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Review Article

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Impact of Omega 3 Fatty Acids on Blood Pressure

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ABSTRACT

Omega-6 and omega-3 fatty acids are the essential fatty acids that cannot be synthesized by the human body. Epidemiological and clinical studies suggest that consumption of omega- 3 polyunsaturated fatty acids (PUFA) contributes to the reduction of cardiovascular mortality through different mechanisms including modulation of cellular metabolic functions, gene expression and beneficial effects on lipid profile or blood pressure. In fact, 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 vasocostricting rather than vasodilating, antithrombotic, anti aggregatory, and anti-inflammatory eicosanoids. The aim of this review is to evaluate the available evidence about the clinical effect of omega-3 PUFA on blood pressure control.

Key Words: *Omega 3 fatty acids, Docosapentaenoic acid, Eicosapentaenoic acid, Blood Pressure, Fish, Nuts.*

INTRODUCTION

Dietary fatty acids (FA) are increasingly recognized as major biologic regulators and it consists of properties that are related to both health outcomes as well as diseases[1-3]. Omega-6 and omega-3 fatty acids are the essential fatty acids that cannot be synthesized by the human body. Docosahexaenoic acid (DHA) is considered as conditionally essential because of its limited formation from ALA and, jointly with eicosapentaenoic acid (EPA), in prevention of cardiovascular disease (CVD) [4]. A high intake of omega-3 PUFA has been associated with cardiovascular protective effects improving endothelial function and reducing atherosclerosis through their beneficial effects on blood pressure (BP), lipid profile, platelet aggregation and also by their anti-inflammatory properties[5]. Hereditary factors seem to be responsible for 30–40% of blood pressure changes in the general population[6] and the rest is explained by environmental factors, especially lifestyle and dietary habits. It is eminent that the type and amount of dietary fat may influence many factors such as insulin resistance or hyperlipidemia.

SOURCES OF OMEGA-3 FATTY ACIDS

The consumption of a variety of fish species including halibut, mackerel, herring and salmon is among the best ways to ensure a good intake of omega-3 fatty acids. Several omega-3 fatty acid supplements are also available, but these provide varying amounts of marine-based EPA and DHA [7, 8]. However, a-ALA, which serves as a precursor of EPA, is also a polyunsaturated omega-3 fatty acid, and is found primarily in plant products such as soybeans, canola oil, flaxseed oil, and leafy vegetables[9]. In a few of epidemiological studies, the consumption of food rich in ALA was found to be correlated with reduced morbidity and mortality from cardiovascular causes[8, 10, 11]. However, ultimately consumption of these marine or plant sources providing omega-3 fatty acids is very much limited in the Indian dietary pattern as the above mentioned fish varieties are not available in the Indian coastal area and similarly consumption of nuts and flax seeds are also very occasional. Hence, the ratio between omega-6 to omega-3 is very high and far beyond the recommended levels. Likewise, in comparison with the western fish and nut consumption pattern still India lags behind the levels.

METABOLISM OF OMEGA 3 FATTY ACIDS

The desaturation and elongation reactions in omega 3 and omega 6 fatty acids are mediated by same sets of enzymes [6- desaturase and elongase]. After desaturation and elongation reactions, linoleic acid turns into dihomo-gamma linoleic acid (DGLA, 20:3 omega-6), which through a new desaturation is converted to arachidonic acid (AA, 20:4 v-6). Arachidonic acid is the precursor of 2 series of prostaglandins, thromboxanes and the 4 series of leukotrienes mediated by cyclooxygenases and lipoxygenases, respectively. According to Biscione et al (2007) and Das et al (2008), both prostaglandins and leukotrienes mediate physiological responses of vasoconstriction, platelet aggregation and inflammatory mediator's synthesis[12, 13]. Further, Cook et al (2002) also state that ALA undergoes desaturation and elongation reactions to form eicosapentaenoic acid (EPA, C20:5), which is a precursor of 3 series of prostaglandins and 5 series of leukotrienes[14]. These prostaglandins are physiologically less potent than those formed from AA (2 series) and their effects in vascular tone, platelet aggregation and inflammation are antagonistic [12]. Finally, EPA can get new reversible elongation and desaturation reactions producing docosahexaenoic acid (DHA, C22:6). In addition, omega -3 PUFA (EPA and DHA) are also the precursor of lipoxins, resolvins and protectins, compounds that modulate inflammation, and serve as endogenous regulators of vascular tone and blood pressure[13].

