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OMEGA-3 (N-3) FATTY ACIDS, CARDIOVASCULAR DISEASE AND STABILITY OF ATHEROSCLEROTIC PLAQUES

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Abstract – Long-chain n-3 polyunsaturated fatty acids are found in oily fish and in fish oils and similar preparations. Substantial evidence from epidemiological and case-control studies indicates that consumption of fish, oily fish and long-chain n-3 fatty acids reduces risk of cardiovascular mortality. Secondary prevention studies using long-chain n-3 fatty acids in patients post-myocardial infarction have shown a reduction in total and cardiovascular mortality with an especially potent effect on sudden death. Long-chain n-3 fatty acids have been shown to beneficially modify a range of cardiovascular risk factors, which may result in primary cardiovascular prevention. However, reduced non-fatal and fatal events and a reduction in sudden death probably involve other mechanisms. Reduced thrombosis following long-chain n-3 fatty acids may play a role. A decrease in arrhythmias is a favoured mechanism of action of long-chain n-3 fatty acids and is supported by cell culture and animal studies. However human trials using implantable cardiac defibrillators have produced inconsistent findings and a recent meta-analysis does not support this mechanism of action. An alternative mechanism of action may be stabilisation of atherosclerotic plaques by long-chain n-3 fatty acids. This is suggested by one published human study which showed that incorporation of long-chain n-3 fatty acids into plaques collected at carotid endarterectomy resulted in fewer macrophages in the plaque and a morphology indicative of increased stability. These findings are supported from observations in an animal model and suggest that the primary effect of long-chain n-3 fatty acids might be on macrophages within the plaque.

Key words: Fatty acid; Fish oil; Cardiovascular disease; Mortality; Inflammation

FISH, N-3 FATTY ACIDS AND LOWER CARDIOVASCULAR DISEASE RISK: MUCH EVIDENCE FROM POPULATION, COHORT AND CASE-CONTROL STUDIES

Some years ago it was documented that Inuit populations in Greenland, Northern Canada and Alaska consuming their traditional diet had much lower cardiovascular mortality than predicted, despite their high fat intake (7,27,54,80). Typically the rate was < 10% of that predicted (54). The protective component was suggested to be the long-chain n-3 polyunsaturated fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) consumed in very high amounts as a result of the regular intake of seal meat and whale blubber (5). Intake of these fatty acids was estimated to average as much as 5 to 15 g/day amongst such populations (5). The Japanese also exhibit a low cardiovascular mortality (109) and the traditional Japanese diet is rich in seafood including oily fish, which contain significant amounts of EPA and DHA. Substantial evidence from epidemiological and case-control studies has now accumulated indicating that consumption of fish or of long-chain n-3 fatty acids reduces the risk of cardiovascular mortality in Western populations (1,2,23,26,28,30,33, 39,42,46,47,49,52,55,56,61,75,81,82,83,91,92,97, 112), although not all studies agree (4). Data from China also provides evidence for a protective

Abbreviations: DART, Diet and reinfarction trial; **DHA,** docosahexaenoic acid; **EPA,** eicosapentaenoic acid; **MI,** myocardial infarction; **MMP,** matrix metalloproteinase; **PG,** prostaglandin; **RCT,** randomised controlled trial; **TX,** thromboxane.

effect of fish and n-3 fatty acid consumption towards cardiovascular disease (111). These studies have been summarised and discussed in detail elsewhere (14,53,64,100,103) and studies of fish have been subjected to two meta-analyses, one related to coronary heart disease mortality (44) and the other to stroke (43). Both of these meta-analyses conclude that those with higher fish consumption have lower risk of stroke incidence and of coronary heart disease mortality than those with lower fish consumption.

