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Review Article

Omega-3 Polyunsaturated Fatty Acids and Human Health
Protective Role in Cardiovascular Disease

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ABSTRACT: The findings of an epidemiological study of Danish Greenland Inuit indicated that fish oil (omega-3 fatty acids) was important in preventing atherosclerotic disease. After that landmark research, large-scale epidemiological studies, clinical outcomes trials, and meta-analyses examined the health benefits of omega-3 fatty acids as part of a diet rich in fatty acids and found statistically significant relative reductions in cardiovascular risk among people consuming omega-3 fatty acids. This article reviews omega-3 studies during the last 50 years and identifies issues relevant to future studies of cardiovascular risk.

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KEYWORDS: omega-3 polyunsaturated fatty acids, cardiovascular disease, hypertriglyceridemia, eicosapentaenoic acid, docosahexaenoic acid

Mortality from atherosclerotic diseases (particularly myocardial infarction [MI]) is high in Western countries. Epidemiological studies have thus focused on differences in lifestyle habits, and in particular dietary habits, between countries that differ in the incidence of atherosclerosis-associated MI. A study of seven countries[1] reported that the mortality rate from ischemic heart disease was lower in Japan and Mediterranean countries than in the United States and Northern European countries and highlighted the role of unsaturated fatty acids, which are abundant in the Japanese and Mediterranean diets. In this context, an epidemiological study of the Danish Greenland Inuit suggested fish oil (omega-3 fatty acids) is important in preventing atherosclerotic diseases.[2] After that landmark study, the health benefits of omega-3 fatty acids as part of a diet rich in fatty acids were extensively researched in large-scale epidemiological studies, clinical outcomes trials, and meta-analyses, the results of which showed a statistically significant reduction in the relative risk of cardiovascular disease (CVD) in persons consuming omega-3 fatty acids.[3–12] In 1983, the first highly purified eicosapentaenoic acid (EPA) preparation for human use was developed in Japan.[13] Omega-3 fatty acids are now widely recognized as having an important role in preventing atherosclerotic disease and a wide range of other diseases and conditions, including diseases of the central nervous system (*e.g.*, dementia) and cardiovascular (CV) system (*e.g.*, arrhythmia, chronic heart failure [CHF]),

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autoimmune diseases (*e.g.*, rheumatoid arthritis, psoriasis), and carcinogenesis, as well as in defense against infection. This review of omega-3 fatty acids presents an overview of their pharmacological features and action, mechanisms of disease control, and clinical effects in relation to CVD and assesses the findings of studies of omega-3 fatty acid preparations currently available as highly purified eicosapentaenoic acid-ethyl ester (EPA-E, Epadel) and eicosapentaenoic acid-ethyl ester/docosahexaenoic acid-ethyl ester (Lotriga; containing the same active ingredients as Omacor® [Pronova BioPharma Norge AS, Lysaker, Norway]/Lovaza® [GlaxoSmithKline plc., Brentford, Middlesex, UK]).[14, 15]

Pharmacology and physiological effects of omega-3 fatty acids on CV risk

Omega-3 fatty acids in the body are not abundantly available as docosapentaenoic acids (DPA) but are instead primarily available as eicosapentaenoic acids (EPA)/docosahexaenoic acids (DHA).[16] Omega-3 fatty acids are incorporated into chylomicron triglycerides (TG) in the gastrointestinal tract and transported to the liver, where EPA and DHA are incorporated into TG as very-low-density lipoproteins (VLDL) and released into the blood stream. Only a small proportion of omega-3 fatty acids are available as free fatty acids, most of which are bound to albumin.[17]

Of all dyslipidemic diseases affecting lipid metabolism, hypertriglyceridemia is the most important CV risk factor.[18–20] Omega-3 fatty acids are reported to reduce serum TG by 24% to 45% in patients with hypertriglyceridemia,[21–23] to increase high-density lipoprotein cholesterol by about 3% and low-density lipoprotein cholesterol by about 5%, and to reduce small dense low-density lipoprotein cholesterol. However, these beneficial effects are difficult to obtain, even with cardioprotective diets rich in omega-3 fatty acids or with small amounts of omega-3 fatty acids, and therefore require consumption of large doses of omega-3 fatty acids.

