Omega-3 fatty acids and blood pressure

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Abstract

Epidemiological and clinical studies suggest that consumption of omega (ω-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. The aim of the study is to review the effects of ω-3 PUFA supplemented as fish oil or blue fish in blood pressure. The analysis of different studies suggests that high doses ω-3 PUFA (≥ 3 g/day) produces a small but significant decrease in blood pressure, especially systolic blood pressure, in older and hypertensive subjects; however, the evidence is not consistent among different studies. ω-3 polyunsaturated fatty acids consumption 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.

Key words: Omega-3 fatty acids: blood pressure: fish oil: diet

Introduction

Linoleic acid (LA; 18:2 ω-6) and α-linolenic acid (ALA; 18:3 ω-3) are essential fatty acids that can not 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)². A high intake of ω-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 properties². Clinical studies suggest that consumption of ω-3 PUFA may reduce blood pressure in hypertensive subjects and patients with other cardiovascular risk factors such as overweight, hyperlipidemia or in patients treated with hemodialysis.

Hereditary factors seems to be responsible for 30–40 % of blood pressure changes in the general population³ and the rest is explained by environmental factors, especially lifestyles and dietary habits. It is well known that the type and amount of dietary fat may influence many factors such as insulin resistance or hyperlipidemia. However, the influence of some macronutrients on blood pressure is not well known and could be of epidemiological importance.

To understand the role of ω-3 PUFA on blood pressure, it is important to know their metabolism and the interactions with their close analogues, the ω-6 PUFA. Both PUFA share the same metabolic and oxidative pathways; however their metabolic end products often have antagonistic physiological effects.

The aim of this review is to evaluate the available evidence about the clinical effect of ω-3 PUFA on blood pressure control.

Data sources and selection criteria

We conducted a systematic review of literature using PUBMED, MEDLINE and EMBASE resources from the inception of each database to February, 2011 using the following search terms: “fatty acids, omega-3”, ”ω-3 PUFA”, “n-3 polyunsaturated fatty acids”, ”fish oil”, ”hypertension” and “blood pressure”. We selected those articles that made reference to blood pressure even though it was not the primary objective of the study.

PUFA metabolism and blood pressure

Polyunsaturated fatty acids (ω-3 and ω-6) undergo a series of desaturation and elongation reactions that are mediated by the same set of enzymes to their respective long-chain metabolites (Fig. 1)⁴. After desaturation and elongation reactions, linoleic acid turns into dihomo-gamma linoleic acid (DGLA, 20:3 ω-6), which through a new desaturation is converted to arachidonic acid (AA, 20:4 ω-6). Arachidonic acid is the precursor of 2 series of prostaglandins, thromboxanes and the 4 series of leukotrienes mediated by cyclooxygenases and

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lipooxygenases, respectively. Both prostaglandins and leukotrienes mediate physiological responses of vasoconstriction, platelet aggregation and inflammatory mediators synthesis\(^{(5,6)}\). ALA undergoes desaturation and elongation reactions to form eicosapentaenoic acid (EPA, C\(_{20}:5\)), that is a precursor of 3 series of prostaglandins and 5 series of leukotrienes\(^{(4)}\). These prostaglandins are physiologically less potent than those formed from AA (2 series) and their effects in vascular tone, platelet aggregation and inflammation are antagonic\(^{(5)}\).

Finally, EPA can get new reversible elongation and desaturation reactions producing docosahexaenoic acid (DHA, C\(_{22}:6\)). 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\(^{(6)}\).

