Omega-3 Polyunsaturated Fatty Acids: Their Potential Role in Blood Pressure Prevention and Management

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Abstract: Omega-3 (ω-3) polyunsaturated fatty acids (PUFAs) from fish and fish oils appear to protect against coronary heart disease: their dietary intake is in fact inversely associated with cardiovascular disease morbidity/mortality in population studies. Recent evidence suggests that at least a part of this protective effect is mediated by a relatively small but significant decrease in blood pressure (BP) level. In fact, ω-3 PUFAs exhibit wide-ranging biological actions that include regulating both vasomotor tone and renal sodium excretion, partly competing with ω-6 PUFAs for common metabolic enzymes and thereby decreasing the production of vasoconstrictor rather than vasodilator and anti-inflammatory eicosanoids. PUFAs also reduce angiotensin-converting enzyme (ACE) activity, angiotensin II formation, Tumor Growth Factor-beta (TGF-β) expression, enhance endothelial nitric oxide (NO) generation and activate the parasympathetic nervous system. The final results are improved vasodilation and arterial compliance of both small and large arteries. Preliminary clinical trials involving normotensive and hypertensive dyslipidaemic patients, diabetics and elderly subjects, confirm this working hypothesis: 3 meta-analyses suggest that PUFAs are able to slightly, but significantly improve arterial hypertension. Future research will clarify if PUFAs supplementation could improve the antihypertensive action of specific BP lowering drug classes and of statins.

Keywords: Fish oil, omega 3 fatty acids, polyunsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid, blood pressure, hypertension, PUFA.

INTRODUCTION

The inverse association between ω-3 PUFA intake and cardiovascular disease morbidity/mortality was established following the observation that the Greenland Inuit had low mortality from coronary heart disease (CHD) despite a fat-rich diet. In the 1970s, the Danish investigators Bang and Dyerberg proposed that this could be because of the ω-3 PUFA high content in the Inuit diet, which consisted largely of fish, seal and whale [1]. In fact, in these subjects plasma ω-3 PUFA concentrations are highly correlated with dietary PUFAs and inversely correlated with diastolic BP [2]. From that preliminary evidences, a large number of studies evaluated the potential beneficial effects of ω-3 PUFAs in inflammatory, autoimmune, renal and cardiovascular diseases [3, 4]. The most interesting data regard heart disease, either secondary to arrhythmias or atherosclerosis [5-7].

In particular, the inverse association between PUFA intake and stroke incidence observed in different longitudinal epidemiological studies [8, 9], even reflected in a slower age-related cognitive decline [10] support the hypothesis that PUFAs could play a significant role in also modulating the main stroke independent risk factor, that is arterial hypertension. However other authors suggest that the observed inverse relationship between PUFA consumption and stroke incidence is the consequence of the atrial fibrillation preventive action of PUFAs [11].

Compared with traditional diets, PUFA intake in industrialized countries has markedly shifted during the past 150 years toward higher amounts of ω-6 PUFAs and lower amounts of ω-3 PUFAs, with a parallel increase in CHD incidence [12]. However, the inverse correlation between PUFA intake and BP may not be true for each ethnicity [13].

Beyond their well-known antiarrhythmic effect and triglycerides lowering action [11], ω-3 PUFAs also have a small but significant BP lowering effect that from an epidemiological point of view could have a relevant impact on cardiovascular disease prevention.

The aim of this review is to critically evaluate the available information about the effect of PUFAs on BP control and prevention of hypertension development.

DATA SOURCES AND SELECTION CRITERIA

We searched PubMed and EMBASE for relevant articles by using the key words “fish”, “fish oils”, “omega 3 fatty acids”, “polyunsaturated fatty acids”, “PUFA”, “Eicosapentaenoic acid”, “EPA”, “Docosahexaenoic acid”, “DHA” and “blood pressure” or “arterial hypertension”, using a combined text word and MESH heading search strategy. Then we cross-matched references with those found in each paper and we cited the most representative ones.

