

Omega-3 fatty acids and blood pressure

Jorge Cabo¹, Rodrigo Alonso² and Pedro Mata^{2*}

¹Internal Medicine Department, Hospital Universitario Santa Cristina, Madrid, Spain

²Internal Medicine Department, IIS-Fundación Jiménez Díaz, Madrid, Spain

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)⁽¹⁾. 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 properties⁽²⁾. 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 population⁽³⁾ 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

* Corresponding author: Pedro Mata, fax +34-915042206, email pmata@fjd.es

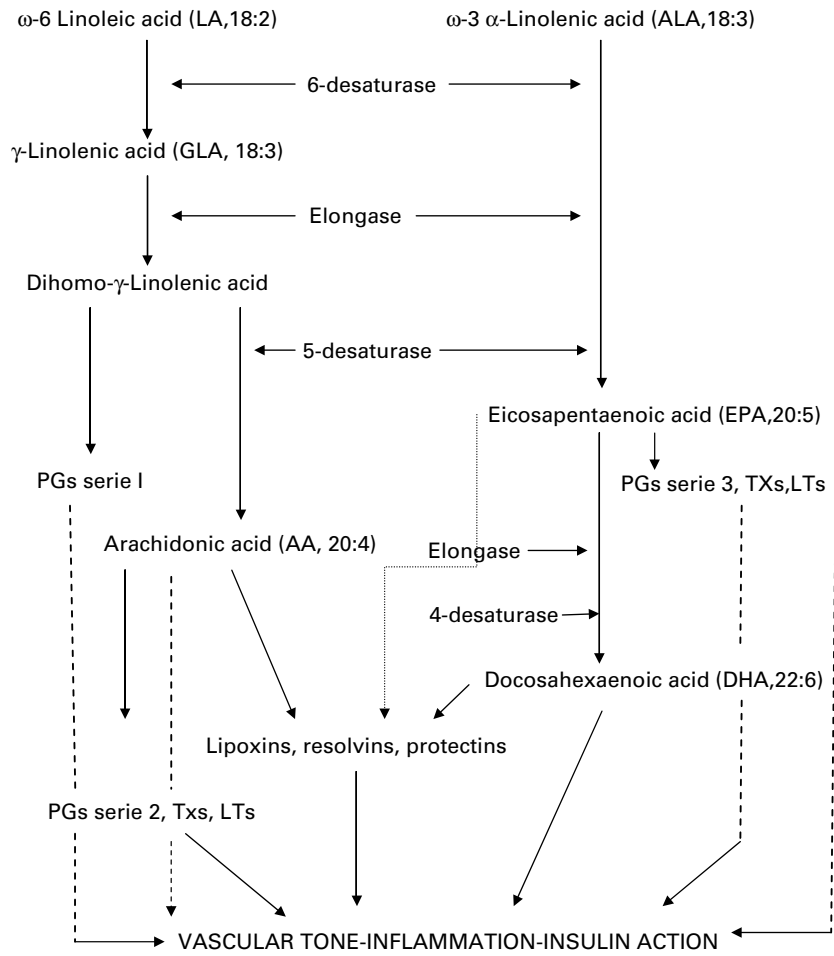


Fig. 1. Metabolism of ω -3 and ω -6 polyunsaturated fatty acids (Sources: PGs, Prostaglandins; Tx, thromboxanes; LTs, leukotrienes).

lipoxygenases, 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, C20:5), 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 antagonistic⁽⁵⁾. Finally, EPA can get new reversible elongation and desaturation reactions producing docosahexaenoic acid (DHA, C22:6). In addition, ω -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 dihomogamma linoleic acid competes with alpha-linolenic acid in the desaturase active site, interfering with the synthesis of ω -3 route precursors (EPA, DHA)^(4,7). Therefore, a disbalance between both ω -3 and ω -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 *et al.* conducted a study in 42 healthy subjects undergoing 4 consecutive diets rich in saturated fat, monounsaturated fat, ω -6 PUFA and ω -3 PUFAs. Although a significant reduction in blood pressure was observed in the last period enriched in ω -3 from fish, there were no differences in the urine excretion of prostanoids between the 4 dietary periods⁽⁸⁾.