There is strong evidence that reductions in TG concentration are caused by mechanisms such as reduced hepatic very-low-density lipoprotein-triglyceride synthesis and secretion and increased TG clearance from chylomicrons and VLDL particles.[24] Elevated TG concentrations are reported to be associated with, and may contribute to, the presence of highly atherogenic, small, dense LDL particles and decreased concentrations of high-density lipoprotein cholesterol — factors associated with increased risk of CV disease.[25]

A meta-analysis of randomized studies[26] reported that omega-3 fatty acids modestly lower blood pressure, possibly because of reduced systemic vascular resistance but not cardiac output after omega-3 fatty acid consumption. Increased production of nitric oxide with omega-3 fatty acids may increase expression of endothelial nitric oxide synthase. Indeed, several randomized studies found that intake of omega-3 fatty acids improves serum markers of endothelial dysfunction, such as E-selectin, VCAM-1, and ICAM-1.[27, 28] A meta-analysis of published studies revealed that omega-3 fatty acid intake improves flow-mediated vasodilation, among other parameters of endothelial function.[29]

A meta-analysis of randomized studies[30] revealed modest reductions in heart rate after omega-3 fatty acid consumption, which suggests that the dose − response relationship for heart rate is not as linear as that for blood pressure, for which the response is clear, even for low doses of omega-3 fatty acids. Omega-3 fatty acids lower heart rate by their direct effects on cardiomyocytes[31, 32] and their indirect effects on improving both circulatory dynamics involving ventricular diastolic filling and vagal tone. Heart rate is associated with CV events, which suggests that CV event reductions attributable to omega-3 fatty acids may be due in part to the effects of omega-3 fatty acids on heart rate.

Omega-3 fatty acids decrease the risk of fatal MI and sudden cardiac death associated with coronary heart disease (CHD),[33] and their anti-arrhythmic properties are of particular interest. Omega-3 fatty acids affect the electrophysiology of ventricular and atrial cardiomyocytes, where EPH/DHA are believed to improve cardiomyocyte excitability and intracellular Ca^{2+} variability by blocking the Na^{+} and Ca^{2+} channels in cardiomyocytes.[31, 32, 34] However, it is unclear if these effects are specific to omega-3 fatty acids, as similar effects were reported for omega-6 fatty acids.

Omega-3 fatty acids affect the fibrinolytic and coagulation systems. A dose of 3 − 15 g of fish oil prolongs bleeding time, but this prolongation is not well correlated with clinical bleeding.[35, 36] Indeed, there is no clear increase in bleeding risk for an omega-3 polyunsaturated fatty acid dose as high as 4 g.

Omega-3 fatty acids also have anti-inflammatory properties. An epidemiological study of Greenland Inuit