These desaturation reactions in humans are slow and inefficient so the production rate of complex derivatives is reduced. Furthermore, 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)\(^{(4,7)}\). 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. The hypothesis of prostanoids synthesis and the effect on blood pressure has not been clearly demonstrated. Lahoz C \textit{et al.} conducted a study in 42 healthy subjects undergoing 4 consecutive diets rich in saturated fat, monounsaturated fat, \(\omega-6\) PUFA and \(\omega-6\) and \(\omega-3\) PUFAs. Although a significant reduction in blood pressure was observed in the last period enriched in \(\omega-3\) from fish, there were no differences in the urine excretion of prostanoids between the 4 dietary periods\(^{(8)}\).
linked to increase production of endothelial nitric oxide (eNO) in animal models, and on the other hand, the L-arginine-NO system increase PUFAs metabolism\(^{(10)}\). In addition, EPA and DHA can inhibit proteinuria development, suppress hypertension in stroke-prone spontaneously hypertensive rats and prevent excessive growth of smooth muscle by inhibiting the transforming growth factor beta (TGF-\(\beta\)) synthesis\(^{(10)}\). Also, it has been reported that DHA promotes vascular smooth muscle apoptosis, perhaps because of a modulatory effect on the renin-angiotensin-aldosterone system. Thus, it has been suggested that through these two mechanisms, DHA help to prevent vascular wall fibrosis and secondary hypertension development\(^{(11)}\). Possible effects of \(\omega-3\) PUFA on blood pressure are shown in Table 1.

**Effects of \(\omega-3\) on cardiac output**

Animal-experimental studies, randomized trials, and large observational studies indicate that consumption of fish and marine \(\omega-3\) PUFAs affects cardiac haemodynamics. Independent effects include lowering of systemic vascular resistance, reduction of resting heart rate, and improvement of cardiac diastolic. These haemodynamic effects could in part account for clinical benefits of fish or fish oil intake, including lower risk of cardiac death and possibly ischaemic stroke, heart failure, and non-fatal coronary events\(^{(12)}\). Regarding heart rate, a meta-analysis including 30 randomized and placebo-controlled trials, shown that \(\omega-3\) PUFA supplements reduced heart rate by 1.6 bpm independent of the amount of the supplements use. In this case it was found a reduction in heart rate of 3 bpm. In this case it was found a reduction in heart rate of 3 bpm. Therefore, the second variable in the blood pressure equation, cardiac output, has few changes in relation to \(\omega-3\) PUFA consumption. The stroke volume increase was offset by a reduction in heart rate. Therefore, the main determinant of changes in blood pressure induced by the \(\omega-3\) PUFA consumption, are changes in systemic vascular resistance.

**Evidence of the effect of \(\omega-3\) PUFA on blood pressure**

Table 2 shows the principal studies evaluating the effect of \(\omega-3\) PUFA on blood pressure.

**Table 1. Possible biological effects of \(\omega-3\) PUFA on blood pressure**\(^{(2)}\)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series 3 prostaglandins production with vasoactive, antiplatelet and anti-inflammatory effects(^{(3)}).</td>
<td></td>
</tr>
<tr>
<td>Interaction with (\omega-6) fatty acids pathway(^{(4)}).</td>
<td></td>
</tr>
<tr>
<td>Suppression of aldosterone secretion(^{(5)}).</td>
<td></td>
</tr>
<tr>
<td>Change in intracellular signal transduction, reduction in plasma viscosity and in the activity of angiotensin converting enzyme(^{(9)}).</td>
<td></td>
</tr>
<tr>
<td>Increase production of endothelial nitric oxide(^{(10)}).</td>
<td></td>
</tr>
<tr>
<td>Changes in ionic channels with influence on the parasympathetic stimulation of vagus nerve reducing heart rate(^{(12)}).</td>
<td></td>
</tr>
<tr>
<td>Changes of myocytes cell membrane improving left ventricular diastolic function(^{(14,15)}).</td>
<td></td>
</tr>
<tr>
<td>Inhibition of transforming growth factor beta (TGF-(\beta)) synthesis(^{(16)}).</td>
<td></td>
</tr>
<tr>
<td>Vascular smooth muscle apoptosis(^{(17)}).</td>
<td></td>
</tr>
<tr>
<td>Prevention of vascular wall fibrosis and secondary hypertension development(^{(12)}).</td>
<td></td>
</tr>
</tbody>
</table>

