Omega-3 Fatty Acids and Cardiovascular Disease

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Abstract

The use of omega-3 fatty acids for the secondary prevention of cardiovascular (CV) events has been endorsed by the American Heart Association. A number of key epidemiologic and randomized trials have been the basis for this recommendation. Initially, the GISSI-Prevenzione and JELIS trials demonstrated significant reductions in CV events with the use of omega-3 fatty acids. More recently, the OMEGA, Alpha Omega, and Rowey et al. [37] studies examining omega-3 supplementation in atrial fibrillation have shown conflicting results. Although more recent trials have not shown the robust benefits that were seen in the earlier ones, the balance of evidence still favors the beneficial effects of omega-3 fatty acids. We would recommend the continuation of omega-3 fatty acids in patients with CV disease and in particular heart failure.

Keywords: Omega-3 fatty acids; Eicosapentaenoic acid; Docosahexaenoic acid; α-Linolenic acid; Coronary disease prevention; Fish oils

Introduction

The use of omega-3 fatty acids for the secondary prevention of cardiovascular (CV) events has been endorsed by the American Heart Association (AHA). A number of key epidemiologic and randomized trials have been the basis for this recommendation. The AHA recommends 1 g/d of omega-3 fatty acids with a mixture of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). The preferential source is oily fish; however, fish oil supplements are considered an acceptable option as well [1]. In addition, the Food and Drug Administration (FDA) has approved an omega-3 fatty acid formulation for the treatment of high triglycerides at a dose of 4 g/d (3.4 g/d of EPA + DHA). This review will summarize current scientific data on omega-3 fatty acids as well as discuss the sources and sustainability of fish oil production.

Benefits of omega-3 fatty acids

Over the past several decades, an abundance of epidemiological, experimental, and randomized controlled studies have been published on the CV effects of omega-3 fatty acids [2]. The bulk of evidence has demonstrated clear CV protective effects [3]. DHA and EPA are the two specific omega-3 fatty acids that have been associated with CV benefit and triglyceride lowering. DHA and EPA are present in varying ratios in oily fish [4]. Commonly consumed fish such as salmon contain EPA to DHA in a ratio of about 1:2. DHA can partially be retro-converted to EPA [5]; however, EPA supplementation has only a modest effect at raising tissue or blood levels of DHA [6]. A meta-analysis [7] of prospective clinical trials and epidemiologic studies demonstrated that the majority of reduction in risk of CHD death is conferred with modest omega-3 fatty acid consumption: 250 to 500 mg/d of DHA + EPA (Figure 1). This diet corresponds to approximately 1-2 servings/wk of oily fish.

Alpha-linolenic acid (ALA) is another form of omega-3 that is found in flaxseed, nuts, and in trace amounts in green leafy vegetables. Humans convert less than 5% of ALA to EPA, and ALA gets converted into DHA even more sparingly [8], so ALA is inadequate as the sole dietary source of omega-3 fatty acids. ALA intake has been inversely associated with CV events in some epidemiological studies, but this has not been corroborated by subsequent studies [3].

Omega-3 fatty acids provides CV benefits through DHA and EPA enrichment of membrane phospholipids [9] which confers several potentially cardio-protective effects, including an increase arrhythmic thresholds [10], reduction in blood pressure [11,12], improved arterial and endothelial function [13], reduced platelet aggregation [14], and a favorable autonomic balance [11,15]. In a large population study of over 100,000 subjects, omega-3 fatty acid intake was shown to be inversely related to the development of type 2 diabetes in women [16]. A meta-analysis by Geleijnse et al. [17], of 22 double blind studies revealed that omega-3 fatty acid intake of about 4 g/d was associated with significant reductions of 1.7 and 1.5 mm Hg in systolic and diastolic pressures, respectively, an effect that was noted to be more pronounced in older patients and in those with higher baseline blood pressure.

Figure 1: Potential dose responses and time courses for altering clinical events of physiologic effects of fish or fish oil intake [7].

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Evidence in CV disease

It has been shown that omega-3 fatty acid supplementation has a profound impact on patient survival and CV events [21]. Starting from a number of early randomized trials, omega-3 fatty acids, either in the form of oily fish or fish oil capsules, reduced all-cause mortality in post-myocardial infarction (MI) patients [29]. Subsequently, 2 major randomized controlled trials examined the effects of supplemental omega-3 fatty acids on CHD risk. The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)-Prevenzione study randomized 11,323 post-MI patients to omega-3 acid ethyl esters (1 capsule/d providing 850 mg of DHA + EPA) or usual care. Treatment with omega-3 fatty acids significantly reduced the risk of death from any cause by 28%. By 4 months, the risk for SCD was decreased by 45% [19]. The next major randomized controlled trial to be published was the Japan EPA Lipid Intervention Study (JELIS) [30] which studied 18,645 hypercholesterolemic patients who were randomly assigned to either statin alone or statin + pure EPA (1.8 g/d). By the end of the 5-year follow-up period, the patients who received EPA had 19% lower major adverse CV events (Figure 2).

