Fish oils and atherosclerosis

José Manuel Silva*, José Brito**, Pedro Figueiredo***, Ávila Costa****, Políbio Serra e Silva*****

Abstract

Epidemiological studies show a significant inverse correlation between fish consumption and atherosclerotic disease. An important fraction of fish oil – polyunsaturated Omega-3 fatty acids, particularly eicosapentaenoic acid - appear to be the mediators of this action, which is the consequence of various metabolic effects, namely: hypolipidemic activity, decreasing the synthesis of triglycerides; 2) platelet antiaggregation, due to the synthesis of thromboxane A3 to the detriment of A2; 3) anti-inflammatory activity, due to a decrease in leukotriene B4 synthesis, a powerful agent for quimiotaxis of neutrophils and monocytes, and an increase in leukotriene B5 synthesis; 4) antithrombotic action, reducing PAI-1 levels; and 5) improvement in tissue perfusion. The consumption of fish oil concentrates appears to be harmless, the only hypothetical exception being diabetes, since it can worsen glycemic control.

Key words: fish oils, polyunsaturated Omega-3 fatty acids, eicosapentaenoic acid, atherosclerosis.

Introduction

Despite having an average life expectancy of only 60 years, Eskimos have a mortality rate by ischemic heart disease (IHD) of just 3.5%. They have a lower incidence not only of myocardial infarction and diabetes, but also of thyrotoxicosis, bronchial asthma, multiple sclerosis and psoriasis. Although their diet is rich in fats, and they present average total cholesterol levels of around 228 mg/dl,[1] analysis showed that much of the fat and calories were derived from the consumption of fatty fish and marine mammals, rich in -3 fatty acids (Omega-3), of which Eskimos consume 5 to 10 g/day, which was considered largely responsible for the low incidence of IHD. In Japan, where fish consumption per capita is 100 g/day, a low incidence of coronary disease is also observed, and the inverse relationship between IHD and fish consumption appears to be dose-dependant.[2] However, other studies previously carried out are not unanimous,[3] therefore doubt remains as to the real role of fish in preventing IHD.

The main Omega-3s are alpha-linolenic acid (C18:3, W-3), eicosapentaenoic acid (C20:5, W-3) and docosahexaenoic acid (C22:6, W-3) [C18 represents the existence of 10 carbon atoms on the molecule, :3 means there are three double bonds and W-3 indicates the location of the first double bond in the third carbon atom, from the methyl end of the fatty acid]. Like linoleic acid (C18:2, W-6), alpha-linolenic acid, which is found in some vegetable oils and green leafy vegetables, is an essential fatty acid. Cold water fatty fish, like mackerel, herring and salmon, are particularly rich in Omega-3, which is synthesized by phytoplankton and zooplankton.[4] However, the ingestion of significant doses of these fatty acids from natural sources is hindered by the fact that boiling and processing of the foods destroy considerable quantities of the Omega- 3 present.[5]

Ingestion of fish or fish oil concentrates results in the incorporation of Omega-3 in the cell membranes, giving rise to multiple actions in various biochemical and cellular actions that can affect the development and progression of atherosclerotic disease and its main complication, thrombosis.[6]

Many of these effects are attributed to the eicosapentaenoic acid,[7] while docosahexaenoic acid, which accumulates in the phospholipids and can be slowly transformed into eicosapentaenoic acid, functions essentially as a store of the latter, although it is also metabolically active.[7] The accumulation of Omega-3 in the tissues, particularly the heart, kidneys, liver and adipose and muscle tissues, is associated with a reciprocal decrease in Omega 6, essentially from

*Ad-hoc Hospital Assistant in Internal Medicine

**Resident to the Pneumology Supplementary Internship

***Resident to the Gastroenterology Supplementary Internship

****Senior Hospital Assistant in Internal Medicine

*****Full Professor at the Coimbra School of Medicine, Medicine Service II of the Coimbra University Hospitals.

arachidonic acid, but also from saturated fatty acids, like lauric and myristic acid, in the cell membranes.[8] It is likely that Omega and 3 and Omega 6 compete in their biological activities, therefore the relative proportion of each in the diet is a determining factor for their respective effects.

