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Omega-3 Fatty Acids

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Estimated Time to Complete: 30 Minutes **Target Audience:** Family Practice, Internal Medicine and Other Primary Care Physicians; Nurse Practitioners and Physician Assistants; Pharmacists; Nurses; Other Health Care Professionals

Description

This learning activity reviews the omega-3 fatty acids, their cardioprotective effects, role in the management of hypertriglyceridemia, recommended intake/dosage, safety, and side effects.

Objectives

Following this learning activity, the learner will be able to:
- Name 3 plant sources high in a-linolenic acid and 3 marine sources high in eicosapentaenoic acid and docosahexaenoic acid.
- Discuss the American Heart Association's recommendations for intake of omega-3 fatty acids from diet or supplements for individuals with and without known coronary heart disease and those with hypertriglyceridemia.
- Discuss how omega-3 fatty acids are believed to reduce the risk of sudden cardiac death.
- Discuss safety and side effect issues related to the consumption of fish and fish oil supplements.

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Thomas E. Kottke, MD, Jodi Chaffin, Pharmacist, and Gary Freeman, MD have indicated no financial interests, affiliations, or intent to discuss unapproved or investigative use of commercial products or devices.

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Essential Fatty Acids Reduce Risk of Sudden Cardiac Death and Treat Severe Hypertriglyceridemia

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Recent evidence from epidemiologic studies and randomized controlled trials suggests that omega-3 fatty acids from plant- and marine-derived sources reduce the risk of death from coronary heart disease in individuals with or without known cardiovascular disease. Marine-derived omega-3 fatty acid supplements are also used to treat severe hypertriglyceridemia. **The cardioprotective effects of omega-3 fatty acids, their role in the management of hypertriglyceridemia, recommended intake/dosage, safety, and side effects are discussed below.**

Omega-3 Polyunsaturated Fatty Acids

The fatty acids consist of a hydrocarbon chain with a hydrophobic methyl group at one end and a hydrophilic carboxyl group at the other. The methyl end is referred to as the *omega* end and the carboxyl end is the *delta* end. The carbon atoms are numbered in order starting from the omega end. The number of double bonds in the fatty acid molecule determines whether the fatty acid is *saturated* (no double bonds), *monounsaturated* (one double bond), or *polyunsaturated* (two or more double bonds). The **polyunsaturated fatty acids** are divided into *omega-6 fatty acids* and *omega-3 fatty acids*. The omega-6 fatty acids have their first double bond at the sixth carbon atom from the omega end and are pro-inflammatory and pro-thrombotic. The omega-3 fatty acids have their first double bond at the third carbon atom from the omega end and are anti-inflammatory, anti-arrhythmic, and anti-thrombotic. Foods high in omega-6 fatty acids include certain vegetable oils (i.e., corn, safflower, sunflower, and cottonseed oil) and meats from animals fed grains high in omega-6 fatty acids. The omega-3 fatty acids include a-linolenic acid (a "short-chain" omega-3 fatty acid) from plant sources (i.e., soybean and canola oil, walnuts, and flaxseed) [(1)] and "long-chain" omega-3 fatty acids including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from oily/fatty fish (i.e., halibut, salmon, mackerel, and herring) [(2)(3)] . The omega-3 and omega-6 fatty acids are considered "essential" fatty acids because humans cannot synthesize them and must obtain them from the diet [(4)(5)].