Several older studies have shown conflicting results, of which the most commonly quoted are the randomized trials reported by Burr et al. [29] and Nilsen et al. [32]. In Burr’s study, patients with angina treated with fish oil capsules had higher rates of SCD than untreated controls. This study was criticized as being “well designed” but sub-optimally “conducted and reported”, and thus its results are questionable [33]. The Nilsen study is thought to be flawed because of the high background intake of fish oils in the Norwegian subjects, possibly masking the treatment effects.

Some of the more recent trials such as the OMEGA trial [34] and the Alpha Omega Trial [35] have also shown some conflicting results. The OMEGA trial [34] is a randomized controlled multi-center trial which enrolled 3851 patients and compared patients receiving 1 g/d of omega-3 fatty acids versus placebo for one year and was unable to show a significant difference in CV outcomes in post-MI patients. This discrepancy could have potentially been from the improvements in medical therapy and stent technology from the decade older trials, thus resulting in a lower number of events in the placebo-treated patients. In addition, enrolled subjects had high levels of fish consumption that increased significantly during the course of the study in both arms. The Alpha Omega trial [35] enrolled 4837 patients into their randomized controlled trial which investigated the supplementation of omega-3 in the form of 18.8 g of margarine per day and also showed no significant differences in CV events in patients with a history of MI. The patients in this trial were also on a modern regimen of CV medications and only received a small supplement of omega-3 (400 mg EPA + DHA or 2 g ALA, each alone, or placebo) which may have not been enough to exert an effect.

Omega-3 fatty acids have been strongly associated with anti-inflammatory effects. Calo et al. [36] showed a significant reduction of post-operative atrial fibrillation (AF) in coronary artery bypass surgical patients. However, in Kowey et al.’s trial [37] of 663 AF patients, omega-3 supplementation did not reduce the recurrence of AF in the 6 month study period. Others have described trends towards reduction in malignant ventricular arrhythmias with omega-3 supplementation.
mortality and CV admissions by 8%. (Figure 3) The Cardiovascular Health Study showed an inverse association in the intake of baked or broiled fish and incidence of HF [45,46]. Further evidence to support the benefit of omega-3 fatty acids in HF patients was reported in the Atherosclerosis Risk in Community study, which showed an inverse relationship between omega-3 polyunsaturated fatty acids (PUFA) and intake and incidence of HF in women [47]. A recent randomized controlled trial conducted by Nodari et al. [48] evaluated 133 patients with chronic HF secondary to non-ischemic cardiomyopathy and demonstrated significant improvements in many HF and major CV parameters at 12 month follow up in the subjects who received 2 g/day omega-3 fatty acid supplementation versus placebo. Left ventricular ejection fraction in the omega-3 arm was increased by 10.4% compared to a decrease of 5.0% in the placebo arm (p<0.001). Significant improvements in exercise capacity, New York Heart Association functional class, re-hospitalization rates, and inflammatory cytokines were also seen with omega-3 PUFA [48].

Low blood levels of DHA + EPA have been reported to be a markers of cardiovascular risk [9]. Red blood cell membrane DHA + EPA levels of > 8% appear to be associated with the lowest risk for CHD death [9,49] and are associated with reduced risk for acute coronary syndromes [50]. Individuals with DHA + EPA < 4% are considered to be at higher risk for CV events [50]. In addition, low blood omega-3 fatty acid levels are associated with increased risk of SCD [51]. Optimal membrane levels of omega-3 fatty acid usually are achieved with consumption of 1 to 1.5 g of DHA + EPA per day, which is an intake similar to that of the average Japanese adult [49].

Best source of omega-3 fatty acids

The AHA recommends a total of 1 g/d of DHA and EPA preferably from oily fish for patients with coronary heart disease (CHD) but considers fish oil supplements as an acceptable alternative [1]. Oily fish is the preferred source of the AHA, but not all fish have the same amount or ratio of DHA and EPA. (Table 1) The question of whether fish or fish oils confer the same beneficial CV effects has been addressed

[10,38-40]. Although omega-3 fatty acids appear to be effective for reducing SCD in the setting of CHD with reduced left ventricular systolic function [41], 3 trials using omega-3 fatty acids in implantable cardioverter defibrillator patients have shown mixed results [38-40]. The most recent trial evaluating major arrhythmic events was a substudy of the GISSI Heart Failure (HF) trial that showed fewer events in the omega-3 arm, but this finding was not statistically significant [42].