Despite the high number studies carried out, some confusion remains as to the effects of Omega-3 concentrates on lipid profile.[2] The possible consensus is that in high doses, Omega-3 are essentially hypotriglyceridemiants, which may be due to a decrease in synthesis and hepatic secretion of VLDL, [9] secondary to the stimulation of free fatty acid oxidation and mitochondrial metabolization,[7] reducing fasting triglyceridaemia levels by 20% to 40% in normal and hyperlipidemic individuals.[10] There appears to be no stimulation of the lipoprotein lipase.[5]

There may be a slight decrease in total cholesterol at the expense of VLDL cholesterol, while LDL cholesterol may increase, particularly in types IIb and IV of the Fredrickson/WHO classification. C-HDL may increase by up to 5%-10%, although the results are inconsistent, probably reflecting their inverse relation with the triglycerides. In relation to apoproteins, a slight increase in Apo AI may occur, alongside the increase in HDL-C, while the opposite effects on ILDL and IDL may balance the variation in apo B100. It will have no significant effect on Lp(a)[9]. Omega-3 have the capacity to prevent induced hypertriglyceridemia induced by the carbohydrates[11] and to reduce postprandial lipemia[10]. Hyperchylomicronemia (type V) also appears to respond well to Omega-3[5].

Eicosapentaenoic acid, which has the same number of carbon acids as arachidonic acid, is incorporated into the platelet membrane, where it is transformed into thromboxane A3 (structural analog to thromboxane A2), and in the endothelial cells, into prostaglandin 13 (analog to prostacyclin); while the first has no platelet and vasoconstrictor agonist activity, the second has powerful vasodilation and prostacyclin platelet antagonist properties,[12,13.14] reducing platelet aggregation and prolonging bleeding time by 20 to 40%.

Leukotrienes, produced from arachidonic acid, contribute to the acute inflammatory response during myocardial infarction.[2] The incorporation of eicosapentaenoic acid in the phospholipids of the membrane of the neutrophils and monocytes leads to a decrease in synthesis of leukotriene B4, a powerful chemotactic agent of neutrophils and monocytes, and a increase in synthesis of leukotriene B5, which is biologically less active than the former, reducing the inflammatory response. By decreasing the chemotactic activity of the circulating monocytes,[15] Omega-3 may, eventually, inhibit the accumulation of macrophages in the intimal layer, interfering with the pathogenic mechanisms of atherosclerosis.

Besides the effects described above, Omega-3 may also inhibit the production, by the endothelial cells, of PDGF (platelet-derived growth factor), [16] a growth factor that plays an important role in smooth muscle cell and fibroblast hyperplasia in the atheromatous plates, stimulating the production of EDRF (endothelium-derived relaxing factor) by the damaged endothelium,[17,18,19] decreasing PAI-1 (plasminogen activator inhibitor-1) concentrations,[20] improving fibrinolytic activity, decreasing fibrinogen levels, [21, 22] recently considered by the European Atherosclerosis Society as a risk factor for IHD[23] - reducing the vasospastic response to catecholamines, arachidonic acid, vasopressin and angiotensin II, [24-25] increasing the red blood cell deformability, reducing blood viscosity,[26] and lowering blood pressure,[25,27,28] an effect that may be partially independent of the endothelium.[25] However, there is some debate as to these effects, as contradictory results have been obtained, and there have been studies which, notably, have found no alteration in values for fibrinogen, PAI-1, plasma viscosity[9] and blood pressure. [29] Differences in fatty acid and cholesterol composition of the fish oil supplements used in the various studies, dosage, and length of administration time may have influenced the results obtained.[8,30]