INTERVENTION STUDIES WITH N-3 FATTY ACIDS

The Diet and Reinfarction Trial (DART) (11) was the first randomised controlled trial (RCT) to investigate the effects of dietary intervention with long-chain n-3 fatty acids on secondary prevention of myocardial infarction (MI). The study showed a 29% reduction in all-cause mortality (mortality was mainly due is cardiovascular events) compared to controls, in men advised to eat approximately 300 g of oily fish (this is 2 or 3 portions) per week, or to take fish oil capsules providing an equivalent intake of long-chain n-3 fatty acids. The GISSI-Prevenzione study (35) enrolled 11,324 post-MI patients and studied the effects of n-3 fatty acids (885 mg EPA+DHA/day) and/or vitamin E with up to 3.5 years follow-up. N-3 fatty acid supplementation significantly lowered the risk of the combined primary outcome of death and non-fatal cardiovascular events. This benefit was due almost entirely to decreased mortality (20% reduction in total deaths, 30% in cardiovascular deaths, 45% in sudden deaths). The reduction in risk of sudden death at 3.5 years in those patients consuming long-chain n-3 fatty acids was already apparent at 4 months and the reductions in risk of cardiovascular mortality and coronary heart disease mortality were apparent within 6 to 8 months of initiating n-3 fatty acid treatment (65). More recently, the largest RCT with n-3 fatty acids to date, the JELIS study (110), found that after a mean follow up of 4.6 years there was a 19% relative reduction in the risk of major coronary events in hypercholesterolaemic subjects given 1800 mg/day EPA as a supplement plus 10 mg/day pravastatin or 5 mg/day simvastatin. However, unlike the previous studies, the reduction in events was related to a reduction in non-fatal coronary events. The population was Japanese, where dietary intake of fish is commonly high, and the investigators postulated differing mechanisms of protective effects of n-3 fatty acids at low and high background intakes. Most recently, the GISSI Heart Failure (GISSI-HF) study (34) investigated whether n-3 fatty acids could improve mortality in patients with symptomatic heart failure of any cause. Seven thousand patients with New York Heart Association heart failure class II-IV were randomised to receive 850 mg per day of long-chain n-3 fatty acids or placebo, and were followed up for a median of 3.9 years. All cause mortality was decreased by 9% in the n-3 fatty acid group, and cardiovascular admissions to hospital were reduced by 8% in that group. This demonstrated that the addition of a long-chain n-3 fatty acid supplement in well treated heart failure patients provides a significant additional clinical benefit to conventional treatment.

A number of systematic reviews and meta-analyses have been conducted to bring together data from studies with n-3 fatty acids reporting mortality as an outcome (9,45,62,77,95,103). Of these, five (9,62,77,95,103) supported a role for increased long-chain n-3 fatty acid intake in reducing cardiovascular mortality; one (45) did not find a clear role for increased n-3 fatty acid intake. Bucher et al. (9) combined data from 11 RCTs studying the effects of increased dietary or supplemental intake of long-chain n-3 fatty acids on coronary heart disease outcomes and with at least 6 months follow up. They concluded that dietary and non-dietary (i.e. from supplements) intake of long-chain n-3 fatty acids reduces overall mortality, mortality due to MI and sudden death in patients with coronary heart disease (9). Studer et al. (95) subjected RCTs involving lipid-lowering interventions (statins, fibrates, resins, niacin, n-3 fatty acids, dietary modification) and reporting mortality outcomes to meta-analysis; outcome measures were mortality from all, cardiac, and non-cardiovascular causes. Using data from 9 studies, they concluded that intake of long-chain n-3 fatty acids reduces overall mortality and cardiac mortality, and that statins and long-chain n-3 fatty acids are the most favourable lipid-lowering interventions with reduced risks of overall and cardiac mortality (95). A systematic review of the literature (RCTs and cohort studies) by Wang et al. (103) on the effects of n-3 fatty acids (consumed as fish or fish oils rich in EPA and DHA or as α-linolenic acid) on cardiovascular disease outcomes and adverse events considered primary and secondary prevention using data from studies > 1 year that reported fish or fatty acid intakes and cardiovascular outcomes. The conclusion was that

the evidence suggests that increased consumption of n-3 fatty acids from fish or fish-oil supplements (but not α-linolenic acid) reduces the rates of all-cause mortality, cardiac and sudden death, and possibly stroke; but that the evidence for the benefits of long-chain n-3 fatty acids is stronger in secondary than in primary prevention (103). Mozaffarian et al. (77) considered both the benefits and risks of fish consumption looking not only at increased n-3 fatty acid consumption from fish or fish oil but also the effects of the associated intake of methylmercury, dioxins and polychlorinated biphenyls in the fish. This meta-analysis concluded that modest consumption of fish or fish oil reduces the risk of coronary heart disease death and sudden death. It also concluded that the benefits of fish or long-chain n-3 fatty acid consumption are likely to exceed the potential risks for adults and, with the exception of a few fish species, also for women of child bearing potential (77). Most recently Leon et al. (62) used data from 12 RCTs studying the effects of increased supplemental intake of n-3 fatty acid on coronary heart disease outcomes. They concluded that long-chain n-3 fatty acids reduce mortality from cardiac causes, and cardiac mortality and sudden death in patients with coronary heart disease (62). There was however no significant reduction in all cause mortality or sudden death when all studies (i.e. those in subjects with and without coronary heart disease) were combined (62).