BIOCHEMICAL CLASSIFICATION AND FOOD SOURCES

Alpha-linolenic acid (ALA; 18:3 ω-3) and linoleic acid (LA; 18:2 ω-6) are essential fatty acids for humans [14]. LA
is the most predominant PUFA in our diet, which is commonly found in vegetable seed oils. ALA is less abundant than LA; ALA is also present in some vegetable oils such as perilla, flaxseed, canola, soybean and walnut oils [15]. Dietary LA is converted to gamma linolenic acid (GLA, 18:3 \( \omega -6 \)) and dihomo-GLA (DGLA, 20:3 \( \omega -6 \)) by specific enzymes (6-desaturase, elongase) that are controlled by genetic hormonal and nutritional factors [16]. Then, DGLA competes with alpha-linolenic acid (ALA, 18:3 \( \omega -3 \)) derived products on the enzyme 5-desaturase for the synthesis of arachidonic acid or eicosapentaenoic (EPA, 20:5 \( \omega -3 \)). EPA is yet elongated and desaturated to docosahexaenoic acid (DHA, 22:6 \( \omega -3 \)) [Fig. (1)] [17]. Fish and fish oils are the main dietary sources of EPA and DHA. The content of EPA and DHA in different kinds of fish is reported in Table 1, but the \( \omega -3 \) PUFA content of fish is also related to the environmental conditions of the fish [18]. Even if less concentrated, EPA and DHA are also available in some vegetables, such as corn (and corn oil), lean meat and meat products, offal, egg yolk, milk and dairy products [19].

PRECLINICAL PHARMACOLOGY OF PUFAS

PUFAs have multiple and complex pharmacological activities, ranging from gene transcription modulation to direct receptor action (Table 2).

As cyclooxygenase (COX) inhibition is often associated with sodium retention leading to oedema and hypertension [20], prostanooids appear to have a role in preventing the development of high BP. On the other hand, prostaglandin E\(_2\) (PGE\(_2\)) and I\(_2\) (PGI\(_2\)) have also been implicated as determinants of renin secretion [Fig. (2)]. In particular, a recent study suggests that PGI\(_2\) plays a critical role in stimulating renin release and promoting hypertension following renal artery stenosis [21].

Patients with uncontrolled essential hypertension have elevated concentrations of superoxide anion (O\(_2^-\)), hydrogen peroxide (H\(_2\)O\(_2\)), lipid peroxides, endothelin, and transforming growth factor-beta (TGF-\(\beta\)) with a simultaneous decrease in endothelial nitric oxide (eNO), superoxide dismutase (SOD), vitamin E and long-chain PUFAs [22]. Physiological concentrations of angiotensin II activate NAD(P)H oxidase and trigger free radical generation (especially that of O\(_2^-\)). Usually, angiotensin II-induced oxidative stress is abrogated by adequate production and release of eNO, which quenches O\(_2^-\) to restore normotension [23]. Angiotensin II also stimulates the production of endothelin and TGF-\(\beta\). TGF-\(\beta\) enhances NO generation, which in turn suppresses TGF-\(\beta\) production [24]. Thus, NO has a regulatory role on TGF-\(\beta\) production and is also a physiological antagonist of endothelin. Antihypertensive drugs suppress the production of O\(_2^-\) and TGF-\(\beta\) and enhance eNO synthesis to bring about their beneficial actions [25].

\( \omega -3 \) PUFAs exhibit wide-ranging biological actions that include regulating both vasomotor tone and renal sodium excretion, partly competing with \( \omega -6 \) PUFAs for common metabolic enzymes and thereby decreasing the production of prothrombotic and vasoconstrictor rather than vasodilator, antithrombotic, anti-aggregatory and anti-inflammatory eicosanoids [26].

Opposite to saturated and trans-fatty acids, \( \omega -3 \) PUFAs contrast the formation of thromboxane A\(_2\) (TXA\(_2\)), a potent vasoconstrictor, and enhance that of PGI\(_1\), a well-known vasodilator [4, 27]. In addition, EPA lowers the tissue levels of arachidonic acid and enhances that of GLA, the precursor of PGE1, another vasodilator agent [26].

