REVIEW

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Fish oil supplementation: Evidence for health benefits

ABSTRACT

Many health claims for fish oil (which contains omega-3 fatty acids) in conditions from Alzheimer disease to Zellweger syndrome are based on indirect evidence. But the evidence is direct for a benefit in coronary heart disease prevention, and the American Heart Association recently issued guidelines for the intake of omega-3 oils. This article answers a series of questions that health care professionals often ask regarding fish oil, such as what are proper dosages, and are there risks of ingesting pollutants by eating more fish or using supplements?

KEY POINTS

The "oilier" the fish, the more omega-3 fatty acids it tends to contain. Oily fish include tuna, sardines, salmon, mackerel, and herring.

The American Heart Association recommends about 1 g of long-chain omega-3 fatty acids per day for those with known coronary heart disease. People with no known heart disease should eat oily fish at least twice a week.

As the fish oil capsules dissolve in the stomach and release the oil, many people experience a "fishy burp." Although obviously not a "side effect" in the usual sense, it can be bothersome. Taking the capsules at bedtime and freezing them can minimize or even eliminate this problem.

Since mercury toxicity is mainly a concern for fetuses and breast-fed infants, the US Food and Drug Administration's advice to avoid contaminated fish is directed primarily at pregnant women, those wanting to become pregnant, and nursing mothers.

*The author has indicated that he is a major stock shareholder and cofounder of OmegaMetrix, a company involved in measuring blood levels of omega-3 fatty acids.

OMEGA-3 FATTY ACIDS, found mainly in fish oils, are said to be beneficial in conditions from Alzheimer disease to Zellweger syndrome. Much of the evidence is circumstantial and indirect, so if and how to use them is still open to question. We do however have solid and compelling evidence that two long-chain omega-3 fatty acids—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—help prevent coronary heart disease.

What follows is a series of answers to questions physicians and their patients are asking about fish oil. In this article, I discuss mainly EPA and DHA fish oils.

ESKIMOS, FISH OIL, AND HEART DISEASE

Much of the interest in a marine diet and fish oil comes from the pioneering study of Greenland Eskimos by Bang and Dyerberg[1] more than 30 years ago. They found that even though these Eskimos had a diet very high in fat, they had a very low rate of ischemic heart disease. Their research spawned numerous research studies and has resulted in recommendations from major public health organizations for increased intake of fish oil, particularly EPA and DHA, for all US adults at risk for coronary heart disease. This remarkable odyssey may one day be viewed as one of the most important advances in the nutritional treatment of coronary heart disease.

WHAT ARE EPA AND DHA?

EPA and DHA are essential fatty acids in which the last double bond is three carbons from the terminal (or the "omega" or "Nth") methyl group. Chemically, they are chains of

