFA. Since AA is the precursor of the pro-inflammatory and pro-thrombotic eicosanoids (prostaglandins, leukotrienes, and thromboxanes), the reduction of AA by increasing omega-3 PUFA decreases the amount of AA-derived eicosanoids. In addition, EPA competes with AA for cyclooxygenase and lipoxygenase enzymes generating eicosanoid derivatives that are less pro-inflammatory and pro-thrombotic than those derived from AA.

Omega-3 PUFA are involved in the production of “specialized pro-resolving mediators” (SPMs) from EPA and DHA through the activity of cyclooxygenase and lipoxygenase enzymes. These molecules include resolvins (E- and D-series), protectins, and maresins. Their amount increases in plasma of subjects with a high intake of omega-3 PUFA and can be found in human milk during the first month of lactation. These molecules are actively involved in the termination (resolution) of an acute inflammatory process by activating local resolution programs

that include inhibition of trans-endothelial neutrophil migration, reduced pro-inflammatory cytokines production, limitation of leukocyte recruitment, enhancement of macrophage uptake of debris, bacteria and apoptotic cells, and tissue repair [25].

Omega-3 PUFA exert their anti-inflammatory properties also by inhibiting other pro-inflammatory mediators (platelet-activating factor, PAF; interleukin (IL)-1, -2, -6, and -8; tumor necrosis factor alpha) and several pro-inflammatory transcription factors (activator protein-1, AP-1; nuclear factor kappa-light-chain-enhancer of activated B cells, nuclear factor (NF)- κ B) [26, 27]. EPA and DHA can disrupt the small heterogeneous membrane microdomains (lipid raft) of inflammatory cells by changing their lipid composition. In these microdomains, several important processes for the cell take place, especially the activation of the pro-inflammatory NF- κ B [28].

In addition, omega-3 PUFA can modulate the activity of inflammasomes. Inflammasomes are a group of sensor and receptor proteins of the innate immunity assembled in an intracytoplasmic complex in response to harmful stimuli [29]. These stimuli consist of exogenous product such as bacterial or endogenous advanced glycation end products (AGEs), cholesterol crystals in atherosclerotic lesions, and oxidized low-density lipoproteins (ox-LDL) [30]. EPA and DHA can inhibit the inflammasome activation through the G-protein receptor (GPR)120/beta-arrestin2-dependent pathway by suppressing the nuclear translocation of the NF- κ B [31] and by stimulating inflammasome autophagy [32].

3.2.2. Omega-3 PUFA in mechanisms of endothelial dysfunction

Several experimental and human studies have demonstrated that omega-3 PUFA can improve endothelial function in both normal and damaged endothelium. In endothelial cells, the incubation with EPA stimulates the production of nitric oxide (NO) through the activation and translocation of the endothelial nitric oxide synthase (eNOS) from caveolae (a special type of cell membrane lipid raft) to the cytoplasm [33]. In experimental studies, NO produced via eNOS after EPA stimulation induced endothelial-dependent vasodilation of arteries [33, 34]. Omega-3 PUFA enhance endothelial-dependent vasodilation also in arteries with a damaged endothelium [35], by reducing plasma levels of the asymmetric dimethylarginine (ADMA), a potent endogenous inhibitor of the eNOS activity [36].

Other mechanisms by which omega-3 PUFA can improve endothelial dysfunction are antioxidation [37], reduction of the vasoconstrictive endothelin-1 (ET-1) [38], and the generation of omega-3 PUFA-derived epoxides from the metabolic pathway of the cytochrome P450 epoxygenases [39]. Recently, Hoshi et al. elucidated with an elegant work that DHA can directly induce relaxation of the vascular smooth muscle cells (VSMCs) and acutely reduce blood pressure in anesthetized mice. This effect was mediated by a direct hyperpolarization of the VSMC induced by DHA through the stimulation of the large-conductance calcium- and voltage-activated potassium channels (BK channels) [40]. The activation of BK channels by DHA depends from the activity of cytochrome P450 epoxygenase, since its selective inhibition abolishes the effect [41].