The picture that emerges from these five systematic reviews and meta-analyses is of clinical benefit from long-chain n-3 fatty acids, especially in at risk individuals. However a meta-analysis by Hooper et al. (45) was more equivocal. RCTs of n-3 fatty acid intake (either α-linolenic acid or EPA plus DHA) for ≥ 6 months in adults (with or without risk factors for cardiovascular disease) with data on a relevant outcome and cohort studies that estimated n-3 fatty acid intake and related this to clinical outcome during at least 6 months were included. The authors concluded that the results of trials were inconsistent and that long-chain or shorter chain n-3 fatty acids do not have a clear effect on total mortality or combined cardiovascular events (45). However, the negative outcome of this analysis was crucially dependent on the inclusion of one trial (DART 2 (10)), which has been excluded from some other meta-analyses because of methodological concerns, and may have been confounded by combining studies of α-linolenic acid and of long-chain n-3 fatty acids. Indeed, Hooper et al. (45) found that when they pooled studies in which participants were given only long-chain n-3 fatty acids and excluded DART 2 they found a significant reduction of mortality that was consistent with the findings of Bucher et al. (9). Importantly, of the six systematic reviews and meta-analyses described here only one (62) includes the results from JELIS (110) (because JELIS was published after the other meta-analyses and reviews) and none include the results from the recent GISSI-HF study (34), and as both of these large studies gave positive outcomes for long-chain n-3 fatty acids with regard to mortality it is likely that an updated meta-analysis including them would be positive.

N-3 FATTY ACIDS AND LOWER CARDIOVASCULAR DISEASE RISK: POSSIBLE MECHANISMS INVOLVED

Long-chain n-3 fatty acid consumption may protect against both the pathological processes leading to the cardiovascular disease (i.e. atherosclerosis) and the processes that ultimately cause death (e.g. MI, stroke). Long-chain n-3 fatty acids favourably affect a number of factors involved in the development of atherosclerosis, indicating that they most likely slow the progression of the disease. For example, elevated fasting and post-prandial plasma triacylglycerol concentrations are now recognised to increase the risk of cardiovascular disease, and long-chain n-3 fatty acids lower both (40,87,106). Typically a 25 to 30% lowering of fasting triglyceride concentrations could be expected from an intake of more than 2 g EPA plus DHA per day. Long-chain n-3 fatty acids also:

- decrease chemoattractant (6,60,93), growth factor (6,102) and adhesion molecule (48,70) production and so could down-regulate processes leading to leukocyte and smooth muscle migration into the vessel wall intima.
- are anti-inflammatory (13,15) and so could decrease inflammatory processes within the vessel wall, which are now recognised to be a major contributory factor in the atherosclerosis (36,87,88).
- have a small, but significant, hypotensive effect in both normotensive and hypertensive individuals, as confirmed in meta-analyses (3,32,73).
- cause endothelial relaxation and promote arterial compliance (19,37,69,96), which might be related to altered nitric oxide production (41).

Thus, long-chain n-3 fatty acids exert effects at many steps involved in the process of atherosclerosis and so they might be expected to decrease or slow this disease. Indeed, including long-chain n-3 fatty acids in the diet has been demonstrated to decrease atherosclerosis in a variety of animal models (12,24,57,74,86,105).