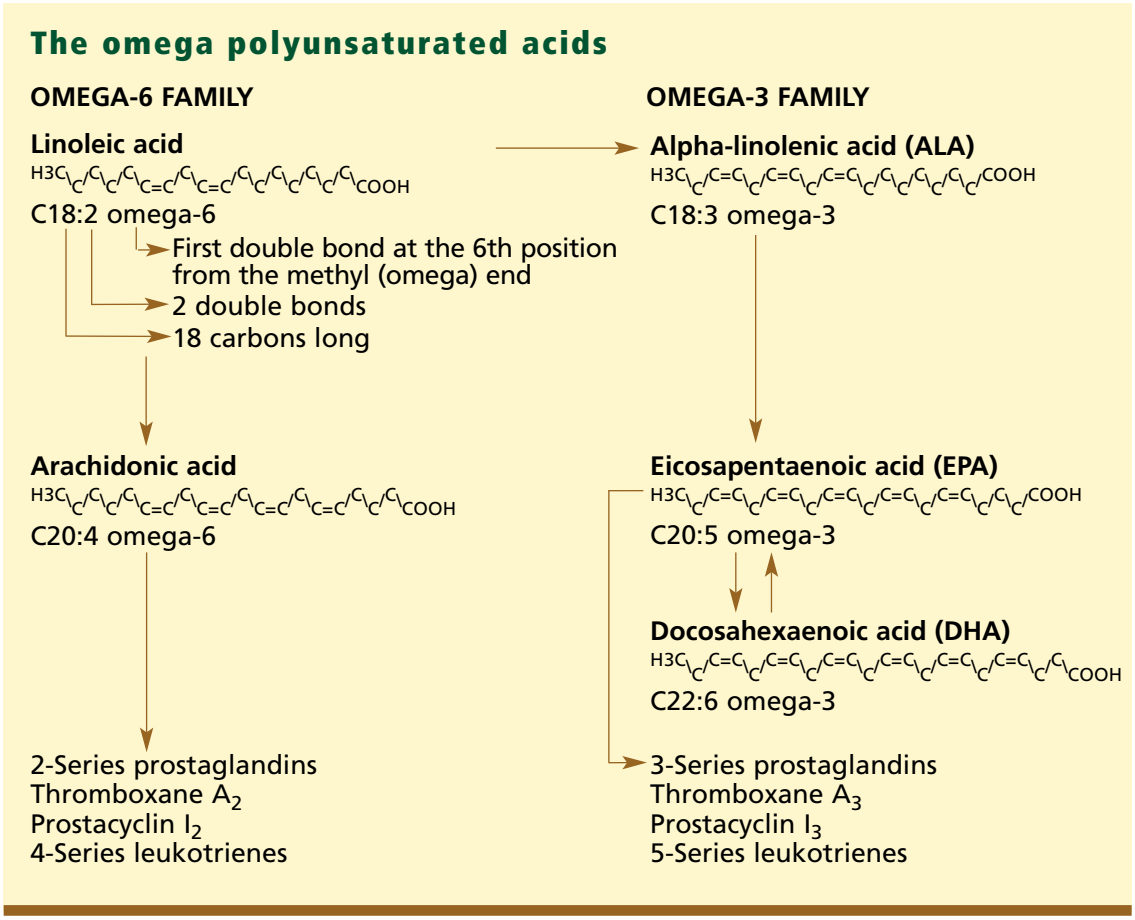

FIGURE 1. The omega-6 and omega-3 families of polyunsaturated fatty acids. Of the omega-3 fatty acids, alpha-linolenic acid is found in plant oils, whereas EPA and DHA are found in fish oils. Both arachidonic acid and EPA are substrates for cyclooxygenases and lipoxygenases, each producing a different family of compounds with differing physiological actions. The nomenclature used to describe fatty acids is illustrated using linoleic acid as an example.

The oilier the fish, the more EPA and DHA

18 to 22 carbon atoms with from three to six double bonds in the chain (FIGURE 1). They are polyunsaturated fatty acids and are referred to as "long-chain" omega-3 fatty acids.

A third omega-3 fatty acid, alpha-linolenic acid (ALA), is sometimes referred to as a short-chain omega-3 fatty acid and is found in certain plant oils but not in fish.

WHAT ARE GOOD DIETARY SOURCES?

EPA and DHA are found almost exclusively in seafood (TABLE 1, TABLE 2). Fish do not produce EPA and DHA. Rather, these oils are synthesized by single-celled marine organisms that fish eat. These fatty acids are essential for fish as well as for humans.

Generally speaking, the "oilier" the fish, the more EPA and DHA are present. Fish that tend to have high concentrations include tuna, sardines, salmon, mackerel, and herring.

Some fungal and algal sources of DHA have been discovered, and these have been cultivated and commercialized primarily to supply the infant formula industry.

ALA, synthesized in plant chloroplasts, is found in leaves and in some seed oils. The richest readily available plant source is flaxseed oil, which contains about 55% ALA by weight (TABLE 3). Other rich sources are camelina, chia, and perilla oils. Of the commonly used vegetable oils, canola oil and soybean oil are reasonably good sources. Certain nuts, primarily walnuts, contain some ALA.

TABLE 1

Omega-3 oil levels in various fish and seafoods*

FISH	GRAMS OF OMEGA-3 OIL PER 3-OZ SERVING	NO. OF OUNCES PER DAY TO EQUAL 1 G EPA/DHA
Tuna		
Light, canned in water, drained	0.26	12
White, canned in water, drained	0.73	4
Fresh	0.24-1.28	2.5-12
Sardines	0.98-1.70	2-3
Salmon		
Sockeye or pink	1.05	3
Chinook	1.48	2
Coho, farmed	1.09	3
Coho, wild	0.91	3
Atlantic, farmed	1.09-1.83	1.5-2.5
Atlantic, wild	0.9-1.56	2-3.5
Mackerel	0.34-1.57	2-8.5
Herring		
Pacific	1.81	1.5
Atlantic	1.71	2
Trout, rainbow		
Farmed	0.98	3
Wild	0.84	3.5
Cod		
Atlantic	0.13	23
Pacific	0.24	12.5
Catfish		
Farmed	0.15	20
Wild	0.2	15
Flounder/Sole	0.42	7
Oyster		
Pacific	1.17	2.5
Eastern	0.47	6.5
Lobster	0.07–0.41	7.5–42.5
Crab, Alaskan king	0.35	8.5
Shrimp, mixed species	0.27	11
Clam	0.24	12.5
Scallop	0.17	17.5

*Omega-3 fatty acid content varies widely with the season, the diet and age of the fish, and the storage and preparation methods. Values based on US Department of Agriculture Nutrient Data Laboratory, available on the Internet at **www.nalusda.gov/fnic/foodcomp/.** Accessed February 2, 2004.