It is clear that faced with this wide spectrum of action, fish oils may have significant antiatherogenic action, which may be more due to the non-lipid effects than to the alterations in lipid profile. A recent ultrasound study in Eskimos demonstrated that the low incidence of ischemic heart disease in this population apparently cannot be attributed to less severed atherosclerotic disease, and in many of the studies that demonstrate a beneficial effect of fish oils on IHD, no significant changes were observed in cholesterol levels. Considering that there are local thrombi in more than 90% of patients with acute myocardial infarction, it is evident that the effects of Omega-3 on eicosanoid production may be more significant than the alterations in lipid profile[4]. Also, in the Lyon

Diet Heart Study, in which the institution of a typical Mediterranean diet, rich in alpha-linolenic acid, led to a 60% reduction in overall mortality, at the end of 27 month follow-up period, the rapid protector effect and the similarity of the lipid profile between the experimental group and the control group suggest that this protector effect may be the result of alterations in thrombogenesis and arrhythmogenesis.[31]

Various studies on pigs, dogs and monkeys appear to confirm the protector role of fish oils.[2] Studies on experimental coronary occlusion demonstrate smaller infarctions, less arrhythmias and less sudden deaths in animals treated with Omega-3.[32,33] However, the results for rabbits, rats and quails are not in agreement.[2] In humans, in restenosis after coronary angioplasty, apparent disagreements were also seen, perhaps due to the different doses of Omega-3 used. Dehmer et al, 1988, obtained a significant reduction in the percentage of patients with restenosis, ranging from 46% (placebo group) to 19% (group that received 3.2 g/day of Omega-3), while Grigg et al, 1989, did not find any significant differences with 1.8 g/day of Omega-3 vs placebo. However, a recent meta-analysis supports the hypothesis that Omega-3 effectively reduces the restenosis rate after coronary angioplasty, in an effect that appears to be dose-dependant, and the authors defend the use of a daily dose of 4 to 5 grams.[36] In a major secondary prevention trial with various dietetic combinations (DART trial), in patients with myocardial infarction, a decrease in overall mortality was found in 29% in the group advised to increase their fish consumption (corresponding to around 300 g of fatty fish per week, around 2.5 g of Omega-3).[37] Necropsy studies show an inverse correlation between the content of the adipose tissue in docosahexaenoic acid and the extension of the coronary atherosclerosis.[38] Total mortality, mortality by IHD and mortality by cardiovascular disease are inversely correlated with fish consumption in men (n=650) who took part in the MRFIT trial after 10.5 years of follow up.[39] During the twenty years of follow-up of the Zutphen population, which took part in the seven countries study, coronary mortality was reduced by more than 50% in the individuals who consumed 30 g of fish a day.[40] Omega-3 provides gives results in the prevention or delay of progression off microvascular complications of diabetes.[41,42]

In the majority of studies carried out with fish oils supplements, the doses administered varied between 2 and 7 g/day. Some of the biochemical and cellular effects of Omega-3 are dose-dependant, and the optimum daily dose is not yet known.[43] Fish oil concentrates should not contain excess A and D vitamins, in order to prevent hypervitaminosis. For example, despite being a source of Omega-3 that is easily available, the doses of cod liver oil needed to ensure the beneficial biological effects of these fatty acids involve a risk of vitamin intoxication.[5] They should also have a high concentration of Omega-3, avoiding an excess of other fatty acids and cholesterol, and must be enriched with antioxidants, due to their sensitivity to oxidation[43] and they may eventually increase the oxidative lability of the LDL.[44]

Without doubt, the majority of epidemiological studies and experiments carried out suggest that the ingestion of fish, because it generally replaces the consumption of foods rich in saturated fats, provides protection against IHD, as seen with the rapid and substantial decrease in incidence of mortality by myocardial infarction in Norway during the II World War, when meat was abruptly replaced with fish in the diet.[3] But further prospective clinical trials are needed, to establish definitively the role of fish oil concentrates in the primary and secondary prevention of IHD.

