

Review Article

Beneficial Effects of Omega-3 Fatty Acids: The Current Evidence

IRENE GAZI, EVANGELOS N. LIBEROPOULOS, VASILIOS G. SAOUGOS, MOSES ELISAF

Department of Internal Medicine, University of Ioannina, Ioannina, Greece.

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High triglyceride (TG) levels have been recognised as an independent risk factor for coronary heart disease (CHD), while severe hypertriglyceridaemia (fasting TGs ≥ 500 mg/dL) significantly increases the risk of acute pancreatitis, a potentially deadly complication.¹⁻³ Moreover, a key feature of the dyslipidaemia associated with the metabolic syndrome as well as diabetes is elevated TG levels.⁴⁻⁶ Fish oil can have a therapeutic role in the treatment of marked hypertriglyceridaemia.

Omega-3 fatty acids (ω -3 FAs), found primarily in fatty fish with high oil content, consist of both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). They can also be found in some leafy vegetables, nuts, and oils as α -linolenic acid. There is increasing evidence that ω -3 FAs exhibit anti-inflammatory, anti-thrombotic, antiarrhythmic and anti-atherogenic effects.^{7,8} Moreover, fish oil supplementation has consistently been shown to display a significant TG-lowering effect.⁹ Effective doses of ω -3 FAs range from 3-5 g/day, which can only be obtained by supplementation. In cases of severe hypertriglyceridaemia, where diet and fibrate therapy are insufficient to achieve normal fasting TG levels, the administration of ω -3 FAs may be useful. In a comprehensive review, Harris et al reported that the administration of 4 g/day of ω -3 FAs decreased TG levels by 25-30%, while producing

an increase in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels of 5-10% and 1-3%, respectively.¹⁰ Additionally, a dose-response relationship was reported to exist between ω -3 FA intake and TG lowering.¹⁰

A small clinical trial including 42 patients with severe hypertriglyceridaemia (TG levels: 500-2000 mg/dL) showed that the administration of an agent composed of highly concentrated ω -3 FA ethyl esters at a daily dosage of 4 g produced a decrease in TG by 45%, total cholesterol (TC) by 15%, very low-density lipoprotein cholesterol (VLDL-C) by 32%, while increasing HDL-C by 13% and LDL-C by 31%.¹¹ The results of another small trial (including 30 patients with TG levels between 354 and 2478 mg/dL) showed that the administration of 4 g/day of ω -3 FAs had a similar effect on lipid and lipoprotein concentration to that of the administration of gemfibrozil 1200 mg/day.¹² Specifically, the administration of ω -3 FAs resulted in a decrease in TC levels by $9 \pm 15\%$, TG levels by $37 \pm 25\%$, VLDL-C by $33 \pm 22\%$, and increased HDL-C by $11 \pm 18\%$ and LDL-C by $30 \pm 31\%$.¹² Moreover, both ω -3 FAs and gemfibrozil led to a more buoyant LDL subfraction profile (i.e. cholesterol concentration decreased in small dense LDL 4 and 5 subfractions and increased in large buoyant LDL 1, 2 and 3 subfractions).¹² Combining 21 trials evaluating lipid outcomes, fish oil

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Address:
Moses Elisaf

Department of
Internal Medicine
Medical School,
University of Ioannina
45110 Ioannina,
Greece
e-mail:
egepi@cc.uoi.gr

consumption resulted in a summary net change in TGs of -27 mg/dL, in HDL-C of +1.6 mg/dL, and in LDL-C of +6 mg/dL.¹³ There was no effect of fish oil on TC.¹³ Across studies, higher fish oil dose and higher baseline levels were associated with greater reductions in serum TGs.¹³