Omega-3 PUFA can modulate endothelial function also by regulating the endocrine activity of the perivascular adipose cells. Experimentally, ALA stimulates the release of adiponectine, an anti-inflammatory, insulin sensitizer, and vasodilating adipokine, from mature adipocytes by inhibiting calcium current through the calcium-permeable nonselective cationic channels [42]. Other metabolic important effects of omega-3 PUFA on the adipose cells are increased sensitivity to insulin through PPAR-gamma and GPR120 stimulation [28, 43] and increased production of anti-inflammatory endocannabinoids [44].

Omega-3 PUFA demonstrate an important endothelium protective and reparative effect. The treatment with EPA partially repairs endothelial damage induced by hyperlipidemia in rabbits [45]. Reparative effects of omega-3 PUFA can be mediated by their capacity to stimulate endothelial progenitor cells availability and by promoting endothelial regeneration and neo-angiogenesis in damaged vessels. These effects have been observed in experimental model of diabetic retinopathy [46] and cerebrovascular ischemia [47], and also in healthy individuals [48]. Recently, an endothelial regenerative effect of omega-3 PUFA has been demonstrated in low cardiovascular risk patients. In these patients, omega-3 PUFA promoted the production of endothelial progenitor cells and reduced the presence of endothelial cell-damaged micro-particles [49].

3.2.3. *Omega-3 PUFA in endothelial dysfunction in human studies*

Endothelial cell function can be indirectly assessed *in vivo* in humans by stimulating endothelial NO production with pharmacological or mechanical stimuli (endothelial-dependent vasodilation) and comparing the induced vasodilatory response with that induced by an exogenous nitrate-donor compounds (endothelial-independent vasodilation) [50]. The difference between endothelial-dependent and -independent vasodilation is proportional to the extent of endothelial dysfunction [51]. Endothelial dysfunction assessed with these techniques is an independent predictor of cardiovascular events and mortality [52]. Omega-3 PUFA have shown to improve endothelial-dependent vasodilation in several RCTs. The results of these studies were summarized in two recent systematic reviews and meta-analyses [53, 54]. In the first were included 16 RCTs involving 901 participants who took a dose of omega-3 PUFA ranging from 0.45 to 4.5 g/day for a mean of 56 days. Omega-3 PUFA slightly improved the flow-mediated vasodilation (FMD) of the brachial artery in treated patients. The effect was present especially in patients affected by a pathological condition respect to healthy subjects and was greater with a higher dose of omega-3 PUFA [53]. In the second meta-analysis were included 23 studies with 1385 participants. The source of omega-3 PUFA was fish oil with a dose ranging from 0.45 to 4.53 g/day and a treatment duration from 2 to 52 weeks. Again, the FMD response of the brachial artery was slightly better in treated patients. However, an inverse association between study quality and the improvement of FMD due to fish oil supplementation was observed and when authors considered only high-quality RCTs (19 studies) no overall effect was observed anymore [54]. Recently, many RCTs of different quality on the effect of omega-3 PUFA on endothelial-dependent vasodilation have been published. However, results of these studies are conflicting and again a final conclusion cannot be drawn [55–59].

4. Effects of omega-3 PUFA on hypertension and hypertensive-related organ damage

The first evidence of the hypotensive effect of omega-3 PUFA was observed more than 30 years ago and was summarized in two seminal systematic reviews and meta-analyses about 10 years later. The first meta-analysis selected 17 controlled clinical trials including 728 normotensive healthy individuals and 291 untreated hypertensive patients without any other comorbidity. The analysis showed a significant blood pressure reduction for SBP and DBP only in hypertensive patients. The omega-3 PUFA-lowering effect was directly related to the baseline levels of blood pressure [60]. The second meta-analysis included 31 controlled clinical trials with 1356 participants who were healthy or at risk for cardiovascular disease. The mean dose of omega-3 PUFA used was of 4.8 g/day as fish or fish oil for 3–24 weeks of treatment. Again, omega-3 PUFA reduced SBP and DBP only in hypertensive patients. Importantly, there was a total dose-response effect of $-0.66/-0.35$ mm Hg/g assumed of omega-3 PUFA [61]. Thereafter, many meta-analyses on the effect of omega-3 PUFA on blood pressure have been published [62–66] and are summarized in **Table 3**. All these meta-analyses confirmed a significant although small hypotensive effect of these fatty acids especially in hypertensive patients who are not taking any antihypertensive drugs. Evidence from observational prospective studies suggests also that baseline omega-3 PUFA intake can be associated with the occurrence of future development of hypertension [67].