\(\omega-3\) PUFA on blood pressure (SBP) and diastolic blood pressure (DBP) in hypertensive subjects were 5.5 and 3.5 mmHg, respectively\(^{(16)}\). Another meta-analysis including 36 studies, 22 of which were double-blind designed and with a duration over 2 weeks, showed a significant 21 mmHg reduction in SBP and 16 mmHg DBP (17/15 mmHg in the double-blind studies) with a median consumption of 3.7 g/day of fish oil. The effect was higher in subjects >45 years and in hypertensive volunteers (SBP \(\geq\) 140/90 mmHg)\(^{(17)}\).

**Meta-analysis studies including type 2 diabetic subjects.** A meta-analysis of 12 randomized trials performed in patients with type 2 diabetes showed a discrete effect on DBP in five trials (\(-1.79\) mmHg, \(P = 0.05\)), but not in SBP and heart rate. Mean \(\omega-3\) dose was 4.6 g/day, ranging from 3 to 8 g/day. The main limitations of the results were the small number of trials available and the sample size of the studies (mean 30.6, range 23–40)\(^{(18)}\). In a recent meta-analysis including 24 trials, the possible beneficial effect of \(\omega-3\) PUFA in patients with type 2 diabetes mellitus was also analyzed\(^{(19)}\). Only 8 of the 24 trials reported blood pressure changes and a total of 747 participants were studied in the trials. The main results showed that \(\omega-3\) supplements did not produce significant changes in SBP or DBP (SBP: \(-0.78\) mmHg \(P = 0.44\), DBP: \(-0.79\) \(P = 0.18\)). The absence of a dose-dependent analysis is a limitation to the results on blood pressure of this meta-analysis.
Table 2. Major studies of the effect of \(\omega-3\) PUFA on blood pressure

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Duration</th>
<th>HT subjects</th>
<th>BP change (mmHg)</th>
<th>Type of study</th>
<th>(\omega-3) dosage (g/day)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appel LJ \textit{et al.}\textsuperscript{(16)}</td>
<td>1993</td>
<td>291</td>
<td>&lt;3M(13/17)*</td>
<td>Yes</td>
<td>-1.05/-2.18</td>
<td>Meta-analysis (RS)</td>
<td>3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lahoz C. \textit{et al.}\textsuperscript{(8)}</td>
<td>1997</td>
<td>42</td>
<td>5 W</td>
<td>No</td>
<td>-5/-1.9</td>
<td>Dietary intervention (F)</td>
<td>3.8</td>
<td>&lt;0.001/(&gt;0.05)</td>
</tr>
<tr>
<td>Bao DQ \textit{et al.}\textsuperscript{(22)}</td>
<td>1998</td>
<td>63</td>
<td>16 W</td>
<td>Yes</td>
<td>-6.3</td>
<td>Dietary intervention (RF)</td>
<td>3.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Geleijnse JM \textit{et al.}\textsuperscript{(17)}</td>
<td>2002</td>
<td>1404</td>
<td>12W</td>
<td>Yes</td>
<td>-4.03/-2.73</td>
<td>Meta-analysis (RS)</td>
<td>3.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Murphy KJ \textit{et al.}\textsuperscript{(17)}</td>
<td>2002</td>
<td>86</td>
<td>6 M</td>
<td>No</td>
<td>-3/-1.9</td>
<td>Dietary intervention (FR)</td>
<td>1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hartweg J \textit{et al.}\textsuperscript{(21)}</td>
<td>2003</td>
<td>248</td>
<td>8.5 W</td>
<td>No</td>
<td>-4/-1.7</td>
<td>Dietary intervention (RF)</td>
<td>1.6-8</td>
<td>0.05</td>
</tr>
<tr>
<td>Ramel A \textit{et al.}\textsuperscript{(23)}</td>
<td>2009</td>
<td>324</td>
<td>8 W</td>
<td>Yes</td>
<td>NA</td>
<td>Cross-sectional</td>
<td>NA</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mcallef MA \textit{et al.}\textsuperscript{(26)}</td>
<td>2009</td>
<td>15</td>
<td>3 W</td>
<td>No</td>
<td>-4.1/0.1</td>
<td>Dietary intervention (RS)</td>
<td>1.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hartweg J \textit{et al.}\textsuperscript{(19)}</td>
<td>2009</td>
<td>747</td>
<td>24 W</td>
<td>No</td>
<td>-0.78/-0.79</td>
<td>Meta-analysis (RS)</td>
<td>2.4</td>
<td>0.44-0.18</td>
</tr>
<tr>
<td>Cicero AF \textit{et al.}\textsuperscript{(20)}</td>
<td>2010</td>
<td>111</td>
<td>12 M</td>
<td>Yes</td>
<td>-2.7/-1.4</td>
<td>Dietary intervention (S)</td>
<td>2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LIPGENE study\textsuperscript{(14)}</td>
<td>2010</td>
<td>486</td>
<td>12 W</td>
<td>Yes</td>
<td>-6.8/-4.5</td>
<td>Dietary intervention (RF)</td>
<td>1-2</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