Effects of ω -3 on renin-angiotensin-aldosterone system, nitric oxide and cell apoptosis

Omega-3 appear to suppress aldosterone secretion compared to physiological stimulus such as angiotensin II, ACTH or K^+ . This effect may be related to changes in intracellular signal transduction, alterations in plasma viscosity or to a lower activity of angiotensin converting enzyme (ACE). ACE is the enzyme that transform angiotensin-I into angiotensin-II, that controls blood pressure and regulates body fluid volume by modulating renin-angiotensin-aldosterone system. The inhibition of this enzyme leads to reduce angiotensin-II production, producing vascular relaxation and reducing aldosterone secretion⁽⁹⁾. Besides, ω -3 PUFA have been

linked to increase production of endothelial nitric oxide (eNO) in animal models, and on the other hand, the L-arginine-NO system increase PUFA 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- β) 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 ω -3 PUFA on blood pressure are shown in Table 1.

Effects of ω -3 on cardiac output

Animal-experimental studies, randomized trials, and large observational studies indicate that consumption of fish and marine ω -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 ω -3 PUFA supplements reduced heart rate by 1.6bpm independent of the amount of ω -3 consumed (95% CI = 0.6 – 2.5, $P = 0.002$)⁽¹³⁾. In those trials lasting ≥ 12 weeks the heart rate reduction was significantly higher than in those studies with a duration < 12 weeks (2.5 bpm vs 0.7 bpm, $P = 0.001$), suggesting that this effect is also dependent of the duration of the supplements use.

Mozaffarian D *et al.*, also tested the hypothesis of the reduction of heart rate by ω -3 PUFA. Data from a cohort study of more than 5000 subjects that consumed a diet with high amount of grilled or baked fish like tuna. Fish consumption of 3 or more times per week was associated with a reduction in heart rate of 3 bpm. In this case it was found a nonlinear dose-response between the amount of ω -3 PUFA consumption and the reduction in heart rate: there was a

substantial reduction in HR when the intake of EPA +DHA was from 0 to 300mg/day, and then a plateau effect was observed with higher doses⁽¹⁴⁾. The mechanisms by which the ω -3 PUFA reduce heart rate are probably through a modification of PUFA content on myocytes cell membrane and secondary changes in ionic channels, influencing the parasympathetic stimulation of vagus nerve.

On the other hand, studies in primates and humans showed that ω -3 PUFA may raise cardiac stroke volume by improving left ventricular diastolic function. This effect occurs even at the beginning of ω -3 PUFA consumption and may be caused by a longer diastolic filling produced by reducing heart rate together with other functional or metabolic changes rather than structural alterations of the left ventricle⁽¹⁵⁾. Therefore, the second variable in the blood pressure equation, cardiac output, has few changes in relation to ω -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 ω -3 PUFA consumption, are changes in systemic vascular resistance.

Evidence of the effect of ω -3 PUFA on blood pressure

Table 2 shows the principal studies evaluating the effect of ω -3 PUFA on blood pressure.

Meta-analysis studies with normotensive and hypertensive subjects. 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.*, 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⁽¹⁶⁾. 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 1.6 mmHg DBP (1.7/1.5 mmHg in the double-blind studies) with a median consumption of 3.7g/day of fish oil. The effect was higher in subjects > 45 years and in hypertensive volunteers (BP $\geq 140/90$ 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 ω -3 dose was 4.6g/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 ω -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 ω -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 1. Possible biological effects of ω -3 PUFA on blood pressure⁷

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

Table 2. Major studies of the effect of ω -3 PUFA on blood pressure

Author	Year	n	Duration	HT subjects	BP change(mmHg)	Type of study	ω -3 dosage (g/day)	P
Appel LJ <i>et al.</i> ⁽¹⁶⁾	1993	291	<3M(13/17)*	Yes	-1.05/-1.98	Meta-analysis RS	3	<0.05
Lahoz C. <i>et al.</i> ⁽⁸⁾	1997	42	5 W	No	-5/-1.9	Dietary intervention F	3.8	<0.001/<0.05
Bao DQ <i>et al.</i> ⁽²²⁾	1998	63	16 W	Yes	-6/-3	Dietary intervention RF	3.6	<0.01
Geleijnse JM <i>et al.</i> ⁽¹⁷⁾	2002	1404	12 W	Yes	-4.03/-2.73	Meta-analysis RS	3.7	\leq 0.01
Murphy KJ <i>et al.</i> ⁽²⁷⁾	2007	86	6 M	No	-3/-	Dietary intervention FR	1	>0.05
Hartweg J <i>et al.</i> ⁽¹⁸⁾	2007	248	8.5 W	No	-/-1.8	Meta-analysis RFS	1.6-8	0.05
Ramel A <i>et al.</i> ⁽²³⁾	2009	324	8 W	Yes	NA	Cross-sectional	NA	>0.05
Micallef MA <i>et al.</i> ⁽²⁶⁾	2009	15	3 W	No	-4/+0.1	Dietary intervention RS	1.4	>0.05
Hartweg J <i>et al.</i> ⁽¹⁹⁾	2009	747	24 W	No	-0.78/-0.79	Meta-analysis RS	2.4	0.44/0.18
Cicero AF <i>et al.</i> ⁽²⁵⁾	2010	111	12 M	Yes	-2.7/-1.4	Dietary intervention S	2	<0.001
LIPGENE study ⁽²⁴⁾	2010	486	12 W	Yes	-6.8/-4.5	Dietary intervention RF	1-2	>0.05

HT: hypertensive; R: randomized; S: ω -3 supplements; F: ω -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.