PUFAs, not only enhance the formation of beneficial PGs, but also suppress angiotensin-converting enzyme (ACE) activity, reduce angiotensin II formation, enhance eNO generation, and suppress TGF-\(\beta\) expression [28]. In rats with high angiotensin II activity, a diet poor in PUFAs is associated to significantly higher BP level [29]. In other experimental animal models it has been observed that the L-arginine-NO system upregulate PUFAs metabolism, so that a correlation between PUFAs concentration and NO endothelial production has been proposed [30]. Following control of hypertension with calcium antagonists, beta-blockers, and ACE inhibitors, the concentration of NO and O\(_2^-\) reverted to normal, whereas those of PUFAs remain low [31]: this could open the possibility of further BP improvement by \( \omega -3 \) PUFA supplementation. The discovery that \( \omega -3 \) PUFA could have a direct BP lowering effect finally justifies why DHA appears to be as effective as or even slightly more effective than EPA [25], even if DHA is not a substrate for the cyclooxygenase and lipooxygenase enzymes involved in eicosanoid metabolism. The role and mechanism of DHA in alterations of vascular response in hypertension still remains questionable [32].

Moreover, pregnant rat dams fed by semisynthetic diet deficient with \( \omega -3 \) PUFAs and offsprings fed with similar diets and other group of rats with normal \( \omega -3 \) PUFA content were compared: inadequate perinatal intake of \( \omega -3 \) PUFA intake was associated with raised mean arterial BP [33]. This observation is confirmed in humans, where consumption of breast milk (that is rich in PUFAs) in perinatal life is associated to a higher PUFA tissue content in infants and to a lower insulin-resistance and hypertension rate in adult life, whereas PUFA deficiency in the perinatal period results in raised BP later in life [34]. PUFA supplementation of the mothers during the first 4 months of lactation is associated to a small but not significant BP reduction in children 2.5 years
old, maybe because breast milk contains per se a sufficient amount of PUFA for physiological control of BP in children [35]. The exact mechanism of maternal milk PUFA effect on children BP has yet to be elucidated, however some authors have postulated the hypothesis that perinatal dietary PUFA deficiency could lead to developmental alteration of membrane bound receptors related to the sodium metabolism, such as hypothalamic osmoceptors or angiotensin II receptor [23, 31, 33]. Patients with essential hypertension and population genetically susceptible to develop arterial hypertension [36] have low concentrations of various PUFAs in their plasma phospholipid fraction. Based on this, it is proposed that PUFAs serve as endogenous regulators of ACE activity, O$_2^\cdot$, eNO generation, and TGF-β expression. Further, PUFAs have actions similar to similar to the so called pleiotropic effect of the 3-hydroxy-3-Methyl-Glutaryl-Coenzyme A reductase inhibitors (statins), inhibiting cyclooxygenase activity, suppressing the synthesis of proinflammatory cytokines, and activating the parasympathetic nervous system, all actions that reduce the risk of major vascular events [37]. Hence, it is proposed that availability of adequate amounts of PUFAs during the critical periods of growth prevents the development of hypertension in adulthood [23]. In addition, statin use has been observed to slightly but significantly reduce BP both in clinical trial setting and at population level [36].

Other lipid mediators of the PUFA vascular action are resolvins and protectins that showed potent anti-inflammatory activity in different experimental models via cyclooxygenase-2 and transcellular processing [38] associated to pro-resolution [39] and neuroprotective actions [40].