ALA: IS IT A SUBSTITUTE FOR EPA AND DHA?

The only known role of ALA, other than as a source of calories, is as a precursor of DHA in adult humans. However, only a small amount of ALA is converted to DHA (from less than 1% to 9%),[2–5] and ALA does not raise plasma DHA levels. One of the primary reasons that ALA is so poorly converted to the longer-chain EPA and DHA is because it is mostly used for energy, whereas EPA and DHA are not.

ALA differs from EPA and DHA not only in structure (FIGURE 1), but also in metabolism and ultimate health effects. The metabolites of EPA and its omega-6 cousin arachidonic acid are the most well known, and include eicosanoids (ie, derivatives of 20-carbon fatty

TABLE 2

Omega-3 fatty acid levels in various fish oil capsule supplements*

CAPSULES	GRAMS OF EPA + DHA PER CAPSULE	NO. OF CAPSULES PER DAY TO EQUAL 1 G EPA + DHA
Cod liver oil†	0.19	5
Standard fish body oil	0.30	3
Omega-3 concentrate	0.50	2
Highly concentrated omega-3	0.7–0.9	1

*Values based on US Department of Agriculture Nutrient Data Laboratory, available on the Internet at **www.nalusda.gov/fnic/foodcomp/**.
†This amount of cod liver oil would provide the US Recommended Dietary Allowance of vitamin A and twice that of vitamin D.

acids) such as the 3-series (2-series for arachidonic acid) prostaglandins, prostacyclins, and thromboxanes, and the 5-series (4-series for arachidonic acid) leukotrienes.[6]

The metabolites of EPA are generally less active than the proinflammatory and prothrombotic metabolites derived from arachidonic acid (FIGURE 1). The omega-3 and the omega-6 fatty acids compete for conversion into these important metabolites. Thus, tissue levels are largely determined by dietary intake levels.[7]

Direct proof of a cardiac benefit of alpha-linolenic acid is lacking

ARE OMEGA-3 FATTY ACIDS CARDIOPROTECTIVE?

What is the evidence that omega-3 fatty acids prevent heart disease? In a word, the evidence is strong for EPA and DHA, and spotty for ALA.

Population studies around the world and within the United States consistently show a protective association between EPA, DHA,[8–11] and ALA[12–14] and heart disease, but a beneficial effect of fish oils is also supported by compelling supplementation studies,[15–17] which are lacking for ALA. Studies comparing populations with low vs high blood levels of marine omega-3 fatty acids found the risk for death from cardiovascular disease to be as much as 90% lower in those with high blood levels.[8,9]

But association does not prove causation. Causation is more clearly demonstrated in randomized, controlled trials. In one such study, the Diet and Reinfarction Trial (DART),[15] about 1,000 British heart patients were simply advised to eat two servings of oily fish a week for 2 years. At the end of the study, 29% fewer people had died in the "fish advice" group than in a similar group not given fish advice. The actual intake of EPA/DHA was not determined in this trial, but it was estimated at about 600 to 900 mg/day. (For reasons that are unclear, the results of the DART could not be reproduced in men being treated for angina.[18])

The largest study to date of omega-3 fatty acids and heart disease was the GISSI-Prevention study (*Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Prevenzione*).[17,19] More than 2,800 Italian heart attack survivors were given purified EPA/DHA in capsule form and were asked to take one per day for 3.5 years. Each capsule provided 850 mg of EPA/DHA in roughly equal amounts. As in the DART, death from any cause was reduced by 20%, and interestingly, sudden death (presumably from a second heart attack) fell by 45% compared with a similar number of patients not given the supplement. These two studies, especially the GISSI-Prevention study, point directly to EPA and DHA as the agents responsible for the cardiovascular health benefit.

Similar studies have been attempted with ALA but have not shown the same benefit. The reasons are not clear. It could be that ALA is ineffective, or perhaps too few patients were studied or that extenuating circumstances obscured a benefit. For example, in a

study from Norway, more than 6,500 men in their 50s were given flaxseed oil supplements providing 5.5 g of ALA per day for 1 year.[20] There was no cardiovascular benefit found compared with a similar group given sunflower seed oil (which contains no ALA). In this study the failure of ALA could have been due to the high content of EPA and DHA in the Norwegian diet, leaving nothing for ALA to do.