Effect of ω -3 supplementation on blood pressure in healthy subjects. In a randomized, placebo-controlled study, 162 healthy subjects received a diet with high proportion of saturated fatty acids or high proportion of monounsaturated fatty acids. Both groups were further randomly assigned to receive supplementation with fish oil (3.6 g n-3 fatty acids/d) or placebo. The main objective was to evaluate the effects of different types of dietary fat on BP in healthy subjects. The results showed that supplementation did not affect blood pressure in healthy volunteers, independent of the amount of fat on diet⁽²⁰⁾. Similar results were observed in a smaller and short-term study performed in 37 healthy volunteers using lower dose of ω -3 PUFA (1 g/day)⁽²¹⁾.

Dietary intervention studies in obese subjects with or without hyperlipemia (cross-sectionals and randomized studies). In a small dietary intervention study⁽²²⁾, 69 volunteers with overweight and treated hypertension, were randomized to 4 different diets: 1) fish diet containing 3.65 g/day of ω -3 PUFA; 2) low-calories diet; 3) combination of both diets and 4) control diet. Subjects consuming high amount of ω -3 reduced SBP and DBP by 6.0 and 3.0 mmHg respectively, similar to the reduction observed in the low-calories diet (5.5/2.2 mmHg); however, the reduction was higher with the combination of both diets (13.0/9.3 mmHg). Heart rate significantly decreased in the fish diet group (3.1 bpm SD 1.4). In conclusion, the combination of fish and low-calories diet was additive in terms of effects on blood pressure, so these results may be relevant in the management of patients with metabolic syndrome.

Ramel A *et al.*⁽²³⁾ analyzed the association in a cross-sectional study between diet, ω -3 PUFA index in red blood cell membranes and cardiovascular risk factors in 324 subjects aged 30-35 years and overweight in Spain, Iceland and Ireland. None of the participants had type 2 diabetes and 32% had high blood pressure. There were no association between red blood cell ω -3 fatty acid composition (ω -3 index) and systolic or diastolic blood pressure. Body mass index was significantly associated with increased blood pressure but no with cholesterol measures.

Recently, it has been published the LIPGENE dietary intervention study⁽²⁴⁾. This study evaluated the effect of ω -3 PUFA on blood pressure in individuals with metabolic syndrome for 12 weeks, randomizing volunteers to one of four isoenergetic diets avoiding weight loss bias. In two diets, 38% of total energy came from fat: one high in saturated fatty acids and another high in monounsaturated fatty acids. In the other 2 diets 20% of energy came from fat: one supplemented with 1-2 g/day of ω -3 and one supplemented with oleic acid or sunflower oil. There were no differences in systolic and diastolic blood pressure between the different diets, and the authors' suggested that the dose of ω -3 was too low compared with other studies, or perhaps the absence of weight loss was important taking into account the relationship between weight loss and blood pressure reduction.

The effect of ω -3 in blood pressure in subjects with hyperlipidemia has been controversial. In a retrospective study, the effect of ω -3 PUFA supplementation during 12 months on blood pressure was evaluated in 111 subjects with

hypertriglyceridemia and high-normal blood pressure without treatment. Subjects received 2 g/day of ω -3 PUFA, containing at least 85 % EPA and DHA with a ratio of 0.9:1.5. The results showed a slight but significant reduction of systolic and diastolic blood pressure (2.7 ± 2.5 , 1.4 ± 4.2 , respectively). In men, there were a significant association between baseline triglyceride levels with change in systolic blood pressure, which might be of interest in the selection of specific subjects in which ω -3 supplementation could be of maximum benefit⁽²⁵⁾.

In another study, 60 hyperlipidemic patients were randomly assigned to one of 4 groups: placebo, fish oil (1.4 g/day of ω -3), plant sterols (2 g/day) and the combination of fish oil and plant sterols. There was a non significant trend to decrease SBP and DBP in the groups containing ω -3 PUFA⁽²⁶⁾. On the other hand, it has been shown that long-term administration of low dose of ω -3 PUFA (1 g/day) do not reduce blood pressure in overweight volunteers with hypertriglyceridemia followed-up during 6 months⁽²⁷⁾.