Omega-3 FAs – general

Omega-3 FAs are a family of naturally occurring polyunsaturated fatty acids (PUFAs). Humans do not possess the necessary metabolic pathways to synthesise the precursor FA (α -linolenic acid), which is essential for the production of the longer bioactive ω -3 FAs.¹⁴ Therefore, these long-chain PUFAs must be obtained either from plant sources or by direct intake of EPA and DHA from marine or industrial products.¹⁴ EPA and DHA are mostly found in seafood, but fish do not actually produce these fatty acids.¹⁵ In fact, these compounds are produced by single-cell marine organisms that are consumed by fish.¹⁵ Fish can be classified into lean, which store fat as TGs in their liver, and fatty (oily), which store fat as TGs in their flesh.¹⁶ The oil that is obtained from these fish is called 'fish oil' and is rich in long-chain fatty acids.¹⁶

There are several experimental and epidemiological data indicating that the consumption of ω -3 FAs decreases the risk of various diseases (see below). The benefit of the high ω -3 FA intake is attributed to their capacity to modulate cellular metabolic functions and gene expression.¹⁴ These actions include the alteration of inflammatory processes in which eicosanoid participate, alterations of cellular membrane structure and functions induced by the incorporation of ω -3 FAs into membrane phospholipids, modulation of various signalling pathways involved in normal and pathological cell functions, as well as their direct effect on gene expression.¹⁴

Omega-3 FAs and risk of cardiovascular disease

It has been reported that 50 to 60% of deaths from cardiovascular disease (CVD) result from sudden cardiac death or sustained ventricular arrhythmias, defined as a death that occurs within the first hour of an acute myocardial infarction (MI).¹⁷ There are numerous observational studies indicating that a high intake of ω -3 FAs is associated with a reduced risk for CVD mortality, MI and sudden death. Although most data for cardioprotective effects come from studies of marine sources, vegetable sources of ω -3 FAs (α -linolenic

acid) may have similar effects through *in vivo* conversion to EPA and DHA.¹⁸

It is known that Inuit populations in northern Canada and Alaska exhibit much lower CVD mortality than predicted, despite the fact that their typical diet includes high fat intake.^{19,20} Japanese people who consume their traditional diet, which is rich in seafood, also have a low prevalence of CVD.²¹ It has been suggested that the protective component in both populations is the high intake of long-chain ω -3 FAs (as much as 5-15 g of FAs/day).²²

Substantial evidence from both epidemiological and observational studies has accumulated, indicating the favourable effects of ω -3 FAs on the reduction of CVD mortality rate.^{16,23,24} However, other studies have failed to report a beneficial association between fish consumption and CVD mortality.^{16,23} This discrepancy might be explained by differences in sudden cardiac death definitions, variability in the end points studied, estimation of fish intake, populations under study, as well as the possible adverse effects of methylmercury (a contaminant found in several fish), which may mask the favourable effects of ω -3 FAs.²⁵⁻²⁹

On the other hand, there are limited data concerning the effect of ω -3 FAs on cerebrovascular disease. Some, but not all, epidemiological studies have shown an inverse relationship between fish intake and the incidence of stroke.³⁰⁻³⁴ It should be noted that the prospective GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico) Prevention Study (see below) did not show any significant effect on the incidence of stroke in subjects receiving 850 mg of supplemental ω -3 FAs daily.³⁵ These discrepancies could be attributed to the different types of stroke; for example, the Zutphen Study showed an inverse relationship between small intakes of fish (one portion per week) and ischaemic stroke, but the risk of haemorrhagic stroke may be increased by high intakes of fish.^{30,36}

Randomised clinical trials have added to the growing evidence of the favourable effect of ω -3 FAs on CVD, especially in secondary prevention. The Diet And Reinfarction Trial (DART) was the first to examine the effects of fish intake on the incidence of a myocardial reinfarction.³⁷ This study reported a 29% reduction ($p < 0.05$) in all-cause mortality over a 2-year period in male MI survivors who received a recommendation to increase their oily fish intake to 200-400 g per week (corresponding to an additional intake of 500-800 mg of ω -3 FAs daily).³⁷ However, no difference between the two groups was found concerning

total CVD events, probably because of the higher incidence of nonfatal MIs in subjects advised to increase their fish intake. The greatest benefit was found in fatal MIs (reduction by 33%, $p < 0.01$).³⁷

Another secondary prevention trial was the Lyon Diet Heart Study, which compared the impact of a Mediterranean diet (rich in α -linolenic acid) with a standard post-infarction diet.³⁸ The study was terminated early after 27 months because of the dramatic benefit observed in the intervention group (combined end point risk ratio 0.27, $p = 0.001$).³⁸ However, this reduction in the combined end point of the study cannot be attributed solely to the effect of ω -3 FAs, since the intervention group followed an overall healthier diet.