In another study, ALA supplementation (2.9 g/day from 20 mL of mustard seed oil) was compared with fish oil supplementation (1.8 g/day) and placebo in 360 patients admitted to an Indian hospital for a suspected heart attack.[21] Although both fish oil and ALA reduced total cardiac events, the reduction was statistically significant only with fish oil. In this case, the number of patients studied may have been too small to confidently detect a beneficial effect of ALA.

In the Lyon Heart Study, which tested the "Mediterranean diet," an increase in ALA from about 500 mg to 1,600 mg per day (from a canola-based margarine) was just one of several dietary changes that together resulted in reduced risk for heart attacks.[22] In this study, it is not possible to unambiguously conclude that it was the ALA that afforded the benefit when so many other factors changed at the same time (eg, less saturated fat and cholesterol and more fruits and vegetables).

WHAT IS THE MECHANISM OF ACTION OF OMEGA-3 FATTY ACIDS?

EPA and DHA appear to reduce the susceptibility of the myocardium to fatal arrhythmias. In large doses they can lower serum triglyceride levels and inhibit platelet function. There are several possible mechanisms by which they exert these effects, but the definitive answer is yet to be found.

Almost all the studies that have looked for mechanisms have used far greater doses of omega-3 oils than were used in GISSI and DART. Intakes of 3 to 20 g or more of EPA/DHA have been studied for effects on blood lipids (notably triglycerides), platelet function, blood pressure, endothelial function, blood vessel flexibility, and inflammation.[23] A recent study of about 1.5 g of EPA/DHA per day found that supplementation appeared to make carotid artery plaques more stable.[24]

TABLE 3

Food sources of alpha-linolenic acid*

FOOD	GRAMS PER TABLESPOON
Flaxseed oil	8.5
Flaxseeds	2.2
Canola oil	1.3
Soybean oil	0.9
Walnuts, English	0.7
Olive oil	0.1

*Based on US Department of Agriculture Nutrient Data Laboratory values; **www.nalusda.gov/fnic/foodcomp/**. Accessed February 2, 2004

Nevertheless, there is very little information on the biological effects of low intakes (less than 1 g/day) used in the major clinical trials. For example, the benefits for total mortality observed in the GISSI Prevention study[17] were unaccompanied by any change in lipid profile, and no other possible mechanisms were examined.

EPA and DHA appear to discourage fatal myocardial arrhythmias

Data from epidemiologic and randomized clinical trials suggest that omega-3 fatty acids decrease the risk of sudden cardiac death, presumably via reduced susceptibility to malignant arrhythmias.[25] The evidence for this mechanism has been derived primarily from animal and cell culture studies, and the physiological relevance to humans consuming less than about 1 g/day of EPA/DHA is not clear.

Nevertheless, according to this theory, as EPA and DHA are incorporated into cellular membranes throughout the body, they do two things. First, they displace the omega-6 fatty acid arachidonic acid (the substrate for synthesis of thromboxane A_2, leukotriene B_4, and all 2-series prostaglandins), which could reduce proinflammatory and prothrombotic processes. While theoretically attractive, there are no clinical trial data showing that high omega-6 intake has adverse cardiovascular effects,[26] and higher tissue levels of arachidonic acid are not associated with increased risk for coronary heart disease.[27,28]

TABLE 4

Informal survey of fish oil capsules for sale in retail outlets in Kansas City in spring/summer 2003*

NAME	EPA/DHA (MG/CAPSULE)	CAPSULES TO PROVIDE 1 G	COST TO PROVIDE 1 G
Kirkland Signature fish oil concentrate	180/120	3	$0.07
Member's Mark omega-3 fish oil	180/120	3	$0.07
GNC Liquid Norwegian CLO (teaspoons)†	460/370	1	$0.11
Spring Valley MaxEPA	180/120	3	$0.13
Origin Natural fish oil concentrate	180/120	3	$0.15
Walgreen's fish oil concentrate	180/120	3	$0.15
Your Life fish oil concentrate	180/120	3	$0.17
GNC fish body oils 1000	180/120	3	$0.19
Natrol omega-3	180/120	3	$0.20
VitaSmart fish oil concentrate	180/120	3	$0.20
Sav-On Fish Oil Concentrate	180/120	3	$0.21
Sundown fish oil	180/120	3	$0.21
Nature Made Fish Oil	216/144	3	$0.22
Omega-3 Enteric Coated	180/120	3	$0.23
Nature's Bounty Natural Fish Oil	180/120	3	$0.25
Nature Made Fish Oil	216/144	3	$0.27
Rexall cholesterol-free fish oil	180/120	3	$0.31
GNC triple cod liver oil (CLO) caps	173/120	3	$0.30
TwinLab emulsified Norwegian CLO† (tablespoons)	516/344	1	$0.44