Levitan et al. [43] further linked omega-3 fatty acids and CV disease by showing that moderate intake of fatty fish and marine omega-3 fatty acids in 39,367 middle-aged or older men was associated with lower rates of HF. In GISSI HF [44], a large randomized placebo-controlled trial of 7046 HF patients, 850 mg/d of EPA + DHA significantly reduced

Figure 3: Kaplan-Meier curve for all-cause death or admissions to the hospital for cardiovascular reasons [44].

<table>
<thead>
<tr>
<th>Type</th>
<th>DHA (gm per 100 g)</th>
<th>EPA (gm per 100 g)</th>
<th>DHA+EPA</th>
<th>Ratio DHA/EPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuna, Bluefin</td>
<td>1.141</td>
<td>0.363</td>
<td>1.504</td>
<td>3.1 : 1.0</td>
</tr>
<tr>
<td>Tuna, Light, canned-in water</td>
<td>0.223</td>
<td>0.047</td>
<td>0.27</td>
<td>4.8 : 1.0</td>
</tr>
<tr>
<td>Tuna, Albacore, canned-in water</td>
<td>0.629</td>
<td>0.233</td>
<td>0.862</td>
<td>2.7 : 1.0</td>
</tr>
<tr>
<td>Salmon, Atlantic, farmed</td>
<td>1.457</td>
<td>0.69</td>
<td>2.147</td>
<td>2.1 : 1.0</td>
</tr>
<tr>
<td>Salmon, Atlantic, wild</td>
<td>1.429</td>
<td>0.411</td>
<td>1.84</td>
<td>3.5 : 1.0</td>
</tr>
<tr>
<td>Salmon, Chinook</td>
<td>0.727</td>
<td>1.01</td>
<td>1.737</td>
<td>1.0 : 1.4</td>
</tr>
<tr>
<td>Salmon, Sockeye</td>
<td>0.7</td>
<td>0.53</td>
<td>1.23</td>
<td>1.3 : 1.0</td>
</tr>
<tr>
<td>Mackerel, Atlantic</td>
<td>0.699</td>
<td>0.504</td>
<td>1.203</td>
<td>1.4 : 1.0</td>
</tr>
<tr>
<td>Herring, Atlantic</td>
<td>1.105</td>
<td>0.909</td>
<td>2.014</td>
<td>1.2 : 1.0</td>
</tr>
<tr>
<td>Trout, rainbow, farmed</td>
<td>0.82</td>
<td>0.334</td>
<td>1.154</td>
<td>2.5 : 1.0</td>
</tr>
<tr>
<td>Trout, rainbow, wild</td>
<td>0.52</td>
<td>0.468</td>
<td>0.988</td>
<td>1.1 : 1.0</td>
</tr>
<tr>
<td>Halibut</td>
<td>0.374</td>
<td>0.091</td>
<td>0.465</td>
<td>4.1 : 1.0</td>
</tr>
<tr>
<td>Cod</td>
<td>0.154</td>
<td>0.004</td>
<td>0.158</td>
<td>38.5 : 1.0</td>
</tr>
<tr>
<td>Haddock</td>
<td>0.162</td>
<td>0.076</td>
<td>0.238</td>
<td>2.1 : 1.0</td>
</tr>
<tr>
<td>Catfish, channel, farmed</td>
<td>0.128</td>
<td>0.049</td>
<td>0.177</td>
<td>2.6 : 1.0</td>
</tr>
<tr>
<td>Catfish, channel, wild</td>
<td>0.137</td>
<td>0.1</td>
<td>0.237</td>
<td>1.4 : 1.0</td>
</tr>
<tr>
<td>Swordfish</td>
<td>0.681</td>
<td>0.087</td>
<td>0.768</td>
<td>7.8 : 1.0</td>
</tr>
<tr>
<td>Grouper</td>
<td>0.213</td>
<td>0.035</td>
<td>0.248</td>
<td>6.1 : 1.0</td>
</tr>
<tr>
<td>Shrimp</td>
<td>0.144</td>
<td>0.171</td>
<td>0.315</td>
<td>1.0 : 1.2</td>
</tr>
</tbody>
</table>

Table 1: Fish content of EPA + DHA [4.21].