Consumption of fish oil concentrates appears to be practically harmless, the secondary effects being limited to a decrease of 5 to 10% in the number of platelets, which may even be beneficial, and is only rarely clinically significant,[45] and occasional slight gastrointestinal intolerance, with meteorism and diarrhea.[29] Its use in diabetes is not established, as it can worsen glycemic controle,[46] an effect which may be dose-dependant and which becomes apparent for doses higher than 7g/day.[42]

The main concern today in relation to the consumption of fish is the possibility of its contamination by heavy metals and organic toxins. For example, fish caught in contaminated waters may be a major source of human contamination with dioxins,[47] the most powerful toxin known to man, which is produced by garbage incineration centers and paper and herbicide manufacturers. A diet that includes a higher quantity of vegetables and seeds, such as purslane, linseed, rapeseed, soya and nuts, rich in alpha-linolenic acid, which may be lengthened and desaturated in eicosapentaenoic and docosahexaenoic acid, may provide a sufficient dietetic Omega-3 supplement. [48]

Considering the positive metabolic effects of

introducing fish to the diet,[49] could the therapeutic doses of fish oils, which are already sold in Portugal as dietetic supplements, in low doses, have measurable consequences in a population that consumes significant amounts of fish and vegetable products, like the Portuguese population? This is the question we will seek to answer in a double blind trial in patients with mixed hypertriglyceridemia or dyslipidemias, in which our service is involved.

References

1. Bang H O. Coronary heart disease and Q-3: epidemiologic aspects in: Fish oil and blood vessel wall interactions, Eds. PM Vanhouttc, Ph Douste-Blazy. John Libbey Eurotext, Paris 1991;pp:109-116.

2. Israel DH, Gorlin R Fish oils In: The prevention of atherosclerosis. J Am Coll Cardiol 1992;19:174-185.

3. Burr ML Fish and ischaemic heart disease In: Nutrition and fitness in health and disease, Simopoulos AP (ed), World Rev Nutr Diet, Bael, Karger 1993:72:49-60.

4. Nordoy A Is there a rational use for n-3 fatty acids (fish oils) in clinical medicine? Drugs 1991; 42(3): 331-342.

5. Davidson MH, Bums JH, Subbaiah PV, Conn ME, Drennan KB, Marine oil capsule therapy for the treatment of hyperlipidemia Arch Intern Med 1991:151:1732-1740.

6. Leaf A, Weber PC Cardiovascular effects of n-3 fatty acids. N Engl J Med 1988:318:549-557.

7. Willumen N, Hexeberg S, Skorve J, Lundquist M, Berge RK, Docosahexanoic acid shows no triglyceride-lowering effects but increases the peroxisomal fatty acid oxidation in liver of rats. J Lipid Res 1993; 34:13-22.

8. Otten W, Wirth C. Iaizzo PA, Eichinger HM. A high omega 3 fatty acid diet alters fatty acid composition of heart, liver, kidney, adipose tissue and skeletal muscle in swine. Ann Nutr Metab 1993; 37:134-141.

9. Schmidt EB n-3 polyunsaturated fatty acids and ischaemic heart disease. Curr Op Lipidol 1993; 4: 27-33.

10. Harris WS. Muzio F. Fish oil reduces postprandial triglyceride concentrations without accelerating lipidemulsion removal rates. Am J Clin Nutr 1993; 58: 68-74.

11. Harris WS. Connor WE, Alam N, Illingworth DR. reduction of postprandial triglyceredemia in humans by dietary n-3 fatty acids. J Lipid Res 1988; 29:1451-1460.

12. Von Schacky C, Fisher S, Weber PC. Long term effects of dietary omega-3 fatty acids upon plasma and cellular lipids, platelet function and eicosanoid formation in man. J Clin Invest 1985; 76: 1626-1631.

13. Knapp HR. Reilly IAG, Alessandrini P, Fitzgerald GA. In-vivo indexes on platelet and vascular function during fish oil administration in patients with atherosclerosis. N Engl J Med 1986; 314: 937-942.