Furthermore from the studies of Cook et al (2002) and Cicero et al (2009) it has been proven that dihomo-gamma linoleic acid competes with alpha-linolenic acid in the desaturase active site, interfering with the synthesis of omega-3 route precursors (EPA, DHA) [14, 15] Therefore, a disbalance between both omega-3 and omega-6 PUFA can affect the peripheral vascular resistance and can have an effect on blood pressure.

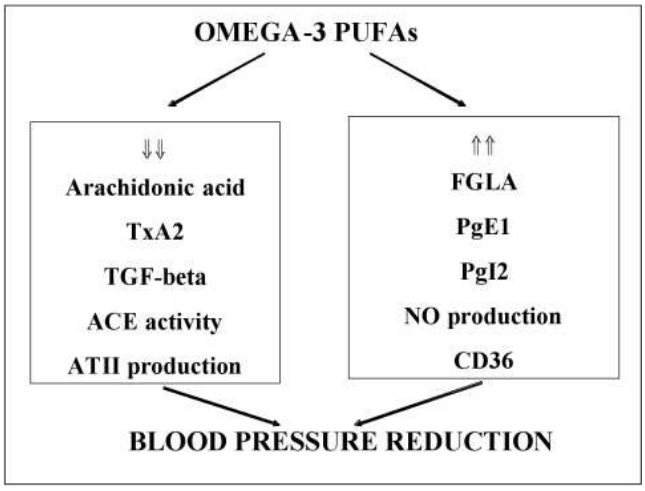
PHARMACOLOGICAL CHARACTERISTICS OF OMEGA 3 FATTY ACIDS

Since cycloxigenase (COX) inhibition is frequently allied with sodium retention leading to edema and hypertension[16], prostanoids appear to have a role in preventing the development of high blood pressure. On the other hand, prostaglandin E2 (PgE2) and PgI2 have also been implicated as determinants of renin secretion. Francois, 2004 from his study suggested that PgI2 plays a critical role in stimulating renin release and promoting hypertension following renal artery stenosis[17].

According to Bhatnagar et. al (2003), omega-3 PUFAs reveal inclusive biological actions such as 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 vasocostricting rather than vasodilating, antithrombotic, anti aggregatory, and anti-inflammatory eicosanoids[18] .

PUFAs not only enhance the formation of beneficial PGs, in addition it also suppress angiotensin-converting enzyme (ACE) activity, reduce angiotensin II formation, enhance eNO generation, and suppress TGF-beta expression [19] (Fig. 1).

Fig. 1: MAIN PHARMACOLOGICAL ACTIVITIES INVOLVED IN OMEGA-3 PUFA ANTIHYPERTENSIVE ACTION



Source: Claudio Borghi , Omega- 3 polyunsaturated fatty acids : their potential role in blood pressure prevention and management, 2006.

CLINICAL EVIDENCE OF THE EFFECT OF OMEGA- 3 FATTY ACIDS IN BLOOD PRESSURE

From an epidemiological point of view, the inverse association between omega-3 PUFA intake and cardiovascular disease morbidity/mortality was established following the observation that the Greenland Inuit had low mortality from coronary heart disease despite a diet that is rich in fat. In the 1970s the Danish investigators Bang and Dyerberg proposed that this could be because of the omega-3 PUFA high content in the Inuit diet, which consisted largely of fish, seal, and whale [20]. Indeed, in these subjects, plasma omega-3 PUFA concentrations were highly correlated with dietary PUFAs and inversely correlated with diastolic blood pressure[21].

Vernaglione et al published a prospective study on the effects of blood pressure and other variables in 24 patients on hemodialysis that who were supplemented with omega-3 fatty acids. The study was designed sequentially, so after baseline evaluation patients had to follow consecutive periods of 4 months with different supplements: 2 g/day of olive oil followed by 2 g/day of omega-3 supplements and finally back to 2 g/day of olive oil. Both SBP and DBP were significantly lower ($P<0{\cdot}05$) at the end of the supplementation period with omega-3 fatty acids. Systolic blood pressure diminished from 131 ± 17·8mmHg in the first phase to 122mmHg (SD 12·8) in the second phase and rose to 129±13·2 mmHg. The effect on DBP was in the same direction: 83±16·3mmHg in the first phase, 71±14·8mmHg in the second phase and 79 ± 6·5mmHg in the last period of the study. Thus, the investigators concluded that administration of omega-3 supplements attenuated vascular reactivity and consequently reduced both systolic and diastolic blood pressure[22].