Species | Range (ppm) | Average (ppm)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Domestic Samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catfish</td>
<td>ND - 0.16</td>
<td>ND</td>
</tr>
<tr>
<td>Cod</td>
<td>ND - 0.17</td>
<td>0.13</td>
</tr>
<tr>
<td>Crab</td>
<td>ND - 0.27</td>
<td>0.13</td>
</tr>
<tr>
<td>Flounder</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Hake</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Halibut</td>
<td>0.12 - 0.63</td>
<td>0.24</td>
</tr>
<tr>
<td>Pollock</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Salmon (canned)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Salmon (fresh or frozen)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Shark</td>
<td>0.30 - 3.52</td>
<td>0.84</td>
</tr>
<tr>
<td>Swordfish</td>
<td>0.36 - 1.68</td>
<td>0.88</td>
</tr>
<tr>
<td>Tuna (canned)</td>
<td>ND - 0.34</td>
<td>0.20</td>
</tr>
<tr>
<td>Tuna (fresh or frozen)</td>
<td>ND - 0.76</td>
<td>0.38</td>
</tr>
</tbody>
</table>

| Import Samples | | |
| Pollock | ND - 0.78 | 0.18 |
| Shark | ND - 0.70 | 0.36 |
| Swordfish | 0.80 - 1.61 | 0.86 |
| Tuna (canned) | ND - 0.39 | 0.14 |
| Tuna (fresh of frozen) | ND - 0.75 | 0.27 |

Table 2: Levels of Methyl Mercury in Commonly Consumed Fish [55].


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in several studies evaluating the various modes of consumption. A recent study compared the effects of supplementing with walnuts versus fatty fish and found that walnut supplementation significantly lowered cholesterol while fatty fish significantly lowered triglycerides [52]. Another study of cod protein supplementation showed significant reductions in CRP when compared to diets containing similar quantities of other types of protein [53]. This would suggest that there may be other elements in a diet of fish intake that may contribute to the CV benefits. The fact that several important nutrients such as vitamin D, phospholipids, and naturally occurring antioxidants are missing in fish oil supplements have some experts advocating dietary intake of fatty fish as the main source of omega-3 fatty acids. However, there is much data from landmark omega-3 trials such as the GISSI-Prevenzione [19] and JELIS [30] trials that clearly indicate that fish oil supplements confer CV benefits. In addition, Harris and colleagues have illustrated that equivalent amounts of EPA and DHA from either a fish diet or a fish oil supplement enrich the omega-3 content of red blood cell membranes equally well [9,54].

A potential drawback to fish consumption over fish oil supplements is that certain fish can contain environmental toxins such as mercury, polychlorinated biphenyls (PCBs), chlordane, dioxins, and dichlorodiphenyltrichloroethane (DDT). Concentrations of these contaminants increase as fish move up the food chain, so top predators (such as swordfish, shark, king mackerel, largemouth bass, and walleye) may not be safe to eat on a frequent basis. (Table 2) On the other hand, many of the most popular fish varieties, such as salmon, shrimp, canned light tuna, pollock, and catfish, are relatively low in these chemical contaminants and are safe to eat up to several times per week [35]. Unfortunately, except for salmon, they are relatively poor sources of EPA and DHA.

Sustainability of wild fish stocks

Reports have documented a rapid worldwide decline in fish stocks over the past 50 years. Populations of some commercially popular fish species have collapsed to only 10% of their historic maximum with over 100 confirmed cases of marine-species extinctions. Worldwide fish stocks could be depleted within 40 years if harvests continue at the current rate [56,57]. This forecast has, however, been severely criticized [58] and may be overly pessimistic. With the current recommendations for omega-3 supplementation, increased pressure on fish stocks can be expected to continue. Furthermore, recommendations for higher levels of fish and/or fish oil consumption for variety of conditions such as hypertriglyceridemia, depression, inflammation, and cognitive impairment will exert further pressure on wild fish stocks. Whether the demand for fish and fish oil supplements can be met in a sustainable manner remains to be seen. Currently, close to 90% of Americans have suboptimal intake of omega-3 fatty acids [59]. Repletion of deficient omega 3 levels should be an important goal both for individual patient care and for public health but may seriously impact our fish sources. Major changes in the way we source omega 3 fatty acid supplements, such as aquaculture (fish farming) and bioengineering seem to be logical and increasingly practical solutions to this conundrum. Non-traditional sources of marine-based omega-3 fatty acids such as algae to produce DHA and yeast to produce EPA are being developed and may help to offload some of the burden of demand. Additionally, the plant-derived omega-3 fatty acids, alpha-linolenic acid (ALA) and stearidonic acid (the delta-6 desaturase product of ALA which can be produced by biotechnology in soybeans) might provide some of the benefits of DHA and EPA but that remains to be firmly established [60].

Conclusions

Although more recent trials have not shown all the robust benefits that were seen in the earlier ones, the balance of evidence still favors the beneficial effects of omega-3 fatty acids in the primary and secondary prevention of CV diseases. We would recommend the use of omega-3 fatty acids in patients with CV disease and in HF, and suggest that the evidence is appealing for it’s use in the primary prevention of CHD.

References