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 *vs.* placebo⁽²⁸⁾. 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. Another study using algae oil (1.5 gr/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.

Acknowledgements

This study was supported by grants G03/181, Hiperlipemias Genéticas Network from the Instituto de Salud Carlos III; and grant 08-2008 from Centro Nacional de Investigaciones Cardiovasculares (CNIC). Competing Interests. The authors have no financial and non-financial competing of interests. Authors' contribution. PM, coordinated the study. JC, RA, PM reviewed the literature in MEDLINE and EMBASE database and wrote the manuscript. All authors' read and corrected draft version and approved the final manuscript.

References

1. Calder PC, Dangour AD, Diekman C, Eilander A, Koletzko B, Meijer GW, Mozaffarian D, Niinikoski H, Osendarp SJ, Pietinen P, Schuit J, Uauy R (2010) Essential fats for future health. *Eur J Clin Nutr.* **64**, Suppl. 4, S1–13.
2. Gebauer SK, Psota TL, Harris WS & Kris-Etherton PM (2006) n-3 fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits. *Am J Clin Nutr* **83**, Suppl. 6, 1526S–1535S.
3. Ward R (1990) Familial aggregation and genetic epidemiology of blood pressure. In *Hypertension, Pathophysiology, Diagnosis and Management*, pp. 81–100 [JH Laragh and BM Brenner, editors]. New York, NY: Raven Press.
4. Cook H & McMaster C (2002) Fatty acid desaturation and chain elongation in eukaryotes. In *Biochemistry of Lipids, Lipoproteins and Membranes*, 4th ed., pp. 181–204 [DE Vance, editor].
5. Biscione F, Pignalberi C, Totteri A, Messina F & Altamura G (2007) Cardiovascular effects of omega-3 free fatty acids. *Curr Vasc Pharmacol.* **5**, 163–172.
6. Das U (2008) Essential fatty acids and their metabolites could function as endogenous HMG-CoA reductase and ACE enzyme inhibitors, anti-arrhythmic, anti-hypertensive,