First author, publication year [Ref.]	Included studies (individuals)	Populations	EPA+DHA (median, g/day)	Duration (median, weeks)	Effect on SBP (mm Hg, 95% CI)	Effect on DBP (mm Hg, 95% CI)
Apple, 1993 [60]	11 (728)	Healthy subjects	3.35	5	-1.0 (-2.0 to 0.0)	-0.5 (-1.2 to 0.2)
	6 (291)	Untreated hypertensive patients	5	8	-5.5 (-8.1 to -2.9)	-3.5 (-5.0 to -2.1)
Morris, 1993 [61]	8 (569)	Healthy subjects	4.3	6	-0.4 (-1.6 to 0.8)	-0.7 (-1.5 to 0.1)
	9 (415)	Hypertensive patients	4.75	6	-3.4 (-5.9 to -0.9)	-2.0 (-3.3 to -0.7)
Geleijnse*, 2002 [62]	27 (1354)	Without hypertension	–	–	-1.03 (-2.40 to 0.14)	-1.17 (-1.91 to -0.43)
	23 (760)	With hypertension	–	–	-3.97 (-5.66 to -2.15)	-2.46 (-3.44 to -1.47)
Dickinson, 2006 [63]	8 (375)	Hypertensive patients	4.5	11	-2.3 (-4.3 to -0.2)	-2.2 (-4.0 to -0.4)
Campbell, 2013 [64]	9 (1049)	Normotensive subjects	2.55	12	-0.50 (-1.44 to 0.45)	-0.53 (-1.24 to 0.19)
	8 (475)	Hypertensive patients	3.4	11	-2.56 (-4.53 to -0.58)	-1.47 (-2.53 to -0.41)

First author, publication year [Ref.]	Included studies (individuals)	Populations	EPA+DHA (median, g/day)	Duration (median, weeks)	Effect on SBP (mm Hg, 95% CI)	Effect on DBP (mm Hg, 95% CI)
Miller, 2014 [66]	56 (3533)	Normotensive subjects	2.6	6.5	-1.25 (-2.05 to -0.46)	-0.62 (-1.22 to -0.02)
	16 (942)	Untreated hypertensive patients	3	6	-4.51 (-6.12 to -2.83)	-3.05 (-4.35 to -1.74)

PUFA, polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CI, confidence intervals.

* Studies included in subgroup analysis were not specified; therefore, no median dose and treatment duration can be calculated.

Table 3. Principal meta-analytical studies on the effects of omega-3 polyunsaturated fatty acids on blood pressure levels in healthy subjects and hypertensive patients.

Another source of omega-3 PUFA, flaxseeds or flaxseed-derived oil, showed anti-inflammatory, antioxidant, and blood pressure-lowering effects in animals and cardiovascular risk patients. Flaxseed is the seed of *Linum usitatissimum*, the richest source of ALA. A recent meta-analysis by Khalesi et al. [68] on 14 trials demonstrated a significant lowering effect on SBP (1.77 mm Hg; 95% confidence interval (CI): -3.45 to -0.09, $P = 0.04$) and DBP (1.58 mm Hg; 95% CI: -2.64 to -0.52, $P = 0.003$) of flaxseeds or flaxseed oil intake. An interesting mechanism suggested for blood pressure reduction of flaxseed was the inhibition of the epoxide hydrolase by ALA that reduced the production of vasoconstrictive oxylipins [69].