Table 1. Content of Omega 3 Fatty Acids of Selected Fish and Seafood

<table>
<thead>
<tr>
<th>FISH</th>
<th>EPA/DHA content (g) per 100 g serving of fish (edible portion)</th>
<th>Amount of fish (in g) required to provide 1 g EPA/DHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuna (fresh)</td>
<td>0.28-1.51</td>
<td>66-357</td>
</tr>
<tr>
<td>Atlantic salmon</td>
<td>1.28-2.15</td>
<td>42.5-70.9</td>
</tr>
<tr>
<td>Mackerel</td>
<td>0.4-1.85</td>
<td>54-250</td>
</tr>
<tr>
<td>Atlantic herring</td>
<td>2.01</td>
<td>50</td>
</tr>
<tr>
<td>Rainbow trout</td>
<td>1.15</td>
<td>87</td>
</tr>
<tr>
<td>Sardines</td>
<td>1.15-2</td>
<td>50-87</td>
</tr>
<tr>
<td>Halibut</td>
<td>0.47-1.18</td>
<td>85-213</td>
</tr>
<tr>
<td>Tuna (canned)</td>
<td>0.31</td>
<td>323</td>
</tr>
<tr>
<td>Cod</td>
<td>0.28</td>
<td>357</td>
</tr>
<tr>
<td>Haddock</td>
<td>0.24</td>
<td>417</td>
</tr>
<tr>
<td>Catfish</td>
<td>0.18</td>
<td>556</td>
</tr>
<tr>
<td>Flounder or sole</td>
<td>0.49</td>
<td>204</td>
</tr>
<tr>
<td>Oyster</td>
<td>0.44</td>
<td>227</td>
</tr>
<tr>
<td>Shrimp</td>
<td>0.32</td>
<td>313</td>
</tr>
<tr>
<td>Scallop</td>
<td>0.2</td>
<td>500</td>
</tr>
<tr>
<td>Cod liver oil capsule</td>
<td>0.19</td>
<td>5</td>
</tr>
</tbody>
</table>

EPA= eicosapentanoic acid, DHA= docosahexanoic acid. Omega 3 content varies markedly depending on species, season, diet, and packaging and cooking methods, and the figures above are therefore rough estimates.

Table 2. Biological Effects of Omega-3 Fatty Acids

- Interaction with omega-6 fatty acids
  Production of inactive leukotrienes and thromboxanes
- Decrease in biological mediators
  IL-1, IL-2, TNF, PGF
- Effect on blood lipoprotein levels
  Decrease in plasma VLDL and triglyceride levels
- Hypotensive effect
  Changes in eicosanoids, in blood viscosity, in hormonal-cellular response, in renin secretion, decreased response to vasopressors
- Decrease in plasma viscosity
- Decreased plasma fibrinogen
- Effects on coagulation
  Prolonged bleeding time, decrease in fibrinogen, factor VII, von Willebrand factor, increased fibrinolysis
- Increased arterial compliance
- Increased production of nitric oxide
- Effects on adhesion molecules
- Decreased ICAM-1, VCAM-1, E-selectin levels.
- Effects on vascular smooth muscle cells
  Modulation of proliferation, migration and apoptosis and improved vasoreactivity by interaction with intracellular calcium dynamics.
In a recent comparative study carried out on rats with high renin hypertension, both aliskiren (a direct renin inhibitor) and ω3 PUFAs showed improved electrical remodelling, decreased arrhythmia induction and low systolic BP, despite cardiac hypertrophy and increased atrial natriuretic peptide levels [41].

Besides NO, eicosanoids and renin related effects, ω3 PUFAs may affect intracellular calcium balance of vascular smooth muscle cells by interaction with K<sup>+-</sup>ATP and Ca<sup>2+</sup> channels and may have role in their proliferation, migration and apoptosis by multiple mechanisms [42].

In Dahl salt-sensitive hypertensive rats, fish oil supplementation has protective effects on long-term hypertension-related organ damage, like cardiac hypertrophy, vascular hypertrophy, glomerulosclerosis, renal tubular abnormalities, and renal function [43].

Several mechanisms for ω3 PUFAs effect on BP are possible [44]. Besides on nitric oxide system, ω3 PUFAs modulate intracellular calcium balance of vascular smooth muscle cells, have natriuretic effect and may have role in their proliferation and migration [45].