The first secondary prevention prospective study that examined the effect of ω -3 FA supplements on clinical events was the Indian Experiment of Infarct Survival-4 study, published in 1997.³⁹ Patients admitted to the hospital with a suspected acute MI were randomised to placebo, mustard oil (providing 2.9 g α -linolenic acid daily) or fish oil capsules (providing 1.8 g of EPA and DHA daily). Total cardiac events as well as nonfatal MIs after 1 year were significantly reduced in both the fish oil and the mustard oil group ($p < 0.01$ and $p < 0.05$, respectively) compared with the placebo group.³⁹

The largest prospective, randomised controlled trial to test the efficacy of ω -3 FAs on secondary prevention of CVD to date is the GISSI-Prevention Study.³⁵ This study involved about 11,000 CVD patients, who were randomised to receive either 850 mg of EPA + DHA daily, 300 mg of vitamin E, both, or neither. After 3.5 years, ω -3 FA supplementation reduced the primary end-point (the cumulative rate of all-cause death, non-fatal MI and non-fatal stroke and the cumulative rate of CVD death, non-fatal MI and non-fatal stroke) by 15% ($p < 0.02$), all-cause mortality by 20% ($p = 0.01$) and induced a marked reduction of 45% in sudden cardiac death ($p < 0.001$). On the other hand, the administration of vitamin E provided no additional benefit.³⁵ Possible disadvantages of this trial may be the lack of a placebo arm and the high drop out rates (>25%).

In contrast, a recent study by Nilsen et al reported no effect of supplementation with 3.5 g of EPA + DHA daily versus corn oil on cardiac events in post MI patients after 1.5 years of intervention.⁴⁰ This finding was attributed to the pre-existing high fish intake in Norway. Moreover, another study including 3114 men with angina showed that ω -3 FAs or oily fish or fish oils may actually increase the risk of death.⁴¹ Specifically, the risk of cardiac death was higher among sub-

jects advised to take oily fish than among those not so advised; the adjusted hazard ratio was 1.26 (95% confidence interval, CI: 1.00-1.58; $p = 0.047$), and was even greater for sudden cardiac death (1.54; 95% CI: 1.06-2.23; $p = 0.025$). The excess risk was largely located among the subgroup given fish oil capsules. This study had a long follow-up (3-9 years), raising the possibility that the cumulative effects of methylmercury found in fish (believed to cause cancer and possibly MI) counterbalanced the benefits of ω -3 FAs.⁴¹ Also, this study looked exclusively at men with angina.

The effect of ω -3 FAs on the angiographic progression was examined in two studies.^{42,43} The first, which tested the effect of the administration of 6 g of ω -3 FAs/day versus olive oil in 59 patients, showed no benefit.⁴² The second was larger (223 patients undergoing coronary angiography), placebo controlled and used conventional ω -3 FA intake (3 g/day for 3 months followed by 1.5 g/day for 21 months).⁴³ The ω -3 FA group exhibited less progression and more regression ($p = 0.04$) compared with the placebo group.

A meta-analysis of 11 randomised controlled trials examining the effect of dietary or supplemental ω -3 FAs in patients with CHD was published in 2002.⁴⁴ According to this meta-analysis, the intake of ω -3 FAs, whether dietary or supplemental, was associated with a 27% reduction in fatal MI ($p < 0.001$), a 31% reduction in sudden death ($p < 0.01$) and a 19% reduction in overall mortality ($p < 0.001$).⁴⁴ However, the groups did not differ in terms of non-fatal MI incidence.