14. Fisher S, Weber PC. Prostaglandin 13 is formed in-vivo in man after dietary eicosapentaenoic acid. Nature 1984; 307:165-168.

15. Schmidt EB, Pederson JO, Jersild C, Ditzel J, Grunnet N, Dyerberg J. The effect of n-3 polyunsaturated fatty acids on lipids, haemostasis, neutrophil and monocyte chemotaxis in insulin dependent diabetes mellitus. J Intern Med (suppl) 1989; 225:201-206.

16. Fox PL, DiCorleto PE. Fish oil inhibit endothelial cell production of platelet-derived growth factor-like protein. Science 1988; 241:453-456.

17. Shimokawa H, Vanhoutte PM. Dietary cod-liver oil improves endothelium dependent responses in hypercholesterolaemic and atherosclerotic porcine coronary arteries. Circulation 1989; 78: 1421-1430.

18. Fleishauer FJ, Lee TC, Nellesson U, Fischell TA. Fish oil improves endothelium-dependent coronary vasodilation in cardiac transplant recipients. Circulation 1990; 82 (suppl III): III 468 (abstr.)

19. McVeigh GE, Brennan GM, Johnston GD, McDermott BJ, McGrath IT, Henry WR, Andrews JW, Hayes JR. Dietary fish oil augments nitric oxide production or release in patients with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1993; 36:33-38

20. Mehta J, Lawson D, Saldeen T. Reduction in plasminogen activator inhibitor-1 (PAI-1) with omega-3 polyunsaturated fatty acids (PUFA) intake. Am Heart J 1988; 116: 1201-1206.

21. Hostmark AT, Bjerkedal T, Kierulf P, Flaten H, Ulshagen K. Fish oil and plasma fibrinogen Br Med J 1988: 297:180-181.

22. Radack K, Deck C, Huster G. Dietary supplementation with low-dose fish-oil lowers fibrinogen levels: a randomized, double-blind controlled study. Ann Intern Med 1989; 111: 757-758.

23. Prevention of coronary heart disease: scientific background and new clinical guidelines. Recommendations of the European Atherosclerosis Society prepared by the international task force for the prevention of coronary heart disease. Nutr Metab Cardiovas Dis 1992; 2: 113-156.

24. Lorentz R, Spengler V, Fischer S, Duhn J, Weber PC. Platelet function, thromboxane formation and blood, pressure control during supplementarion of the Western diet with cod liver oil. Circulation 1983; 67:504-511.

25. Engler MB, Engler MM, Ursell PC. Vasorelaxant properties of n-3 polyunsaturated fatty acids in aortas from spontaneously hypertensive and normotensive rats. J Cardiovascular Risk. 1994; 1 (1): 75-80.

26. Enrst E. Effects of n-3 fatty acids on blood rheology. Journal of Internal Medicine 1989; 225(suppl 1): 129-132.

27. BØnaa KH, Bjerve KS, Straume B, Gram IT, Thelle D. Effect of eicosapentanaeoic and docosahexaenoic acids on blood pressure in hypertension: a population-based intervention trial from the Tromso Study. N Engl J Med 1990; 322: 795-801.

28. Moms MC, Sacks F, Rosner B. Does fish oil lower blood pressure? A meta-analysis of controlled trials. Circulation 1993; 88: 523-533.

29. Lofgren RP, Wilt TJ, Nichol KL, Crespin L, Pluhar R, Eckfeld J. The effect of fish oil supplements on blood pressure. Am J Public Health 1993; 83: 267-269.

30. Nozaki S, Kubo M, Takemura K, Matsuzawa Y, Tarui S. Effects of purified eicosapentaenoic acid ethyl ester (EPA) on lipoprotein composition. Circulation 1990; 82 (suppl III): III 477 (abst.)

31. Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, Guidollet J, Touboul P, Delaye J. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 1994; 343; (8911): 1454-1459.

32. Hock CE, Holahan MA, Reibel DK. Effect of dietary fish oil on myocardial phospholipids and myocardial ischemic damage. Am J Physiol 1987; 252: 554-560.