Omega-3 Fatty Acids and Cardiovascular Disease

A large number of epidemiologic and observational studies and a limited number of randomized controlled trials have demonstrated an inverse relationship between the risk of cardiovascular disease and the consumption of fish, fish oil, and a-linolenic acid. This is particularly true for sudden death from cardiac disease [(6)]. **Overall, an increased intake of these nutrients may reduce the risk of sudden cardiac death by as much as 50%** [(7)(8)]**.** The relationship between blood levels/intake of omega-3 fatty acids and the risk of sudden cardiac death is linear and the authors of one meta-analysis have estimated that each 20 g/day (5 ounces/week) increase in fish consumption is associated with a 7% lower risk of coronary heart disease mortality. If the negative association between high levels of omega-3 fatty acid intake and risk of sudden death is causal, increasing consumption of omega-3 fatty acids by the population is predicted to have a large effect on sudden death compared to distributing automated external defibrillators (AEDS) or prescribing implantable cardiac defibrillators (ICDs). There is also evidence from epidemiologic studies suggesting that an increased intake of omega-3 fatty acids reduces the risk of non-fatal myocardial infarction and coronary artery disease by 40%-60%.

It is believed that omega-3 fatty acids reduce the risk of sudden cardiac death through anti-arrhythmic effects on ischemic myocardium. Omega-3 fatty acids appear to stabilize the electrical activity of cardiomyocytes by occupying the SN2 position on phospholipids in the cell membrane. When ischemia occurs, omega-3 fatty acids (particularly EPA and DHA) occupying these sites are released, inhibiting sarcolemmal ion channels, and helping to prevent the local initiation and propagation of ventricular tachycardia. Omega-3 fatty acids may also reduce the risk of atrial fibrillation, particularly in post-operative patients who have undergone coronary artery bypass surgery. Although theoretical models suggest that omega-3 fatty acids should reduce the risk of ventricular tachycardia or ventricular fibrillation in patients with an implantable cardiac defibrillator, this has not as yet been confirmed in randomized controlled trials.

Hypertriglyceridemia

Long-chain omega-3 fatty acids lower plasma triglyceride levels, particularly in persons with severe hypertriglyceridemia (>500-750 mg/dL), by inhibiting the synthesis of very-low-density lipoprotein (VLDL) and triglyceride in the liver [(9)]. Human studies indicate that approximately 4 g per day of EPA+DHA reduce serum triglyceride concentrations by 25-30%, increase low-density lipoprotein (LDL cholesterol) levels by 5-10%, and increase high-density lipoprotein (HDL cholesterol) levels by 1-3%. **Note that omega-3 fatty acids do not have a significant effect on total cholesterol levels and are not recommended for treatment of hypercholesterolemia alone.**

Recommendations for Omega-3 Fatty Acids Intake
Typical population-based recommendations for omega-3 fatty acids intake include 0.8 to 1.1 g/day of a-linolenic acid and 0.3 to 0.5 mg/day of EPA+DHA. The average dietary intake of a-linolenic acid in the United States is generally adequate (1.4 g/person/day), while the average intake of EPA+DHA is deficient (0.1 to 0.2 g/person/day). An appropriate intake of these nutrients can be accomplished by using liquid vegetable oils containing a-linolenic acid (i.e., soybean and canola oil) and by consuming two fatty fish meals per week (one 4 ounce serving per week provides approximately 0.14 g of EPA+DHA per day; two servings of fatty fish per week would provide about 0.3 g of EPA+DHA per day).

The American Heart Association has issued the following recommendations regarding the intake of omega-3 fatty acids:

- **For Patients *Without* Documented Coronary Heart Disease**
  Eat a variety of oily/fatty fish at least twice a week. Include oils and foods rich in a-linolenic acid (flaxseed, canola, and soybean oils; flaxseed and walnuts). Although not specifically recommended by the American Heart Association, individuals who are unable or unwilling to eat fish regularly could consider taking a daily fish oil supplement.
- **For Patients *With* Documented Coronary Heart Disease**
  Consume approximately 1 g of EPA+DHA per day, preferably from oily/fatty fish. EPA+DHA supplements could be considered in consultation with a physician.
- **For Patients Needing Triglyceride Lowering**
  Two to four grams of EPA+DHA per day provided as capsules under a physician's care.