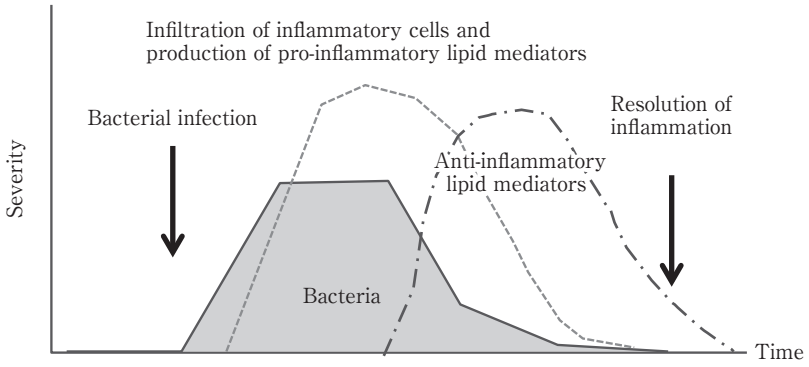

Fig. 1 Proposed model of acute inflammation in wound infection

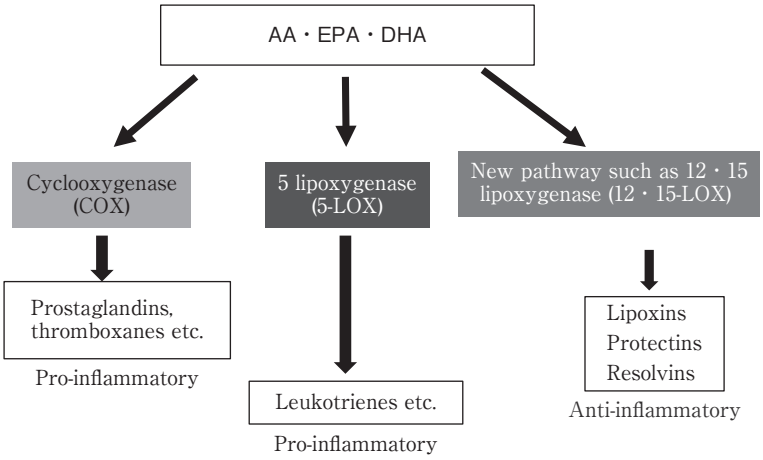

Fig. 2 Pro- and anti-inflammatory lipid mediators in arachidonic cascade
AA: arachidonic acid, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid

people[37] found that autoimmune diseases such as bronchial asthma and psoriasis were extremely rare among Inuit subsisting primarily on fish. Several subsequent animal and human studies provided evidence that omega-3 fatty acids, particularly EPA, have anti-inflammatory and immunomodulatory properties.[38–41]

The omega-6 fatty acid arachidonic acid is stored within cell membranes, released in response to cell stimulation, and metabolized by pro-inflammatory lipid mediators, such as prostaglandin and leukotriene, in the arachidonic acid cascade, thus aggravating pre-existing inflammation. Omega-3 fatty acids are also stored within cell membranes, where they replace and thus reduce storage of arachidonic acid. Furthermore, while omega-3 fatty acids are metabolized by pro-inflammatory lipid mediators in the arachidonic acid cascade, as is arachidonic acid, their active metabolites are assumed to be less potent than those of arachidonic acid, thus tipping the balance toward inhibition of inflammation.[42]

It is important to note that atherosclerosis is reported to be suppressed in leukotriene receptor B-knockout mice[43] and with EPA.[44] DHA has not received as much attention as EPA, but it was recently reported that inflammation suppression was greater for DHA-rich fish oil than for EPA-rich fish oil. In addition, DHA-rich fish oil prolonged survival in a mouse model of systemic lupus erythematosus, a typical autoimmune disease.[45] The mechanisms involved were shown to be resolvins and neuroprotectins produced from omega-3 fatty acids, particularly DHA, at the end of an inflammatory process (Fig. 1).[46] These metabolites were reported to be potent anti-inflammatory lipid mediators (Fig. 2).[47] Progression of atherosclerosis is suppressed in mice overexpressing 12/15-lipoxygenase, which overproduce these anti-inflammatory lipid mediators.[48] However, the role of these anti-inflammatory mediators in human atherosclerosis remains to be determined.

Omega-3 fatty acids and CVD

The amount of fish oil required for its clinical effects on CVD to become manifest and the time required for onset of action vary in relation to the disease being treated. In addition, the clinical outcomes for fish oil vary greatly in relation to the endpoints used to evaluate its effectiveness.

Risk reductions in CHD-related mortality and sudden cardiac death are the most important CVD risk − lowering benefits of omega-3 fatty acids. A meta-analysis of large-scale prospective cohort studies and randomized studies[33] reported that fish and fish oil consumption reduced CHD-related mortality and sudden cardiac death, although these beneficial effects did not exhibit a linear dose − response relationship. A subsequent meta-analysis of 13 randomized controlled trials[49] found a significant reduction in cardiac death after fish oil supplementation; however, this effect was nonsignificant after adjustment for multiple covariates. These findings indicate that fish oil might reduce fatal MI or sudden cardiac death.