*This is not an exhaustive list, and periodic sale prices may be lower than these retail prices. Sales tax is not included. Many other products are available via the Internet, but shipping and handling charges must be considered in determining overall cost.
†This is a liquid; therefore, doses are in teaspoons or tablespoons instead of capsules.

The AHA recommends 1 g of EPA/DHA per day

Second, as EPA and DHA are released from membrane phospholipids in response to ischemic stress, they directly interact with and inhibit the L-type calcium channels and the fast, voltage-dependent sodium channels. This essentially decreases the resting membrane potential, which makes it more difficult for ventricular fibrillation to develop. Thus, these fatty acids behave somewhat like physiological calcium channel blockers and beta-blockers. The detailed molecular mechanisms remain to be elucidated.

WHAT IS THE RECOMMENDED INTAKE OF OMEGA-3 OILS?

For general cardioprotection, the American Heart Association (AHA) recommends[23] about 1 g of EPA/DHA daily for patients with known coronary heart disease. For people with no known heart disease, the AHA recommends eating oily fish at least twice a week, or about 500 mg of EPA/DHA per day. Much higher intake, ie, from 2 to 4 g per day, is needed to lower triglyceride levels, and this should be done in consultation with a physician.

The AHA's nutrition committee recommends oily fish as the preferred source of omega-3 fatty acids (TABLE 1, TABLE 2) but acknowledges that, for people who cannot or will not eat enough fish to meet this target, an EPA/DHA supplement could be considered in consultation with their physician.

At present, we have no compelling data to suggest that either EPA or DHA is the primary, active component. They appear to act in synergy. Thus, products that contain both in ratios ranging from 2:1 to 1:2 are probably equally beneficial, although this has not been rigorously examined.

HOW MUCH FISH? HOW MANY CAPSULES?

TABLE 1 and TABLE 2 give the amounts of certain types of fish and fish oil capsules needed to provide 1 g of EPA and DHA per day. Generally, this requires almost daily consumption of oily fish. For oily fish like salmon, one 3-oz portion per day can provide 1 g of EPA/DHA.

Fish oil capsules vary widely in amounts and ratios of EPA and DHA (TABLE 4). The consumer must pay close attention to the amount of EPA and DHA per capsule. As noted above, we have no compelling evidence to choose a product that is composed primarily of one or the other omega-3 fatty acid. A supplement with an EPA/DHA ratio between 2:1 and 1:2 is best, and one to four capsules may have to be taken daily to provide about 1 g of EPA/DHA. This can cost anywhere from 7 cents to $1 or more, depending on the product. A recent issue of Consumers' Report examined 16 different brands of fish oil capsules and concluded that all were free of pollutants and contained amounts of EPA and DHA that were reasonably close to their label claims.[29]

The US Food and Drug Administration (FDA) currently allows omega-3 fatty acid supplements to bear the following qualified health claim: "Consumption of omega-3 fatty acids may reduce the risk of coronary heart disease. The FDA evaluated the data and determined that, although there is scientific evidence supporting the claim, the evidence is not conclusive."[30]

WHAT ABOUT MERCURY AND OTHER TOXINS IN FISH?

In general, eating fish or taking fish oil capsules does not present a health hazard. There are, however, concerns of mercury toxicity and other environmental pollutants that need to be addressed.

Mercury

Mercury can indeed "bioconcentrate" in fish at the top of the marine food chain, and this has prompted the FDA to issue an advisory regarding four species of fish: king mackerel, shark, swordfish, and tile fish (also known as golden bass or golden snapper). Since mercury toxicity is mainly a concern for fetuses and breast-fed infants, the FDA's advice to avoid such fish is directed primarily at pregnant women, those wanting to become pregnant, and nursing mothers.

Fish oil capsules contain no mercury. Mercury (actually methyl mercury, the toxic form) is water-soluble, not oil-soluble,[31] so when the oil is extracted from the fish, the mercury (and lead, cadmium, and other heavy metals) stays behind in the fish meal.

The methyl mercury content of selected fish can be found at **www.cfsan.fda.gov/~frf/sea-mehg.html**; accessed February 2, 2004.