A recent meta-analysis of randomised controlled trials examined the effects of various hypolipidaemic agents and diets on mortality rate.⁴⁵ According to the results of this meta-analysis, the risk ratio for ω -3 FAs was 0.77 (95% CI: 0.63-0.94) for overall mortality and 0.68 (95% CI: 0.52-0.90) for cardiac mortality.⁴⁵ However, a new systematic review has found that long- and short-chain ω -3 FAs may have no effect on mortality, CVD events, or cancer.⁴⁶ This meta-analysis included a total of 48 randomised controlled studies and 41 cohort studies of ω -3 FA intake, in the form of dietary supplements in most cases. Included studies had a follow-up of ≥ 6 months and provided outcome data on total mortality, CVD events, or cancer. Overall, total mortality was non-significantly reduced by 13% (relative risk 0.87, 95% CI: 0.73-1.03) and CVD events by 5% (relative risk 0.95, 95% CI: 0.82-1.12).⁴⁶ The conflicting results derived from this meta-analysis may be explained by the inclusion of a large study showing no benefit of ω -3 FA intake⁴¹ (see above). This study was not included in previous meta-analyses. Nev-

ertheless, the evidence for a reduction in CVD events and mortality with ω -3 FAs may be less conclusive than we earlier believed.⁴⁷

The results of the JELIS (Japan EPA Lipid Intervention Study) were recently announced during the American Heart Association Scientific Sessions.⁴⁸ According to JELIS, the administration of 1.8 g/day of highly purified EPA capsules in patients taking low doses of various statins resulted in a significant decrease in the incidence of major coronary events (MCE), largely driven by a reduction in unstable angina (hazard ratio for MCEs and unstable angina of 0.81 and 0.76, respectively).⁴⁸ However, the addition of EPA to low-dose statin therapy was not associated with an alteration in the incidence of sudden cardiac death (hazard ratio for sudden cardiac death: 1.06).

Omega-3 FAs – possible mechanisms of action

Omega-3 FAs favourably modulate various factors participating in the development of atherosclerosis, indicating that they probably slow the progression of the disease.¹⁶

TGs

As already mentioned the administration of about 4 g/day of ω -3 FAs can lead to a 25-30% decrease in fasting TG levels.^{10,11} According to our experience, the addition of highly concentrated ω -3 FA ethyl esters (2-4 g/day) to existing fibrate treatment leads to a further improvement in serum TGs in cases of hypertriglyceridaemia refractory to fibrate monotherapy (unpublished data). Moreover, postprandial triglyceridaemia is especially sensitive to chronic ω -3 FA intake, even in small doses (<2 g/day).^{49,50} The mechanisms by which ω -3 FAs act on TG metabolism mainly involve the suppression of hepatic VLDL synthesis and secretion.⁵¹⁻⁵³ Furthermore, the conversions of VLDL to intermediate-density lipoprotein (IDL), VLDL to LDL, and IDL to LDL are significantly increased;⁵² this may partly explain the increase in LDL-C levels observed in ω -3 FA-treated patients.⁵¹ On the other hand, ω -3 FAs do not significantly alter the fractional catabolic rates of apolipoprotein (apo) B in VLDL, IDL, or LDL or alter the catabolism of the chylomicron remnants.⁵² Therefore, ω -3 FAs effectively lower the plasma concentration of TGs, chiefly by decreasing VLDL production but not by altering the catabolism of apo B-containing lipoprotein or chylomicron remnants.⁵²