Endothelial dysfunction, that partly explains reduced vascular dilatation, appears to predict future adverse CHD outcomes. Fish oil supplementation significantly improves endothelial function measured in term of NO- and flow-mediated dilatation and vasodilation of resistance vessels of the forearm [47]. Systemic arterial compliance index, which reflects distensibility in elastic proximal large arteries, was equally improved with 3g DHA (+27%) and 3g EPA (+36%), whereas consumption of the placebo did not, in a double-blind, parallel design, placebo-controlled randomized trial [48]. Thus, it can be suggested that incorporation of EPA/DHA to membrane phospholipids could increase arterial compliance [49]. Tomiyama et al. showed that EPA supplementation, 1.8 g/day is able to attenuate age-related increase in arterial stiffness in dyslipidemic patients as well as distensibility of the common carotid artery [50]. Left ventricular function also improved in patients taking either EPA or DHA [51]. These effects appear not to be related to alterations in vascular responses to norepinephrine, angiotensin II or potassium [52].

Two different meta-analyses carried out in early 1990s concluded that ω3 PUFAs effect on BP is dose-dependent, with a minimal efficacious dose of 3 g/day [53] and valuable as a BP decrease of -0.66/-0.35 mmHg/g ω-3 PUFAs [54].

In a dietary intervention study, 69 overweight (BMI >25 kg/m²) medically treated hypertensive subjects were randomly assigned to either a daily fish meal (3.65 g/d of ω3-PUFA), a weight reduction regimen, the 2 regimens combined, or a control regimen for 16 weeks; 63 subjects completed the study. Both systolic and diastolic BP, body weight and heart rate significantly decreased in the fish diet group compared with the control diet group, even after adjustment for changes in urinary sodium, potassium, or the sodium/potassium ratio, as well as dietary macronutrients [55]. From this data it appears that weight loss in overweight people can augment the effects of eating fish on ambulatory 24 h BP: if confirmed, this observation could be relevant for the management of metabolic syndrome patients. Less than 3-5 g/day doses may also be recommended for cardiovascular risk reduction other than hypolipidemic or hypotensive benefits, especially for the patients with metabolic syndrome [56] and the use of ω-3 index which is described as a combined percentage of EPA and DHA of total fatty acids in red blood cell membranes was proposed to be measured for cardiovascular risk establishment [57].

An observational study was carried out in which the effects of fish-derived ω3 PUFAs on BP, platelet fatty acid levels and heart rate variability (an independent protective factor against cardiovascular mortality), were investigated in 43 subjects (male 24, female 19, aged 18 to 62 years) with type 1 diabetes mellitus, and 38 subjects (male 24, female...
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14, aged 37 to 77 years) with type 2 diabetes [58]. Fish intake was significantly associated with platelet membrane DHA levels. According to the platelet DHA levels, patients were divided into 3 tertiles, the first tertile had the lowest DHA level, the third tertile the highest DHA level and the second tertile was in between. Compared with the first tertile, the third tertile had a significantly lower DBP. In a further double blind, randomized, placebo-controlled human study, it was found that EPA and DHA differed in their effects on BP and heart rate [59]. In this trial, 55 overweight subjects, aged 20-65 years, were randomized to 4 g/d of purified EPA, DHA, or placebo (olive oil) capsules for 6 weeks. Compared with the placebo group, DHA significantly reduced both SSBP and DBP (measured over 24 h) by 5.8 and 3.3 mmHg, and the wakening SSBP and DBP by 3.5 and 2.0 mmHg, respectively (p<0.05). Relative to the placebo group, heart rate over a 24-h period, when awake and when asleep were significantly reduced by 3.5±0.8, 3.7±1.2, and 2.8±1.2 bpm, respectively. On the other hand, EPA showed no significant effect on BP and heart rate. However, this study did not test if the EPA-DHA association has additive or synergic effects on BP. The authors explain the antihypertensive effect of DHA, suggesting that there may be a significant cardiac component, as demonstrated by the concomitant reduction in heart rate, possibly mediated by effects on autonomic nerve function or β-adrenergic receptor activity.

In one meta-analysis of randomized controlled trials, fish oil was found to cause heart rate reductions especially significant in patients with high basal heart rate and longer duration of treatment [60]. This also supports the idea of autonomic nerve or β-receptor involvement in its effects.