In the same way, Bonna et al(1990) conducted a population based, randomized, 10 week dietary supplementation trial in which the effects of 6g per day of 85 percent eicosapentaenoic and docosahexaenoic acids were compared with those of 6g per day of corn oil in 156 men and women with previously untreated stable, mild essential hypertension and from the observation, it was concluded that eicosapentaenoic and docosahexaenoic acid could reduce blood pressure in essential hypertension, depending on increases in plasma phospholipids omega 3 fatty acids[23].

In yet another dietary intervention study, 69 overweight (BMI >25 kg/m2) medication-treated hypertensive subjects were randomized to either a daily fish meal (3.65 g/dL of omega-3 PUFA approximately), a weight reduction regimen, the two regimens combined, or a control regimen for 16 weeks. Sixty-three subjects completed the study. Systolic (SBP) and diastolic (DBP) blood pressure, body weight and heart rate significantly decreased in the fish diet group when compared with the controlled diet group, even after adjustment for changes in urinary sodium, potassium, or the sodium/potassium ratio, as well as dietary macronutrients. From this data it could be argued that weight loss in overweight people can augment the effects of eating fish on ambulatory 24h blood pressure[24].

With reference to heart rate variability (an independent protective factor against cardiovascular mortality), an observational study was carried out in which the effects of fish-derived omega-3 PUFA on blood pressure, platelet fatty acid levels and heart rate, 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 14, aged 37 to 77 years) with type 2 diabetes mellitus. The study found that fish intake was significantly positively associated with platelet membrane DHA levels. The subjects were grouped into three tertiles according to their DHA levels. Such a change in DHA in the third tertiles had a significantly lower diastolic BP and higher 24-hour heart rate variability (increased heart rate variability has a beneficial effect on dysrhythmia) which in turn confirms that fish diet is effective in reducing blood pressure[25].

A cohort study of 20 year follow up was done by Xun et al (2011) where a cohort of 4508 American adults aged 18-30, without hypertension at baseline in 1985, were enrolled. Six follow-ups were conducted at examinations in 1987, 1990, 1992, 1995, 2000 and 2005. Diet was assessed by a validated interviewer-administered quantitative food frequency questionnaire at exams in 1985, 1992 and 2005. Incident hypertension was defined as first occurrence at any follow-up examination of systolic blood pressure (BP) $\geq$ 140 mmHg, diastolic BP $\geq$ 90 mmHg or taking antihypertensive medication. And their study revealed that the Participants in the omega 3 fatty acids administered group had a significantly lower incidence of hypertension against those in the lowest quartile of omega- 3 fatty acid consumption[26].

Mort et al (1999) conducted a double blind, placebo study where 59 overweight, mildly hyperlipidemic men were randomized to 4g/d of purified EPA, DHA OR Olive oil (placebo) capsules and continued their usual diets for 6 weeks. The study results suggested that DHA as the principal omega 3 fatty acids in fish and fish oils was responsible for reduction of blood pressure and heart rate in humans[27].

Theobald H et al., conducted a randomized, double-blind and placebo controlled study in which 38 healthy subjects were treated for 3 months with 0·7 g/day of DHA vs. placebo. Diastolic blood pressure in patients treated with DHA fell 3·3 mmHg, in comparison with placebo (P >0·01). There were no significant differences in resting heart rate and SBP[28]. Another study done by sanders et al (2006), using algae oil (1·5 g/day of DHA and 0·6 g/day of docosapentaenoic acid) showed no differences in blood pressure between the control group and the group supplemented with the oil, perhaps due to low doses of omega-3 provided either by the combination with omega-6 fatty acid[29].

Different meta-analysis have shown that relatively high doses of omega-3 PUFA, generally more than 3 g/d, can lead to clinically relevant BP reductions in individuals with untreated hypertension. In the meta-analysis of Appel et al.,(1993) including 17 clinical trials (11 in normotensives and 6 in untreated hypertensive subjects), the reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in hypertensive subjects were 5·5 and 3·5 mmHg, respectively[30]. In another meta-analysis including 36 studies, 22 of which were double-blind designed and with a duration over 2 weeks, showed a significant 2·1mmHg reduction in SPB and 1·6mmHg DBP (1·7/1·5mmHg in the double-blind studies)
with a median consumption of 3·7 g/day of fish oil. The effect was higher in subjects more than 45 years and in hypertensive volunteers (BP > 140/90 mmHg) [31].