Arrhythmias

Much interest has been focused on the potent effect of ω -3 FAs on fatal MI and particularly on sudden cardiac death, suggesting a possible influence on the incidence of these acute events.^{26,35,37,54-57} Proposed mechanisms for this finding include a direct effect on the myocardium itself, rather than their effects on blood lipids.²³ Experimental data on animal models indicate that ω -3 FAs derived from fish exhibit an antiarrhythmic effect, and this effect has been confirmed in cultured rat myocytes.⁵⁸⁻⁶⁰ The incorporation of ω -3 FAs in myocytes leads to the modification of eicosanoid pathways, alterations of the membrane fat composition, as well as direct effects on myocardium.⁵⁹ Another possible effect of ω -3 FAs on cardiac arrhythmias is that they may influence heart rate variability (low heart rate variability is considered to increase post-MI mortality).⁶¹ A recent study examined the effects of EPA and DHA (2.6 g/day) versus olive oil in 402 patients with implanted cardioverter/ defibrillators.⁶² This study showed a trend toward a prolonged time to the primary end-point (ventricular tachycardia or fibrillation or death from any cause) in the group that received EPA and DHA compared with the olive oil group (risk reduction of 28%, $p=0.057$). Furthermore, when probable events were added to the analysis, the risk reduction became significant (risk reduction of 31%, $p=0.033$).⁶²

Thrombosis and haemostasis

Another possible anti-atherogenic property of ω -3 FAs includes their anti-thrombotic effect. This is primarily mediated by a competitive reduction in the conversion of arachidonic acid to thromboxane A₂ (TXA₂), a potent promoter of platelet aggregation and prostacyclin I₂ (PGI₂), a potent inhibitor of platelet aggregation.⁶³ High doses of ω -3 FAs act as a substrate for cyclo-oxygenase 2 (COX-2). This reaction leads to the production of TXA₃, a less potent promoter of platelet aggregation, and to PGI₃, which has similar effects to PGI₂.⁶³ Thus, it seems that ω -3 FAs promote a less thrombotic environment.^{16,63}

Inflammation

Another mechanism by which ω -3 FAs may reduce the incidence of acute cardiovascular events is their well-established anti-inflammatory effects.^{7,8,14,16} Inflammation plays a key role in the progression of atherosclerosis.⁶⁴ It was recently reported by Dwyer et al that high intake of ω -3 FAs inhibits leukotriene-mediated in-

flammatory pathways, in contrast to a high intake of ω -6 FAs, which promotes these pathways.⁶⁵ Moreover, EPA and DHA reduce the expression of ICAM-1 (intercellular cell adhesion molecule 1) and VCAM-1 (vascular cell adhesion molecule 1) on endothelial cells and monocytes.⁶⁶⁻⁶⁸ Furthermore, there is evidence that dietary fish oil decreases the generation of chemoattractants, such as leukotriene B₄, PAF (platelet-activating factor), MCP-1 (monocyte chemoattractant protein-1), PDGF (platelet-derived growth factor), as well as interleukins and TNF α (tumour necrosis factor- α).⁶⁹⁻⁷³ Thies et al showed that the administration of fish oil supplements (providing 1.4 g of EPA and DHA daily) increased plaque stability through structural changes.⁷⁴ Specifically, the incorporation of these fish oils into the arterial wall lipids led to a decreased number of arterial wall macrophages and thin fibrous caps, which are well established markers of plaque instability.⁷⁴

In addition, there is substantial evidence that an increased dietary intake of α -linolenic acid reduces levels of several inflammation markers, such as high sensitivity C-reactive protein (hs-CRP), interleukin-6 and cellular adhesion molecules.⁷⁵⁻⁷⁷ However, the evidence regarding the effects of ω -3 FAs on hs-CRP is inconclusive.¹³

Blood pressure

Omega-3 FAs seem to exhibit a small dose-dependent hypotensive effect. Morris et al found in a meta-analysis that hypertensive subjects consuming 5.6 g of ω -3 FAs daily had a blood pressure reduction of 3.4/2.0 mmHg.⁷⁸ Appel et al found a decrease of 5.5/3.5 mm Hg in blood pressure in untreated hypertensive subjects after the administration of \geq 3 g ω -3 FAs daily.⁷⁹ DHA seems to be more effective than EPA in lowering blood pressure.⁸⁰ On the other hand, the addition of ω -3 FAs to the diet had no significant effect on blood pressure in healthy subjects.⁸¹