Despite the potential for protection against atherosclerosis, much interest has been focussed on the potent protective effect of long-chain n-3 fatty acids towards fatal MI (11,23,35,92), and particularly towards sudden death (1,2,35,46), suggesting that they influence acute events. Several studies also report protection against non-fatal MI (46,61,83,92), which is consistent with a lowered risk of acute events be they non-fatal or fatal. Two mechanisms are considered to contribute to the strong protective effect of long-chain n-3 fatty acids towards acute cardiovascular events, especially those that are fatal. The first is an anti-thrombotic effect of long-chain n-3 fatty acids. This is mediated largely through changes in eicosanoid generation from the n-6 fatty acid arachidonic acid. Arachidonic acid is released from cell membrane phospholipids by the increased activity of phospholipase A_2 following stimulation of platelets and endothelial cells. Metabolism of free arachidonic acid by cyclooxygenase-2 gives rise to thromboxane A_2 (TXA_2), a potent promoter of platelet aggregation, and to prostacyclin I_2 (PGI_2), a potent inhibitor of platelet aggregation. One of the characteristic features of increased availability of long-chain n-3 fatty acids, especially EPA, is a reduction in the content of arachidonic acid in membrane phospholipids in platelets (38,90,101) and presumably also endothelial cells, thus decreasing the amount of substrate available for eicosanoid synthesis. Therefore, n-3 fatty acids are associated with a decrease in production of TXA_2 and PGI_2. Furthermore, EPA, which is readily incorporated into cell membrane phospholipids, is released by the action of phospholipase A_2 and also acts as a substrate for cyclooygenase. The products produced (e.g. TXA_3 and PGI_3) have a different structure from those produced from arachidonic acid and this can affect their biological potency. TXA_3 has a weaker pro-aggregatory effect than does TXA_2. In contrast PGI_2 and PGI_3 have similar anti-aggregatory potencies. Therefore, the effect of long chain n-3 fatty acids is to promote a less thrombotic environment (101).

The second mechanism that might be important is an anti-arrhythmic action of long-chain n-3 fatty acids; ventricular arrhythmias underlie 80 to 90% of sudden cardiac deaths. Studies in rats, dogs and marmosets suggest that long-chain n-3 fatty acids from fish oil have anti-arrhythmic effects (67,68,78). These effects can be mimicked in cultured cardiomyocytes (51,59). The presence of n-3 fatty acids in cardiomyocyte membrane phospholipids decreases electrical excitability and modulates the activity of ion (e.g. sodium, potassium, calcium) channels (107,108), effects that are claimed to promote electrical stability in the cell and prevent arrhythmias. In addition to anti-arrhythmic actions due to their effects on ion channels, long-chain n-3 fatty acids might influence resting heart rate (a high resting heart rate increases risk of sudden cardiac death) and heart rate variability (low heart rate variability is associated with sudden death and with increased mortality post-MI) and this might have an anti-arrhythmic effect via the autonomic nervous system. A number of intervention trials with long-chain n-3 fatty acids investigating resting heart rate have been performed. Thirty of these have been subject to meta-analysis which found that EPA+DHA decreased resting heart rate if the baseline rate was > 69/minute (76). Christensen et al. reported a positive correlation between the n-3 fatty acid content of platelets and heart rate variability in patients with type-1 diabetes mellitus (21). These workers also reported increased heart rate variability in MI survivors given 5200 mg EPA + DHA/day for 12 weeks (20). Although this dose is substantially higher than those given in the secondary prevention studies, these studies are suggestive of two potential ways by which long-chain n-3 fatty acids could affect cardiac arrhythmias: via modulation of ion channels and by modulation of heart rate and its variability. Over the last few years several studies directly assessing the effect of long-chain n-3 fatty acids on atrial fibrillation (16) and ventricular arrhythmias (8,58,85) have been performed. An intervention with 1700 mg EPA+DHA per day for at least 5 days before elective coronary bypass grafting and until hospital discharge significantly decreased (by 54%) development of atrial fibrillation in the post-operative period compared with conventional treatment (16). Three studies used implantable cardiac defibrillators (ICD) to monitor occurrence of arrhythmias in response to treatment with long-chain n-3 fatty acids (8,58,85). One of these was positive showing a 42% lower occurrence over 12 months in subjects receiving 2400 mg EPA+DHA/day (mainly as

DHA) (58). The other two studies were negative (8,85). A recent meta-analysis using data from these three studies found no significant effect of long-chain n-3 fatty acids on ICD intervention (62).