Other pollutants

Organic pollutants are potentially another matter, however. These are oil-soluble compounds that can find their way via the marine food chain into fish oils.[32] Although present in very small amounts, using highly sensitive instruments these compounds can be detected in some fish oil products, most often in cod liver oil.

Fish oil concentrates, the most commonly used supplements, are not derived from the liver of the fish, but from the muscle, and so they are lower in pollutants than liver oils. A recent Consumers' Union independent analysis of fish oil capsules from 16 different vendors sold in the United States found no significant contamination with either metals or chlorinated hydrocarbons.[29]

Fish oil supplements are permitted to claim that they 'may reduce the risk of coronary heart disease'

IS WILD FISH BETTER THAN FARMED FISH?

Both wild fish and farmed fish are good sources of omega-3, as seen in TABLE 1.

As the public demand for fish such as high-quality salmon has increased, so has the popularity of fish farming. These farms operate much like a feed lot for cattle, where uniform feeding and conditions for exercise (or lack thereof) result in products of uniform composition. Farmed fish are fed rations that contain fish protein and fish oil, so farmed fish also contain omega-3 fatty acids.

The omega-3 content of wild fish is more unpredictable and depends on the maturity of the fish and when it is caught. For example, salmon caught as they are just beginning their

upstream journey to spawn are much richer in oil than when they are caught far upstream because they utilize their fat stores for energy and eat very little during their freshwater migration.

On the other hand, farmed fish may contain somewhat higher amounts of organic pollutants, since the fish oil put into their feed is not stripped of these compounds in the way that oil intended for human use is. Hites et al[33] called attention to this recently in a report published in the journal *Science*. However, the amounts of contaminants reported are small and exaggerated and do not outweigh the benefits of eating farmed salmon.

IS ONE FISH OIL FORMULATION BETTER THAN ANOTHER?

Fish oil supplements are available as a triglyceride-based form or as a methyl or ethyl ester form. Previous work in our laboratory showed that serum levels of EPA/DHA were raised equally well with a triglyceride or a methyl ester preparation.[34] Thus, there is little justification for choosing one formulation over the other.

Amounts of contaminants in farmed salmon are small and do not outweigh the benefits

Omega-3 products in the methyl ester or ethyl ester form are usually more concentrated than triglyceride forms: ie, fewer capsules per day are required to achieve target intakes. They are also more expensive. In the GISSI-Prevention study, an ethyl ester product was used (Omacor, Pronova Biocare, Oslo, Norway), which contains 850 mg of EPA/DHA ethyl esters per 1-g capsule. Omacor is not currently available in the United States.

DHA vs EPA

There is also little evidence that one of the two long-chain omega-3 fatty acids is more cardioprotective than the other. While some studies have pointed to blood pressure benefits specific to DHA[35] or to triglyceride-lowering specific to EPA,[36] these studies utilized about eight times the dose of DHA and EPA used in the GISSI-Prevention study. The evidence to date for clinical benefit has been generated with a combination of EPA and DHA, and until compelling evidence from low-dose studies with pure fatty acids is available, there is no scientific justification for emphasizing one long-chain omega-3 fatty acid over the other.

WHEN SHOULD CAPSULES BE TAKEN? HOW CAN THE 'FISHY BURP' BE AVOIDED?

Fish oil capsules can be taken at any time, with or without meals.

As the capsules dissolve in the stomach and release the oil, many people experience a "fishy burp." This may first occur within 15 minutes and can recur during the next few hours if gastric emptying is particularly slow. Although obviously not a "side effect" in the usual sense, it can be bothersome. Taking the capsules at bedtime or freezing them can minimize or even eliminate this problem. Enteric coated capsules are also available.

ARE OMEGA-3 OILS BENEFICIAL IN NONCARDIAC CONDITIONS?

Emerging evidence indicates potential noncardiac benefits of increased intake of omega-3 fatty acids. Omega-3 fatty acids have shown benefits in rheumatoid arthritis,[37] systemic lupus erythematosus,[38] Crohn disease,[39] ulcerative colitis,[40] and immunoglobulin A nephropathy.[41] There is also increasing evidence that diets high in fish may protect against the development of Alzheimer disease[42–45] and prostate cancer.[46–48]

HOW DO YOU KNOW IF YOU'RE GETTING ENOUGH OMEGA-3?

Although it is important to try to consume recommended amounts of omega-3 fatty acids, it is often difficult to know how much one is actually getting. Fish have highly variable amounts of these fatty acids, and label claims on capsules are not regulated and thus may or may not be true. And even if one knew his or her intake accurately, differences in digestion, absorption, tissue distribution, and metabolism produce different tissue levels in each person. Consequently, one cannot rely on a specific intake to produce an optimal blood level.