4.1. Studies with ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) evaluates blood pressure levels over 24 h giving information on daytime and nighttime blood pressure profiles and their circadian variations. ABPM is a useful tool for the diagnosis of hypertension and for definition of the full-day efficacy of antihypertensive treatments. Several observational and interventional studies have evaluated the effect of omega-3 PUFA on ABPM, though with inconsistent results [70, 71]. We followed up a group of uncomplicated hypertensive patients who were advised to take a diet rich of PUFA by assuming a fish meal three times a week for 6 months. ABPM parameters and omega-3 PUFA enrichment of red blood cell plasma membranes were evaluated at baseline and at the end of the study. Twenty-four-hour and nighttime SBP/DBP were reduced only in patients that increased omega-3 PUFA in cell membranes and the effect was more pronounced in patients with a lower baseline omega-3 PUFA content [72]. Our findings underline the importance of the baseline omega-3 PUFA status in cell membranes as a determinant of the hypotensive effect of these fatty acids. Also, our observation might explain the discrepancy observed among previous studies that did not assess the compliance to dietary prescriptions.

The different effect of EPA and DHA on blood pressure was evaluated by Mori et al. in a small RCT of overweight mild hyperlipidemic men. Specifically, at the end of the follow-up only DHA treatment reduced 24 h and daytime ambulatory SBP/DBP with respect to placebo

(5.8/3.3 and 3.5/2.0 mm Hg, respectively). Also, DHA treatment was effective to reduce 24-h, daytime, and nighttime heart rate [73].

4.2. Arterial stiffness

Arterial stiffening is caused by the loss of vascular elasticity due to factors such as aging and atherosclerosis. It depends from the structural properties of the arterial wall that affect the manner in which pressure, blood flow, and arterial diameter change within each heartbeat. Arterial stiffness depends from the balance between extracellular proteins and their distribution along the arterial wall. An increased arterial stiffness is associated with hypertension and it is an independent direct predictor of cardiovascular events. The measurement of velocity of the pulse-wave propagation (pulse-wave velocity, PWV) between two vascular points is an accepted method to assess arterial stiffness [74]. Pase et al. summarized in a systematic review the effect of omega-3 PUFA supplementation on PWV and other indexes of arterial stiffness. Ten trials met the inclusion criteria with 550 participants randomized to take a dose of omega-3 PUFA ranging from 0.64 to 3.00 g/day or placebo for a period of 6–105 weeks. Studies involved healthy subjects and patients with overweight, diabetes, hypertension, and dyslipidemia. The treatment with omega-3 PUFA improved arterial stiffness and the effect was independent of changes in blood pressure, heart rate, or body mass index. Neither significant heterogeneity nor publication bias was detected [75]. The same author showed recently in a new larger RCT on healthy subjects that a high dose of fish oil (6 g/day) but not a low dose (3 g/day) could reduce aortic pulse pressure and aortic augmentation pressure, two indirect measures of central blood pressure and arterial stiffness, respectively [76].

The reasons for improvement of arterial stiffness with the use of omega-3 PUFA can be related to the hypotensive, anti-inflammatory, and antioxidative effects of these fatty acids, as well as to their ability to improve endothelial cell function. A low maternal habit in fish consumption during pregnancy is an independent predictor of arterial stiffness later in the childhood life but not of elevated blood pressure [77]. The inverse association between maternal omega-3 PUFA intake and arterial stiffness persists with child aging and it is independent of the individual's fish consumption [77, 78]. Additional evidence of the beneficial effect of omega-3 PUFA on the vascular structure comes from the inverse association between omega-3 PUFA intake and the cross-sectional diameter of arteries. It was demonstrated that a larger brachial artery diameter is a significant independent predictor of future cardiovascular events [79, 80]. Accordingly, we and other authors have reported an inverse association between the brachial artery cross-sectional diameter and the consumption of fish or the concentration of circulatory omega-3 PUFA [81, 82]. We reported also that the membrane content of omega-3 PUFA is directly associated with the extent of the vasodilatory response to sublingual nitrate administration, supporting the evidence of a beneficial effect of these fatty acids on the vascular wall [82].