33. Matsukura T, Miyagawa M, Satoh K, Mineo S, Yanagisawa A, Ishikawa K. Effect of dietary fish oil on infarct size in feline myocardial ischemia. Circulation 1990; 82 (suppl.III): III 39 (abstr.).

34. Dehmer GJ, Poma JJ, Van Den Berg EK, Eichhom EJ, Prewilt JB, Campbell WB, Jennings L, Willerson JT, Schmitz JA. Reduction of the rate of early restenosis after coronary angioplasty by a diet supplemented with n-3 fatty acids. N Engl J Med 1988; 319:733-740.

35. Grigg LE, Kay TWH, Valentine PA, Larkings R, Flower DJ, Manolas EG, O'Dcs K, Sinclair AJ, Hopper JL, Hunt D. Determinants of restenosis and lack of effect of dietary supplementation with eicosapentaenoic acid on the incidence of coronary artery restenosis after angioplasty. J Am Coll Cardiol 1989; 13: 665-672.

36. Gapinski JP, VanRuiswyk JV, Heudebert GR, Schectman GS. Preventing restenosis with fish oils following coronary angioplasty. A meta-analysis. Arch Intern Med; 1993; 153: 1595-1601.

37. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetman PM, Elwood PC, deadman NM. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: die and reinfarction trial (DART). Lancet 1989; 2: 757-761

38. Seidelin KN, Myrup B, Fischer-Hansen B. n-3 fatty acids in adipose tissue and coronary artery disease are inversely related. Am J Clin Nutr 1992; 55: 1117-1119.

39. Dolececk TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the multiple risk factor intervention trial. Proc Soc Exp Biol Med, 1992; 200: 177-182.

40. Lorenz R. Q-3 fatty acids and risk of atherosclerosis. In: Fish oil and blood-vessel wall interactions, Eds. PM Vanhoutte, Ph Douste-Blazy. John Libbey Eurotext, Paris 1991; 99: 133-139.

41. Jensen T, Stender S, Goldstein K, Holmer G, Deckert T. Partial normalisation by dietary cod-liver oil of increased microvascular albumin leakage in patients with insulin-dependent diabetes and albuminuria. N Engl J Med 1989; 321: 1572-1577.

42. Berthezene f. Q-3 fatty acid and diabetes mellitus. In: "Fish oil and blood vessel wall interaction, Eds. PM Vanhoutte, Ph Douste-Blazy. John Libbey Eurotext, Paris 1991; pp: 129-131.

43. Kristensen SD, De Caterina R, Schmidt EB, Endres S. Fish oil and ischaemic heart disease. Br Med J 1993; 70: 212-214.

44. Suzukawa M, Abbey M, Nestel PJ. Effect of fish oil fatty acids on LDL size, oxidizability and uptake by macrophages. Atherosclerosis 1994; 109:73.

45. Goodnight SH, Fisher M, Fitzgerald GA, Levine P. Assessment of therapeutic use of dietary fish oil in atherosclerotic vascular disease and thrombosis. Chest 1989; 95 (suppl 2) 19S-25S.

46. Glauber H., Wallace P, Griver K, Bretchel G. Adverse metabolic effect of omega-3 fatty acids in non-insulin-dependent diabetes mellitus. Ann Intern Med 1988; 108: 663-668.

47. Svensson BG, Nilsson A, Hanson M, Rappe C, Akesson B, Skerfving S. Exposure to dioxins and dibenzofurans through the consumption of fish. N Engl J Med 1991; 324: 8-12.

48. McKeigue P. Diets for secondary prevention of coronary heart disease: can linoleic acid substitute for oily fish. Lancet 1994; 343 (8911): 1445.

49. Ozerova IN, Shuvaeca TI, Kalinkina OM, Perova NV, Oganov RC. Long term intake of fish enriched diet in patients with coronary heart disease. Atherosclerosis 1994; 109:72.