LONG-CHAIN N-3 FATTY ACIDS AND STABILITY OF ATHEROSCLEROTIC PLAQUES

Recently a third mechanism has been suggested to play a role in the protective effects of long-chain n-3 fatty acids towards acute cardiovascular events: the well-documented anti-inflammatory effects of long-chain n-3 fatty acids may be important. Inflammation is recognised to play a key role in the progression of atherosclerosis (88,89), and so decreased inflammatory activity as a result of dietary exposure to n-3 fatty acids could alter the progression of the disease. However, the rupture of an atherosclerotic plaque, which is the acute event that exposes the plaque contents to the highly pro-thrombotic environment of the vessel lumen, is, essentially, an inflammatory event (36,84). The characteristics of an atherosclerotic plaque that make it vulnerable to rupture include a thin fibrous cap and increased numbers of inflammatory cells such as macrophages (29,84,94). Long-chain n-3 fatty acids might act to stabilise atherosclerotic plaques by decreasing infiltration of inflammatory and immune cells (e.g. monocyte/macrophages and lymphocytes) into the plaques and/or by decreasing the activity of those cells once in the plaque. An intervention study conducted in patients awaiting carotid endarterectomy showed that long-chain n-3 fatty acids are incorporated from dietary fish oil supplements (providing 1400 mg EPA+DHA/day) into advanced atherosclerotic plaques and that this incorporation is associated with structural changes consistent with increased plaque stability (98) (see Table 1). The morphology of carotid plaque sections was characterised according to the American Heart Association classification (94). Plaques from patients treated with fish oil were more likely to be Type IV (fibrous cap atheromas: well-formed necrotic core with an overlaying thick fibrous cap) than those from the placebo group (odds ratio 1.19; Table 1). Conversely, plaques from patients treated with fish oil were less likely to be Type V (thin fibrous capo atheromas – thin fibrous cap infiltrated by macrophages and lymphocytes) than those from the placebo group (odds ratio 0.52). Thus, there were more plaques with a well formed fibrous cap, rather than a thin inflamed cap, in the fish oil group. Infiltration by macrophages was investigated using immunohistochemistry. It was found that plaques from patients given fish oil were more likely to be less heavily infiltrated with macrophages than those in the placebo group (Table 1). A follow-up study, OCEAN (ClinicalTrials.gov identifier NCT00294216), using 1775 mg EPA+DHA/day as ethyl esters has published some findings in abstract form only (17,18). The study confirms higher EPA content of carotid plaque phospholipids in patients receiving long-chain n-3 fatty acids and that a higher EPA content of the plaque is associated with lower plaque inflammation and instability. Matrix metalloproteinases (MMPs) are intimately involved in cap thinning, and so higher expression has been associated with greater plaque vulnerability to rupture (31,50,71,72,79, 99). OCEAN identified that mRNA levels for some important MMPs (MMP-7, -9, and -12) were lower in plaques from patients who had received n-3 fatty acids (17,18). These findings have been confirmed in a recent animal study (66). ApoE deficient or LDL-receptor deficient mice were fed a Western-type diet or the same diet plus EPA for 12 weeks. EPA reduced aortic lipid deposition, consistent with earlier animal studies (74,86). EPA resulted in increased plaque collagen and decreased macrophage numbers in the plaque. The authors concluded that EPA had stabilised the atherosclerotic lesions. In separate in vitro studies, EPA attenuated cytokine-induced expression of adhesion molecules by endothelial cells, confirming earlier studies (22,25,104), and attenuated cytokine-induced expression of MMP-2 and MMP-9 by a macrophage cell line (66). There was a tendency for dietary EPA to reduce aorta MMP-2 and MMP-9 in apoE deficient mice (66).

Since it is the vulnerability of the plaque to rupture rather than the degree of atherosclerosis that is the primary determinant of thrombosis-mediated acute cardiovascular events (84), it is likely that the findings of Thies et al. (98) and OCEAN (17,18), replicated in an animal model (66), are clinically relevant. This might explain the significant protective effects of long-chain n-3 fatty acids towards both fatal and non-fatal cardiovascular events, which are so far not fully explained. These observations suggest that the primary effect of long-chain n-3 fatty acids might be on macrophages. Certainly macrophage

activity is a key component of plaque instability (63). Macrophage numbers within the plaque might be decreased due to fewer monocyte/macrophages entering the plaque as a result of decreased adhesion molecule expression on endothelial cells and/or the monocyte/macrophage itself, which would act to limit movement of monocyte/macrophages into the plaque. Future studies should focus on a greater understanding of the anti-inflammatory effects of long-chain n-3 fatty acids in atherosclerotic plaques, especially examining how macrophage numbers and activities are influenced.

Table 1. Major findings of Thies et al. (98).

	EPA in carotid plaque phospholipids (% of total fatty acids)*	Plaque morphology (% of plaques)		Macrophage staining (% of plaques)	
		Type IV	Type V	Moderate	Heavy
Placebo group	0.6 ± 0.4	59.6	29.8	13.2	84.2
Fish oil group	1.1 ± 0.6	71.7	15.1	38.1	61.9
Significance of difference between groups (P)	< 0.0001	0.041	0.027	0.011	0.026

*mean ± SD

Other articles in this theme issue include references (113-124).

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