Since aging is another important determinant of arterial stiffening and hypertension, it is interesting to note that blood levels of omega-3 PUFA are inversely related with telomere shortening, a marker of cell senescence, in patients with coronary heart disease [83]. Telomere shortening reflects the generation of oxidative stress and inflammation that characterizes

cellular ageing, and omega-3 PUFA might protect cells and slow this process. In a group of overweight patients, supplemental intake of omega-3 PUFA for 4 months increased omega-3 to omega-6 ratio in plasma phospholipids and this ratio was associated with telomeres length of leukocytes. In this study, omega-3 PUFA reduced also the proportion of plasma F2-isoprostanes, a marker of lipid peroxidation and oxidative stress [84]. Similar results were reported in elderly individuals with mild cognitive impairment [85].

4.3. Atherosclerotic lesions

Omega-3 PUFA have shown to modulate atherosclerotic plaque formation and stability. The carotid intima-media thickness (cIMT) is an early marker of atherosclerotic damage that precedes plaque formation and is easily assessed in humans by ultrasonography. We have recently demonstrated that a diet rich of fish for 1 year can reduce cIMT of patients with uncomplicated hypertension. This effect was observed only in those patients who were compliant with dietary prescription [86]. Similar findings on early atherosclerotic lesions were reported in other studies with different populations [87–89], but not in all those that have investigated this problem [90]. Interesting observation by Skilton and coworkers might help to explain these discrepancies. These authors demonstrated that a factor, which significantly affects the benefit of PUFA supplementation to slow cIMT progression, is the presence of an impaired prenatal growth [91]. As a consequence, dietary omega-3 PUFA supplementation in children with a history of impaired prenatal growth is protective from subsequent carotid wall thickening [92].

In addition to their preventive effect on the formation of atherosclerotic plaques, omega-3 PUFA could stabilize existing plaques. In patients with carotid stenosis, fish oil supplementation increases omega-3 PUFA content of plaques. This was associated with a thickening fibrous cup and reduction of intra-plaque inflammation and macrophage infiltration [93]. Similar results were obtained in another group of patients awaiting endarterectomy in which omega-3 PUFA supplementation reduced the intra-plaque content of foam cells and T-lymphocytes and lowered the expression of metalloproteinases, interleukins, and intracellular adhesion molecules [94]. Omega-3 PUFA supplementation can act favorably also on less critical plaques, as those not responsible for an acute coronary syndrome (non-culprit lesions) [95]. Although the beneficial effects of omega-3 PUFA on atherosclerotic plaques are mainly attributed to their anti-inflammatory and antioxidant properties, it was shown that these fatty acids increase the amount of cholesterol of high-density lipoprotein (HDL) [96–98] and reduce plasma levels of lipoprotein(a) [99, 100]. Finally, some studies have shown that omega-3 PUFA intake can enhance the beneficial effects of cardio-protective drugs such as statins and the acetylsalicylic acid [101–104].

Despite the evidence of many effects of omega-3 PUFA in opposing the atherosclerotic process, meta-analytical studies on their use in primary and secondary cardiovascular prevention provided inconclusive results [5].

5. Conclusions

This chapter has analyzed the effects of omega-3 PUFA on blood pressure and their potential benefit for the treatment of hypertension and its related organ damage. Substantial evidence supports the existence of a small hypotensive effect of these fatty acids in hypertensive patients that appears more related to the use of DHA and dietary compliance. Evidence in support of a protective effect of omega-3 PUFA on hypertension-related organ damage is much weaker. Lack of a clear benefit from marine food or other sources of these fatty acids in cardiovascular prevention has limited their use in the clinical practice. Nonetheless, a regular fish intake remains recommended by international guidelines.

Research on omega-3 PUFA has provided many interesting results in the cardiovascular field, but new areas need to be explored. Although effective in hypertensive patients, no studies have evaluated the effects of omega-3 PUFA on specific types of hypertension-related organ damage such as left ventricular hypertrophy, nephroangiosclerosis, and retinopathy. The role of omega-3 PUFA during pre-natal development and potential effects on post-natal cardiovascular outcomes will also need further investigation.

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