Another meta-analysis of 36 randomised trials, a mean reduction in SSBP of 2.1 mmHg and in DBP of 1.6 mmHg were found [61], and these are significantly inferior to that reported in some single trials. The main reason of this low observed effect is that in the meta-analysis the trials with low dosed or not purified formulations were also included, and in some the BP reduction was not a main outcome of the study. In this analysis, fish oil showed better antihypertensive effect in older and hypertensive patients that may be due to a greater BP lowering activity of ω-3 PUFAs in patients with arterial stiffness and/or microvascular dysfunction, by improving endothelial dysfunction. However not all authors agree with these conclusions [62].

Recently, Sanders et al showed that PUFAs extracted from marine algae (not from fish) have no effects on the BP levels of 79 patients randomized to 4 g/day (providing 1.5 g DHA and 0.6 g EPA) or placebo in a 4-weeks double-blind randomized trial [63]: because it is hard to think that the same chemical compound could exert different biological effect depending on the source, it is more plausible that the low dosages of EPA and DHA tested were not sufficient to show a detectable effect on BP.

The PUFAs antihypertensive effect appears to be particularly evident in subjects at high risk for cardiovascular disease, such as haemodialysis patients in which 2 g PUFA 4 months supplementation was associated to a significant lower systolic (-9±16 mmHg), diastolic (-11±15 mmHg) and mean BP (11±15 mmHg) when compared with 2 g olive oil [64]. In normotensive adults, PUFA supplementation appears not to have significant effect on BP values if compared with saturated and monounsaturated fatty acids [65]. However, 5 mL fish oil supplementation is significantly associated to lower SSBP levels (-6.3 mmHg 95% CI 0.9, 11.7, P = 0.02) in children taking a mixed in milk-formulation for 1 year, as compared with control children [66].

It has then hypothesized, but not yet demonstrated, that PUFA could exert a more clinically evident antihypertensive effect in insulin-resistant subjects such as metabolic syndrome patients [56]. This effect has been confirmed in a recent meta-analysis carried out on diabetic patients, in which the PUFA supplementation is associated with a slight but significant mean 1.8 mmHg (95%CI 0.0-3.6, p = 0.05) diastolic BP decrease [67]. In contrast with these hypotheses and to what was observed by Morris et al. about a possible dose-effect of PUFA on BP [68], a very recent cross-over clinical trial observed that a very low dose of DHA (0.7 g/day) for 3 months is able to significantly reduce diastolic BP by 3.3 mmHg (95% CI -6.1 to -0.6; P = 0.01), apparently without altering endothelial function or arterial stiffness in middle aged slim and normotensive subjects [69]. Again contrasting results are available: another trial shows that a fat meal containing 5 g EPA results in acute changes in vascular tone, independent of changes in oxidative stress [70]. The main problem of evaluating the effects of PUFA supplementation on vascular reactivity are the different experimental models, measuring instruments and PUFA doses and type used, so that a conclusion can not be derived.

Further clinical research is needed to evaluate the real antihypertensive effect of EPA and DHA, their differential effects (not yet clear), and to identify the best responders or candidates for that treatment.

SAFETY DATA

Any recommendations regarding fish and fish oils consumption should be balanced against safety issues. Side effects such as fishy aftertaste are uncommon, and gastrointestinal complaints are infrequent at moderate intakes [3]. Some reports show that fish oil may worsen glycaemic control in diabetes, but recent data exclude that this adverse effect is common when diabetics are adequately treated [71, 72]. Concerns have also been raised regarding adverse effects on low density lipoprotein (LDL) cholesterol plasma level and oxidative stress, but increases in LDL cholesterol are modest and studies into oxidative stress have been contradictory. Overall these effects are unlikely to be dominant given the apparent cardiac benefits of ω-3 PUFAs [73]. Therefore, ω-3 PUFAs may exert dose-related effect on bleeding time, but an objective assessment of the evidence for clinically significant bleeding reveals that such concerns are unfounded [74].