In aim of exploring platelet function and cytokines on administration with n-3 fatty ascids, Doenyas et. al, 2012 in his study including thirty-two hypercholesterolemic patients aged 30-70 years with hypercholesterolemia controlled by statins, received sequential treatments with placebo followed by 1.9 g/day of N-3fatty acids for 23 weeks. Scheduled clinical visits included physical examination; 24-h blood pressure measurement, endothelial function evaluated by pulse wave analysis, analyses for platelet function, inflammation markers [interleukin (IL)-6, plasminogen activator inhibitor-1 (PAI-1)] and oxidative stress parameters (STAT-8-Isoprostane) were undertaken at baseline, after placebo treatment, and after 6 and 20 weeks of N-3fatty acid intake. Their study results concluded that Platelets functions were significantly inhibited, whereas endothelial function parameters were unaltered. IL-6 significantly decreased whereas PAI-1and STAT-8-Isoprostane levels remained unaffected. Daytime blood pressure significantly decreased; however, night-time pressure and heart rate remained unchanged[32].

Cerbone et al (2010) conducted a study in 14 healthy volunteers, by providing a one-month supplementation of a preparation of EPA and DHA super imposable to that employed in the GISSI Prevenzione study, in parallel with changes in the plasma and platelet content of EPA and DHA, caused an impaired platelet aggregation in response to collagen or ADP that was independent of thromboxane biosynthesis[33]. Such impaired aggregation correlated (p=0.036 and 0.068, respectively) with changes in the intracellular pH (pHi) of the Na+/H+ reverse transport. In addition to platelet function, the latter mechanism is important as to lymphocyte function and blood pressure control[34, 35].

In a comprehensive review on the issue of whether[36], ω-3 fatty acids are capable of reducing blood pressure[37, 38], to improve arterial and endothelial function[39], and to favourably affect the autonomic tone of the vessels[37, 39]. In a meta-regression analysis of 22 double-blind randomised trials on blood pressure response to fish oil supplementation[40] , consumption of ~ 4.0 g/day of ω-3 fatty acids was associated with a significant 1.7– and 1.5-mm Hg reduction in systolic and diastolic blood pressure. Such reductions were maximal in older patients and in those with higher blood pressures. A 2 mm Hg reduction in blood pressure yields to a 4% reduction in mortality due to CAD[41].

DIETARY GUIDELINES

There are several dietary guidelines for FA [42]. In these guidelines there is convergence recommending at least 250 mg/day EPA + DHA or at least 2 servings/week of fish, preferably oily fish. For pregnant women, nursing mothers, and young children, these recommendations are modified. The American Heart

Association 2020 Strategic Impact Goals defined consumption of at least 2 3.5-oz servings/week of fish, preferably oily fish, as one of five primary dietary metric that characterized ideal cardiovascular health[43]. The 2010 US Dietary Guidelines for Americans recommended for individuals with higher and average CVD risk 2 4-oz seafood servings/week, which should provide an average of at least 250 mg/day EPA + DHA (1,750 mg/week) [44].

CONCLUSION

Omega-3 PUFAs have always been an essential component of human diets and could provide simple and safe protection against different types of cardiovascular disease the main cause of death in developed countries. Dietary intake or supplementation of omega 3 polyunsaturated fatty acids might have a place in the control of patients with mild hypertension before starting drug treatment and of those who prefer changes of lifestyles like diet. A high intake of these PUFA can be achieved consuming blue fish like salmon, mackerel, herring, tuna and sardines twice to three times a week to achieve at least an amount of 500 mg/ day of EPA/DHA, or daily supplements of fish oil. As per the evidences quoted above it is understood that even in developed countries the ratio between omega 6: omega 3 is not as per the guidelines, nevertheless it is worsening in developing countries like India as it is arbitrary where the awareness on the significance of omega 3 fatty acids as well the availability of it is not substantial, hence policy makers should consider reducing mortality and morbidity due to cardiovascular diseases by framing intensive strategies through health care systems in order to bring down the ratio of omega 6 to omega 3 in an acceptable range that would reduce untoward prognosis of CVD.

Conflict of interest: Authors represent no conflict of interest

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