However, secondary prevention trials did not show a clear benefit for fish oil,[50, 51] perhaps in part because many of the study participants had been treated with aspirin, angiotensin-converting enzyme inhibitors, β-antagonists, and statins during the studies. The large-scale Risk and Prevention Study[52] did not show that fish oil clearly reduced CHD-related mortality in patients with multiple CVD risk factors. A possible reason for the failure of these secondary prevention studies to show obvious benefits for fish oil is that the study participants had received aggressive pharmacotherapy, which may have reduced the effectiveness of omega-3 fatty acids against cardiac death. The authors of the studies indicated that larger sample sizes would be needed in order to yield statistically significant results.

In contrast, several observational studies[4, 7–9, 11] found that fish oil helped prevent non-fatal MI and acute coronary syndrome, although subsequent large-scale randomized studies reported mixed outcomes. Some found benefits for fish oil, most importantly protection against CV death; [6, 10, 12] other studies failed to show such benefits.[50, 51, 53, 54] Indeed, a meta-analysis of randomized trials[49] found that the risk for non-fatal CVD was lower for persons receiving fish oil, but the decreases were nonsignificant. Thus, the benefits of fish oil for non-fatal CVD are unclear.

A prospective cohort study of 2735 adults without CHF[55] reported that the concentration of omega-3 polyunsaturated fatty acids in blood was inversely correlated with CHF incidence in elderly adults. Other cohort studies[30, 56] reported that increased intake of boiled or grilled, but not fried, fish helped prevent CHF onset. However, very few studies have investigated the protective effects of omega-3 polyunsaturated fatty acids against new-onset CHF, and additional data from primary prevention settings are needed. With respect to secondary prevention, a large-scale randomized, double-blind, placebo-controlled trial of 7046 patients with existing CHF[12] found a significant survival benefit among those given omega-3 fatty acids (Lotriga). The researchers noted improvements in left ventricular ejection rate after a mean treatment duration of 3.9 years.[57] These findings resulted in fish oil being described as effective against CHF in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[58]

A few small-scale randomized studies of patients with defibrillators for ventricular tachycardia[59–61] reported that fish oil yielded mixed results; meta-analyses[62, 63] showed no significant benefit. These studies varied in design; thus, new, better-designed studies are required in order to establish definitive conclusions. A study of fish oil for patients with atrial fibrillation (AF)[64] reported reductions in the risk for developing AF. However, a subsequent large-scale randomized study[65] showed no reduction in the incidence of postoperative AF, and meta-analyses of published studies[65, 66] reported that fish oil had no benefit against AF. Thus, fish oil intake has an unclear effect in preventing postoperative AF and in secondary prevention of AF in patients with existing AF. Large-scale, prospective intervention studies are required in order to determine if fish oil protects against new-onset AF in non-AF patients.

Meta-analyses of relatively large, prospective cohort studies[67, 68] showed that fish oil intake was not correlated with the incidence of hemorrhagic stroke but was inversely correlated with the incidence of ischemic stroke in those receiving a moderate dose of fish oil. However, prospective intervention studies yielded inconsistent results. A sub-analysis of the Japan EPA lipid intervention study (JELIS) of Epadel (highly purified EPA)[69] showed no benefit for primary prevention of stroke but some benefit in secondary stroke prevention. Other studies[50, 54] showed that fish oil had no protective effect against stroke onset.

Table 1 Large-scale clinical studies of omega-3 fatty acids conducted to date [5, 10, 12, 52, 54].

Study	GISSI-P	JELIS	GISSI-HF	ORIGIN	GISSI-R&P
Subject background	Prior MI (within 3 mo.)	Hypercholesterolemia (≥250 mg/dl) (Primary 80.3%, secondary 19.7%)	CHF	IGT/IFG/DM	Multiple CV risks
Baseline TG (mg/dl)	162.1	154.2	NA	omega-3: 142 Control: 140	omega-3: 150 Control: 150
Omega-3 preparation	EPA/DHA	EPA	EPA/DHA	EPA/DHA	EPA/DHA
Dosage (g/day)	1	1.8	1	1	1
Number of subjects	11324	18645	7046	12612	12513
Follow-up (mo.)	42	55.2	47	74.4	60
CV event reduction	Yes	Yes	Yes	No	No
Statin use	29%	100%	23%	54%	62%
Use of ACE-I/ARB	41%	?	94%	71%	75%
Use of antiplatelets	88%	14%	87%	79%	60%
Study period	1993-1995	1994-2006	2002-2005	2003-2005	2004-2007
Publish	Lancet 1999	Lancet 2007	Lancet 2008	NEJM 2012	NEJM 2013