Endothelial function

Omega-3 FAs may improve endothelial function by causing endothelial relaxation and arterial compliance, possibly through improved endothelium-mediated vasodilatation induced by altered nitric oxide production.⁸²⁻⁸⁷

Omega-3 FAs and risk of cancer

Omega-3 FAs are purported to reduce the risk of

cancer but studies have reported mixed results. A recent meta-analysis including cohorts from many countries and with different demographic characteristics does not provide evidence to suggest a significant association between ω -3 FAs and cancer incidence.⁸⁸ Thus, dietary supplementation with ω -3 FAs is unlikely to prevent cancer.

Omega-3 FAs and risk of dementia

A recent systematic review of four studies that assessed the effects of ω -3 FAs on the incidence and treatment of dementia reported a trend in favour of ω -3 FAs (fish and total ω -3 consumption) toward reducing risk of dementia and improving cognitive function.⁸⁹

Recommended intake of ω -3 FAs

From the presented data it seems that the administration of ω -3 FAs could be useful in the secondary prevention of MI and particularly of sudden cardiac death. Thus, long chain ω -3 FA consumption should be encouraged in all subjects and especially to those at high risk of CVD. Table 1 summarises the American Heart Association (AHA) recommendations for fish oil intake.²³

Safety profile of ω -3 FA intake

The Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) recently released an updated consumer advisory on fish intake.⁹⁰ There are some concerns about mercury contamination and other pollutants.⁹⁰ Pregnant women, nursing mothers and children should avoid consuming fish

Table 1. American Heart Association (AHA) recommendations for fish oil (<http://www.americanheart.org>).

Patient population	Recommendation
Without documented coronary artery disease	Two fatty (preferably) fish servings per week.
With documented coronary artery disease	Approximately 1 g of EPA and DHA per day, preferably from fatty fish. Alternatively, fish oil supplements (under a physician's monitoring)
Triglyceridaemia	2-4 g of EPA and DHA per day as capsules (under a physician's monitoring)

EPA – eicosapentaenoic acid; DHA – docosahexaenoic acid.

Table 2. Risk of side effects of various intakes of omega-3 fatty acids (adapted from reference 23).

Dose	Fishy aftertaste	Gastrointestinal disorders	Clinical bleeding	Glycaemic control*	Rise in LDL-C†
<1 g/day	Low	Very low	Very low	Very low	Very low
1 to 3 g/day	Moderate	Moderate	Very low	Low	Moderate
>3 g/day	Likely	Moderate	Low	Moderate	Likely

*In patients with impaired glucose tolerance and diabetes. †In patients with hypertriglyceridaemia.
LDL-C – low-density lipoprotein cholesterol.

with high concentrations of mercury. Although the safety of low intakes of ω -3 FAs is not considered a problem, some side effects of ω -3 FAs may occur at high doses (Table 2).⁷ The most common and totally benign is a fishy aftertaste. Other possible side effects include increases in LDL-C levels, a bleeding tendency, gastrointestinal disturbances and a worsening of glycaemic control in diabetic patients. Patients taking doses higher than 3 g per day should monitor their lipid and glycaemic profile and should be aware of a potential increase in clinical bleeding.

Conclusion

Fish oil intake, either dietary or supplemental, may exhibit beneficial effects on total and CVD mortality. Additionally, ω -3 FAs at a dosage of 3 to 5 g daily can lead to a significant decrease (of about 30%) in TG levels. This decrease can be extremely useful in cases of refractory hypertriglyceridaemia, where the risk of pancreatitis and CVD is high. Moreover, evidence does exist concerning the secondary prevention benefits derived from EPA and DHA intake (intakes ranging from 0.5 to 1.8 g/day reduce the subsequent cardiac and all-cause mortality). AHA dietary guidelines outline the significance of including at least two servings of fish per week. More randomised controlled clinical trials in the primary prevention setting should be conducted.

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