HT: hypertensive; R: randomized; S: \(\omega-3\) supplements; F: \(\omega-3\) rich fish intake. W: weeks; M: months. For meta-analysis, the average time of duration is shown, (*) in 13 of 17 studies, the duration was <3 months.
Differential effects of EPA and DHA on blood pressure. Some clinical trials have suggested that EPA and DHA have differential hemodynamic effects. DHA may be more favorable in reducing blood pressure and heart rate, although not all trials show conclusive results. In this sense, 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 versus placebo(29). Diastolic blood pressure in patients treated with DHA fell 3.5 mmHg, in comparison with placebo (P < 0.01). There were no significant differences in resting heart rate and SBP. Another study 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 ω-3 provided either by the combination with ω-6(29).

The effect of ω-3 on blood pressure has also been analysed in 59 overweight men with hyperlipidemia randomized to receive either 4 g/day of EPA, 4 g/day of DHA or olive oil (as control group) during 6 weeks, maintaining the rest of nutrients in their regular diets. The study showed that only in the DHA group there was a significant reduction of blood pressure and heart rate compared with placebo. The average reduction in SBP/DBP was 5.8/3.3 mmHg, while heart rate fell 3.5 (SD 0.8 bpm). EPA did not show statistically significant effect on either blood pressure or on heart rate.(30)

Effect of ω-3 in blood pressure in other populations. Recently, Vernaglione L. et al.(31) published a prospective study on the effects on blood pressure and other variables in 24 patients on hemodialysis who were supplemented with ω-3. 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 ω-3 supplements and finally back to 2 g/day of olive oil. Both SBP and DBP were significantly lower (P<0.05) at the end of the supplementation period with ω-3. Systolic blood pressure diminished from 131 ± 17-8 mmHg in the first phase to 122 mmHg (SD 12.8) in the second phase and rose to 129 ± 13.2 mmHg. The effect on DBP was in the same direction: 83 ± 16.3 mmHg in the first phase, 71 ± 14.8 mmHg in the second phase and 79 ± 6.5 mmHg in the last period of the study.

Conclusions

The evidence of the effects of ω-3 PUFA on blood pressure is not consistent, and the reduction obtained in different studies is mild, but higher using doses ≥ 3 g/day supplemented as fish oil or blue fish, in older population and hypertensive subjects. On the other hand, consumption of ω-3 can reduce cardiovascular risk in hyperlipemic, diabetic or hypertensive subjects preventing the increase in blood pressure. Therefore, further clinical studies are necessary to determine the impact of blood pressure reduction on cardiovascular risk in homogeneous population using ω-3 PUFA supplementation.

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.

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