NA: not applicable, mo: months
GISSI-P: Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardico Prevenzione, JELIS: Japan EPA Lipid Intervention Study, GISSI-HF: GISSI-Heart Failure, ORIGIN: Outcome Reduction with Initial Glargine Intervention, GISSI-R&P: GISSI Risk and Prevention Trial, MI: myocardial infarction, CHF: congestive heart failure, IGT: impaired glucose tolerance, IFG: impaired fasting glycaemia, DM: diabetes mellitus, CV: cardiovascular, TG: triglycerides, EPA: eicosapentaenoic acids, DHA: docosahexaenoic acids, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, NEJM: New England Journal of Medicine

Thus, the effects of fish oil on CVD vary widely in relation to the endpoints used and may be attributable to differences in omega-3 fatty acid dosage and duration of use and patient characteristics (particularly disease severity and use of concomitant medications) in the studies. Fish oil may not offer sufficiently potent protective effects against CVD risk, and any benefits might be masked in simple meta-analyses. These possibilities should be considered when conducting studies or interpreting study results.

Large-scale clinical studies of omega-3 fatty acids and issues to be resolved

The effects of fish oil on CVD vary widely in relation to the endpoints evaluated and may be attributable to omega-3 fatty acid dosage and duration of use and patient characteristics (particularly lifestyle, disease severity, and use of concomitant drugs) in studies. Omega-3 fatty acids have been commercially available for 20 years in many countries, and several large-scale studies have examined their effects[5, 10, 12, 52, 54] (Table 1). Early studies showed they were effective for secondary prevention of CV events[5, 10] and for reducing all-cause mortality in patients with CHF.[12] While Omacor® was found to be ineffective in several recent studies,[52, 54] these studies had several major limitations, including the low dose of omega-3 fatty acids used, insufficient statistical power, and enrollment of patients with normal or nearly normal baseline triglyceride levels.[70]

Two ongoing long-term CV interventional outcomes studies are investigating high-dose, prescription-strength omega-3 fatty acids. One is Reduction of Cardiovascular Events with EPA-Intervention trial (REDUCE-IT; NCT01492361), which is investigating Vascepa containing high-purity icosapent ethyl, the ethyl ester of EPA. Outcomes Study to Assess STatin Residual Residual Risk Reduction with EpaNova in HiGh CV Risk PatienTs with Hypertriglyceridemia (STRENGTH; NCT02104817) trial is investigating Epanova® [AstraZeneca plc., Cambridge, UK], which contains omega-3 fatty carboxylic acids, to evaluate reduction of CV events in patients with persistently high triglyceride levels who have a high risk for CV events and are receiving statin therapy. The results are expected to clarify the potential role of omega-3 fatty acids in reducing CV risk.

Conclusion

Ever since a series of epidemiological studies of the Greenland Inuit were published in the late 1970s,

numerous epidemiological/observational and large-scale randomized studies have investigated the effectiveness of omega-3 fatty acids against atherosclerotic diseases, particularly CHD-related fatal MI and sudden cardiac death. However, the effectiveness of omega-3 fatty acids for secondary prevention of non-fatal MI and CHD has not been established, as their effects may be diminished or less apparent in aggressively treated patients. Nevertheless, omega-3 fatty acids have a wide range of therapeutic properties: they improve lipid metabolism, lower blood pressure and heart rate, counteract arrhythmia, improve vascular endothelial function, and counteract clotting and inflammation.

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April	1989	Visiting Research Instructor, US-Japan Biomedical Research Laboratories, School of Medicine, Tulane University (LA, USA)
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April	1994	Medical Quarantine Officer of Narita Airport Quarantine, Ministry of Health, Labour and Welfare (Chiba, Japan)
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