Measuring blood levels of EPA and DHA would seem the surest way to know if cardioprotective levels have been achieved.

Unfortunately, there is no standardized and generally accepted method for doing this. We have taken the approach of measuring the amount of EPA/DHA in red blood cell membranes, expressed as a percent of total fatty acids. There is a growing rationale for targeting a value of over 8% for maximal cardioprotection (unpublished observations).

REFERENCES

1. **Dyerberg J, Bang HO, Stoffersen E, Moncada S, Vane JR.** Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? Lancet 1978; 2:117–119.
2. **Emken EA, Adlof RO, Gulley RM.** Dietary linoleic acid influences desaturation and acylation of deuterium-labeled linoleic and linolenic acids in young adult males. Biochim Biophys Acta 1994; 1213:277–288.
3. **Burdge GC, Wootton SA.** Conversion of alpha-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. Br J Nutr 2002; 88:411–420.
4. **Pawlosky RJ, Hibbeln JR, Novotny JA, Salem NJ.** Physiological compartmental analysis of alpha-linolenic acid metabolism in adult humans. J Lipid Res 2001; 42:1257–1265.
5. **Pawlosky RJ, Hibbeln JR, Lin Y, et al.** Effects of beef- and fish-based diets on the kinetics of n-3 fatty acid metabolism in human subjects. Am J Clin Nutr 2003; 77:565–572.
6. **Calder PC.** Dietary fatty acids and the immune system. Nutr Rev 1998; 56:S70–S83.
7. **Lands WEM, Libelt B, Morris A, et al.** Maintenance of lower proportions of (n-6) eicosanoid precursors in phospholipids of human plasma in response to added dietary (n-3) fatty acids. Biochim Biophys Acta 1992; 1180:147–162.
8. **Siscovick DS, Raghunathan TE, King I, et al.** Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. JAMA 1995; 274:1363–1367.
9. **Albert CM, Campos H, Stampfer MJ, et al.** Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med 2002; 346:1113–1118.
10. **Rissanen T, Voutilainen S, Nyyssönen K, Lakka TA, Salonen JT.** Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events. The Kuopio Ischaemic Heart Disease Risk Factor Study. Circulation 2000; 102:2677–2679.
11. **Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS.** N-3 polyunsaturated fatty acids, fatal ischemic heart disease and non-fatal myocardial infarction in older adults. The Cardiovascular Health Study. Am J Clin Nutr 2002; 76:319–325.
12. **Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC.** Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. BMJ 1996; 313:84–90.
13. **Djousse L, Pankow JS, Eckfeldt JH, et al.** Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study. Am J Clin Nutr 2001; 74:612–619.
14. **Hu FB, Stampfer MJ, Manson JE, et al.** Dietary intake of a-linolenic acid and risk of fatal ischemic heart disease among women. Am J Clin Nutr 1999; 69:890–897.
15. **Burr ML, Fehily AM, Gilbert JF, et al.** Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989; 2:757–761.
16. **von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H.** The effect of dietary w-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1999; 130:554–562.
17. **Marchioli R, Barzi F, Bomba E, et al.** Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation 2002; 105:1897–1903.
18. **Burr ML, Ashfield-Watt PA, Dunstan FD, et al.** Lack of benefit of dietary advice to men with angina: results of a controlled trial. Eur J Clin Nutr 2003; 57:193–200.
19. **GISSI-Prevenzione Investigators.** Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E in 11,324 patients with myocardial infarction: results of the GISSI-Prevenzione trial. Lancet 1999; 354:447–455.
20. **Natvig H, Borchgrevink CF, Dedichen J, Owren PA, Schiotz EH, Westlund K.** A controlled trial of the effect of linolenic acid on incidence of coronary heart disease. The Norwegian vegetable oil experiment of 1965-66. Scand J Clin Lab Invest 1968; 105(suppl):1–20.
21. **Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M.** Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian Experiment of Infarct Survival–4. Cardiovasc Drugs Ther 1997; 11:485–491.
22. **de Lorgeril M, Salen P, Martin JL, et al.** Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999; 99:779–785.
23. **Kris-Etherton PM, Harris WS, Appel LJ.** Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 2002; 106:2747–2757.
24. **Thies F, Garry JM, Yaqoob P, et al.** Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. Lancet 2003; 361:477–485.
25. **Leaf A, Kang JX, Xiao YF, Billman GE.** Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. Circulation 2003; 107:2646–2652.
26. **Hooper L, Summerbell CD, Higgins JP, et al.** Dietary fat intake and prevention of cardiovascular disease: systematic review. BMJ 2001; 322:757–763.
27. **Luostarinen R, Boberg M, Saldeen T.** Fatty acid composition in total phospholipids of human coronary arteries in sudden cardiac death. Atherosclerosis 1993; 99:187–193.
28. **Paganelli F, Maixent JM, Duran MJ, Parhizgar R, Pieroni G, Sennoune S.** Altered erythrocyte n-3 fatty acids in Mediterranean patients with coronary artery disease. Int J Cardiol 2001; 78:27–32.
29. Omega-3 oil: fish or pills? Consumer Reports, 2003; 68 (July) 30–32.
30. **US Food and Drug Administration, Center for Food Safety and Applied Nutrition.** Letter regarding dietary supplement health claim for omega-3 fatty acids and coronary heart disease. October 31, 2000. Available from **www.cfsan.fda.gov/~dms/ds-ltr11.html.** Last accessed January 15, 2004.
31. **Ebel JG, Jr., Eckerlin RH, Maylin GA, Gutenmann WH, Lisk DJ.** Polychlorinated biphenyls and p,p'-DDE in encapsulated fish oil supplements. Nutr Rept Intl 1987; 36:413–417.
32. **Jacobs MN, Santillo D, Johnston PA, Wyatt CL, French MC.** Organochlorine residues in fish oil dietary supplements: comparison with industrial grade oils. Chemosphere 1998; 37:1709.
33. **Hites RA, Foran JA, Carpenter DO, Hamilton MC, Knuth BA, Schwager SJ.** Global assessment of organic contaminants in farmed salmon. Science 2004; 303:226–229.
34. **Harris WS, Zucker ML, Dujovne CA.** Omega-3 fatty acids in hypertriglyceridemic patients: triglycerides vs. methyl esters. Am J Clin Nutr 1988; 48:992–997.
35. **Mori TA, Bao DQ, Burke V, Puddey IB, Beilin LJ.** Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans. Hypertension 1999; 34:253–260.
36. **Rambjor GS, Walen AI, Windsor SL, Harris WS.** Eicosapentaenoic acid is primarily responsible for the hypotriglyceridemic effect of fish oil in humans. Lipids 1996; 31:S45–S49.
37. **Volker D, Fitzgerald P, Major G, Garg M.** Efficacy of fish oil concen-