More specific concerns regarding dietary fish relate to environmental contaminants, and a recent study showed that mercury in fish may attenuate their cardioprotective effects [75]. However, a recent risk-benefit analysis of changes in population fish consumption concluded that reduced fish intake because of poisoning fear, the net public health impact is negative [76]. Moreover, contaminants accumulate in larger, predatory fish, and consumption of a variety of fish (or of fish oil supplements) should minimize any possible
adverse effects [4]. And consumption of equal amounts of EPA and DHA from oily fish weekly or in the form of capsules daily are equally effective [77].

Finally, no significant negative interaction has been observed until now between antihypertensive therapy and fish oil supplementation [78].

DISCUSSION

Despite the development of always more efficacious and safe pharmacological treatments, cardiovascular diseases remain the leading cause of death and invalidity in developed countries [79]. Arterial hypertension is one of the most relevant independent cardiovascular diseases risk factors and recent studies show that the maintenance of normal BP level in not frankly hypertensive subjects is associated with a significant reduced incidence of cardiovascular events [80]. Of course, it is not plausible to pharmacologically treat all subjects with normal-high BP and all international guidelines [81, 82] stress the relevance of an adequate dietary and lifestyle intervention in order to reach and maintain optimal BP levels. Moreover, in our era of multiple pharmacological treatments for cardiovascular diseases some researchers believe that simple dietary interventions or nutritional supplements may be a more natural and acceptable method of providing benefits, and patients appear very keen to spontaneously use different dietary supplements (whose efficacy is not always evident) to reduce their BP, without asking for information from their physicians [83].

Both health professionals and the public are increasingly interested in the supposed role of ω-3 PUFAs from fish and fish oils in the prevention and management of CHD, mainly related to their well-known metabolic and anti-thrombotic effects [3]. A recent systematic review confirmed that PUFA intake is associated to a reduced all-cause and cardiovascular mortality, more evident in patients in secondary prevention of CHD [84].

Moreover, the worldwide use of PUFA supplementation has recently received a large implementation even in fields unrelated to cardiovascular diseases, such as neurology (epilepsy), psychiatry (psychosis, severe depression), rheumatology (osteoarthritis, psoriasis), clinical immunology (allergy), gastroenterology (inflammatory bowel diseases), and nephrology (autoimmune nephropathies) (i.e. chronic renal failure, congestive heart failure) [19].

Some active research lines are trying to clarify which specific sub-categories of subjects at cardiovascular risk could obtain the maximal benefit from an EPA/DHA supplementation and which is the more cost-effective dosage and EPA/DHA ratio to be employed. In the specific context of BP management it is probable that the on-going GISSI-Heart Failure study, designed to evaluate the effect of EPA/DHA supplementation or statin treatment on the prognosis of patients affected by congestive heart failure, could furnish relevant data as it regards the BP control in both groups of treatment. Because of the specific mechanism of action of PUFA it could also be interesting to study if PUFA could improve the antihypertensive action of specific BP lowering drug classes and of statins. Future guidelines for hypertension management maybe will suggest to increase the nutritional intake of EPA/DHA or to supplement it in order to prevent BP increases or improve BP control, especially in subjects that could have special benefit for other concomitant pathologies (e.g. dyslipidaemias, rheumatological disorders, congestive heart failure or chronic renal failure) [85].

Because of large amount of dyshomogenous evidence on the effects and exact dosing of PUFAs in the medical literature, it is difficult to have a systematic evaluation of data but the preliminary data suggest that a adequate PUFA dietary intake or supplementation (2-4 g/day) could slightly but not significantly reduce systolic and diastolic BP level and prevent BP increase in either dyslipidaemic, diabetics, elderly, normotensive and hypertensive subjects, contributing to their cardiovascular disease protective role. Besides current evidence of beneficial effects of PUFAs on atherosclerosis and arrhythmias prevention in high risk subjects, future research will identify which categories of subjects will more significantly benefit form PUFA supplementation in order to maintain adequate levels of BP, and the most efficacious EPA/DHA ratio.

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