- anti-atherosclerotic, anti-inflammatory, cytoprotective, and cardioprotective molecules. *Lipids Health Dis* **7**, 37.
7. Cicero AF, Ertek S & Borghi C (2009) Omega-3 polyunsaturated fatty acids: their potential role in blood pressure prevention and management. *Curr Vasc Pharmacol* **7**, 330–337.
 8. Lahoz C, Alonso R, Ordovás JM, López-Farré A, de Oya M & Mata P (1997) Effects of dietary fat saturation on eicosanoid production, platelet aggregation and blood pressure. *Eur J Clin Invest* **27**, 780–787.
 9. Fischer R, Dechend R, Qadri F, Markovic M, Feldt S, Herse F, Park JK, Gapelyuk A, Schwarz I, Zacharzowsky UB, Plehm R, Safak E, Heuser A, Schirdewan A, Luft FC, Schunck WH & Muller DN (2008) Dietary n-3 polyunsaturated fatty acids and direct renin inhibition improve electrical remodeling in a model of high human renin hypertension. *Hypertension* **51**, 540–546.
 10. Das UN (2004) Long-chain polyunsaturated fatty acids interact with nitric oxide, superoxide anion, and transforming growth factor-beta to prevent human essential hypertension. *Eur J Clin Nutr* **58**, 195–203.
 11. Engler MM, Engler MB, Pierson DM, Molteni LB & Molteni A (2003) Effects of docosahexaenoic acid on vascular pathology and reactivity in hypertension. *Exp Biol Med (Maywood)* **228**, 299–307.
 12. Mozaffarian D (2007) Fish, n-3 fatty acids, and cardiovascular haemodynamics. *J Cardiovasc Med* **8**, Suppl. 1, S23–S26.
 13. Mozaffarian D, Geelen A, Brouwer IA, Geleijnse JM, Zock PL & Katan MB (2005) Effect of fish oil on heart rate in humans: a meta-analysis of randomized controlled trials. *Circulation* **112**, 1945–1952.
 14. Mozaffarian D, Gottdiener JS & Siscovick DS (2006) Intake of tuna or other broiled or baked fish versus fried fish and cardiac structure, function, and hemodynamics. *Am J Cardiol* **97**, 216–222.
 15. McLennan PL, Barnden LR, Bridle TM, Abeywardena MY & Charnock JS (1992) Dietary fat modulation of left ventricular ejection fraction in the marmoset due to enhanced filling. *Cardiovasc Res* **26**, 871–877.
 16. Appel LJ, Miller ER III, Seidler AJ & Whelton PK (1993) Does supplementation of diet with 'fish oil' reduce blood pressure? A meta-analysis of controlled clinical trials. *Arch Intern Med* **153**, 1429–1438.
 17. Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR & Kok FJ (2002) Blood pressure response to fish oil supplementation: meta-regression analysis of randomized trials. *J Hypertens* **20**, 1493–1499.
 18. Hartweg J, Farmer AJ, Holman RR & Neil HA (2007) Meta-analysis of the effects of n-3 polyunsaturated fatty acids on haematological and thrombotic factors in type 2 diabetes. *Diabetologia* **50**, 250–258.
 19. Hartweg J, Farmer AJ, Holman R & Neil A (2009) Potential Impact of omega-3 Treatment on cardiovascular disease in type 2 diabetes. *Curr Opin Lipidol* **20**, 30–38.
 20. Rasmussen BM, Vessby B, Uusitupa M, Berglund L, Pedersen E, Riccardi G, Rivellese AA, Tapsell LL, Hermanen K, Kanwu study group, *et al.* (2006) Effects of dietary saturated, monounsaturated, and n-3 fatty acids on blood pressure in healthy Subjects. *Am J Clin Nutr* **83**, 221–226.
 21. Shah AP, Ichijui AM, Han JK, Traina M, El-Bialy A, Meymandi SK & Wachsner RY (2007) Cardiovascular and endothelial effects of fish oil supplementation in healthy Volunteers. *J Cardiovasc Pharmacol Ther* **12**, 213–219.
 22. Bao DQ, Mori T, Burke V, Puddey IB & Beilin LJ (1998) Effects of dietary fish and weight reduction on ambulatory blood pressure in overweight hypertensives. *Hypertension* **32**, 710–717.
 23. Ramel A, Pumberger C, Martinez AJ, Kiely M, Bandarra NM & Thorsdottir I (2009) Cardiovascular Risk Factors in young, overweight, and obese European adults and associations with physical activity and omega-3 index. *Nutr Res* **29**, 305–312.
 24. Gulseth HL, Gjelstad IM, Tierney BC, Shaw DI, Helal O, Hees AM, Delgado J, Leszczynska-Golabek I, Karlström B, Lovegrove J, Defoort C, Blaak EE, Lopez-Miranda J, Dembinska-Kiec A, Risérus U, Roche HM, Birkeland KI & Br Drevon CA (2010) Dietary fat and blood pressure modifications in subjects with the metabolic syndrome in the dietary intervention LIPGENE study. *J Nutr* **104**, 160–163.
 25. Cicero AF, Derosa G, Di Gregorio V, Bove M, Gaddi AV & Borghi C (2010) Omega 3 polyunsaturated fatty acids supplementation and blood pressure levels in hypertriglyceridemic patients with untreated normal-high blood pressure and with or without metabolic syndrome: a retrospective study. *Clin Exp Hypertens* **32**, 137–144.
 26. Micallef MA & Garg ML (2009) Anti-inflammatory and cardioprotective effects of n-3 polyunsaturated fatty acids and plant sterols in hyperlipidemic individuals. *Atherosclerosis* **204**, 476–482.
 27. Murphy KJ, Meyer BJ, Mori TA, Burke V, Mansour J, Patch CS, Tapsell LC, Noakes M, Clifton PA, Barden A, Puddey IB, Beilin LJ & Howe PR (2007) Impact of foods enriched with n-3 long-chain polyunsaturated fatty acids on erythrocyte n-3 levels and cardiovascular Risk factors. *Br J Nutr* **97**, 749–757.
 28. Theobald Middleaged HE, Goodall AH, Sattar N, Talbot DC, Chowienczyk PJ & Sanders TA (2007) Low-dose docosahexaenoic acid lowers diastolic blood pressure in men and women. *J Nutr* **137**, 973–978.
 29. Sanders TA, Gleason K, Griffin B & Miller GJ (2006) Influence of an algal triacylglycerol containing docosahexaenoic acid (22:6n-3) and docosapentaenoic acid (22:5n-6) on Cardiovascular Risk Factors in Healthy Men and Women. *Br J Nutr* **95**, 525–531.
 30. Mori TA, Bao DQ, Burke V, Puddey IB & Beilin LJ (1999) Docosahexaenoic acid but not eicosapentaenoic Acid lowers ambulatory blood pressure and heart rate in humans. *Hypertension* **34**, 253–260.
 31. Vernaglione L, Cristofano C & Chimienti S (2008) Omega-3 polyunsaturated fatty acids and proxies of cardiovascular disease in hemodialysis: a prospective cohort study. *J Nephrol* **21**, 99–105.