trate in the treatment of rheumatoid arthritis. J Rheumatol 2000; 27:2343–2346.
38. **Walton AJ, Snaith ML, Locniskar M, Cumberland AG, Morrow WJ, Isenberg DA.** Dietary fish oil and the severity of symptoms in patients with systemic lupus erythematosus. Ann Rheum Dis 1991; 50:463–466.
39. **Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S, Miglioli M.** Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. N Engl J Med 1996; 334:1557–1560.
40. **Stenson WF, Cort D, Beeken W.** Dietary supplementation with fish oil in ulcerative colitis. Ann Intern Med 1992;116:609–614.
41. **Donadio JV, Bergstralh EJ, Offord KP, Spencer DC, Holley KE, for the Mayo Nephrology Collaborative Group.** A controlled trial of fish oil in IgA nephropathy. N Engl J Med 1994; 331:1194–1199.
42. **Morris MC, Evans DA, Bienias JL, et al.** Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 2003; 60:940–946.
43. **Kalmijn S, Launer LJ, Ott A, Witteman JC, Hofman A, Breteler MM.** Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol 1997; 42:776–782.
44. **Kyle DJ, Schaefer E, Patton G, Beiser A.** Low serum docosahexaenoic acid is a significant risk factor for Alzheimer's dementia. Lipids 1999; 34:S245.
45. **Heude B, Ducimetiere P, Berr C.** Cognitive decline and fatty acid composition of erythrocyte membranes: the EVA study. Am J Clin Nutr 2003; 77:803–808.
46. **Giovannucci E, Rimm EB, Colditz GA, et al.** A prospective study of dietary fat and risk of prostate cancer [see comments]. J Natl Cancer Inst 1993; 85:1571–1579.
47. **Terry P, Lichtenstein P, Feychting M, Ahlbom A, Wolk A.** Fatty fish consumption and risk of prostate cancer. Lancet 2001; 357:1764–1766.
48. **Norrish AE, Skeaff CM, Arribas GL, Sharpe SJ, Jackson RT.** Prostate cancer risk and consumption of fish oils: a dietary biomarker-based case-control study. Br J Cancer 1999; 81:1238–1242.

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