Omega-3 Fatty Acid Supplements
The most common fish oil capsules in the United States provide 180 mg of eicosapentaenoic acid and 120 mg of docosahexaenoic acid (approximately 0.3 g of EPA+DHA) in 1000 mg of fish oil. Other non-prescription fish oil products contain different amounts of EPA and DHA and patients should be advised to check the label of each product carefully in order to achieve their desired EPA+DHA dose. A prescription fish oil product (Omacor®) contains approximately 465 mg of eicosapentaenoic acid and 375 mg of docosahexaenoic acid (approximately 0.9 g of EPA+DHA daily) and is roughly equivalent to 3 fish oil capsules each containing 0.3 g EPA+DHA. This product would be most appropriate for patients needing triglyceride lowering or as an EPA+DHA supplement for patients with documented coronary heart disease.

Safety
Certain fish may contain high levels of environmental toxins such as mercury [(10)], polychlorinated biphenyls (PCBs) [(11)], and organochlorine pesticides [(12)]. The Food and Drug Administration and the Environmental Protection Agency have issued safety guidelines related to the consumption of these fish [(13)]. With the possible exception of the consumption of certain fish species by pregnant or nursing women and young children, the nutritional benefits of eating fish are likely to far exceed the health risks. The manufacturing process used for most fish oil capsules ensures that they are essentially free of these toxins.

Side Effects
Omega-3 fatty acids /fish oil supplements are "generally recognized as safe" at dosages up to 3 g/day by the Food and Drug Administration. Higher dosages may be associated with a higher risk of bleeding. Common side effects associated with omega-3 fatty acid/fish oil supplements include a fishy aftertaste and gastrointestinal symptoms such as nausea, belching, and bloating. The risk of various side effects from the ingestion of omega-3 fatty acid supplements/fish oil is summarized below:

Dose	GI Upset	Clinical Bleeding	Fishy Aftertaste	Worsened Glycemia	?LDL-C
Up to 1g/d	Very low	Very low	Low	Very low	Very low
1-3 g/d	Moderate	Very low	Moderate	Low	Moderate
>3 g/d	Moderate	Low	Likely	Moderate	Likely

CONCLUSIONS

- **Numerous studies have demonstrated an inverse relationship between an increased intake of omega-3 fatty acids from plant and fish sources and the risk of sudden death from cardiac disease.** This effect appears to be largely mediated by the anti-arrhythmic effects of these nutrients on ischemic cardiomyocytes.

- **High-dose EPA+DHA lowers triglyceride levels by 25% to 30% and may be used as part of a comprehensive program for the treatment of severe hypertriglyceridemia.**

- **The recommended intake of omega-3 fatty acids varies depending upon whether the desired goal is primary or secondary prevention** (i.e., whether or not the patient has cardiac disease). High-dosages of fish oil supplements are needed to treat severe hypertriglyceridemia.

- **Some fish high in EPA+DHA contain high levels of environmental toxins such as mercury, PCBs, and organochlorine pesticides.** These fish should be consumed cautiously by women who might become pregnant, women who are pregnant, nursing mothers, and young children. Fish oil supplements contain very low amounts of these toxins.

- **The most common side effects associated with fish oil supplements are fishy aftertaste and gastrointestinal symptoms such as nausea, belching, and bloating.**

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1) The a-linolenic acid content of selected plant sources is summarized below:

Source	Grams of a-linolenic acid/100 g of raw material
Flaxseed	20.0
Butternuts	8.7
English walnuts	6.8
Soybeans (raw)	3.2
Leeks	0.7
Wheat germ	0.7
Purslane	0.4
Almonds	0.4
Pinto beans	0.3
Barley bran	0.3
Kale	0.2
Chickpeas	0.1
Avocados	0.1
Strawberries	0.1
Peanuts	0.003
Canola oil	1.3 g/tbsp
Flaxseed (linseed) oil	8.5 g/tbsp
Soybean oil	0.9 g/tbsp

2) The EPA+DHA content of selected fish sources is summarized below:

Source	Grams of EPA+DHA/100 g of raw material
Mackerel	2.5
Atlantic herring	1.6
Albacore tuna	1.3
Chinook salmon	1.4
Anchovy	1.4
Coho salmon	0.8
Greenland halibut	0.9
Rainbow trout	0.5
Atlantic cod	0.4
Atlantic white shrimp	0.4
Catfish	0.3
Northern lobster	0.2
Flounder	0.2

3) Purslane is an herbaceous weed/vegetable found throughout the world and in all 50 States. It is the only known plant source of EPA. You may have Common Purslane (*Portulaca oleracea*) growing somewhere in your lawn or garden (particularly if your lawn has bare patches or areas of thin grass). Please refer to the Wikipedia reference titled “Common Purslane” (http://en.wikipedia.org/wiki/Common_Purslane) to view a picture of this common edible weed and read more about it. Purslane is also a good source of a-linolenic acid and certain antioxidants (betacyanins and betaxanthins).

4) Fish are also unable to synthesize EPA and DHA. EPA and DHA are made by cold water algae. These organisms are ingested by fish and their EPA and DHA is incorporated into fish oil.

5) Limited amounts of a-linolenic acid may be elongated and desaturated in the body to EPA through an inefficient enzymatic process using ?6 desaturase. The rate of conversion is usually less than 5% and is influenced by an individual’s intake of omega-6 fatty acids which serve as a competitive substrate for ?6 desaturase.

6) Half a million people die suddenly each year. For half these people, sudden death is the first indication that they have coronary heart disease.

7) A recent clinical review concluded that the relative risk of cardiac death was reduced by 14.6% (95% CI, 8% to 21%) for each 100 mg/d intake of EPA+DHA up to a total risk reduction of 36% (95% CI, 20% to 50%) for an EPA+DHA intake of 250 mg/d (there seemed to be little additional risk reduction with higher intakes). Assuming that one-quarter to one-half of deaths in middle-aged populations and populations with known CHD respectively are due to CHD death, the authors concluded that an increased intake of EPA+ DHA in these populations would reduce total mortality by an average of 14%.

8) Low rates of coronary heart disease are found in countries where fish is an important component of the diet (e.g., Japan and Greenland).

   The DART study involved 2033 Welsh men who were randomized to receive or not receive advice regarding three dietary factors following recent myocardial infarction. The dietary advice included increasing fatty fish intake (200-400 g of fatty fish or three fish oil capsules per day). The individuals advised to increase their intake of fatty fish had a significant 29% reduction (RR 0.71, 95% CI 0.54-0.93) in both cardiac and total mortality over a 2-year interval compared with those not receiving this advice.

   The GISSI-Prevenzione trial involved 11324 patients with a history of recent myocardial infarction who were randomized to receive supplements of fish oil 1g/d (850-882 mg of EPA+DHA), vitamin E 300 mg daily, both fish oil and vitamin E, or neither for 3.5 years. Those individuals receiving fish oil exhibited a 20% reduction in all-cause deaths, 30% reduction in cardiovascular deaths, and 44% reduction in sudden death compared with those not receiving fish oil. A subsequent analysis of the GISSI-Prevenzione data demonstrated that the mortality benefit associated with fish oil was apparent after only 3 months of treatment.

   A study from the Nurses Health Study reported an inverse association between fish consumption, omega-3 fatty acids, and CHD death. Compared with women who rarely ate fish (less than once per month), the risk for CHD death was 21%, 29%, 31% , and 34% lower for fish consumption 1-3 times per month, once per week, 2-4 times per week, and >5 times per week.

   A population based, nested, case-control study found that the consumption of 5.5 g of omega-3 fatty acids per month (equivalent to two fatty fish meals per week) was associated with a 50% reduced risk of primary cardiac arrest.

   In the US Physicians’ Health Study, men who consumed fish at least once weekly had a relative risk of sudden death of 0.48 versus men who consumed fish less than once per month.

   A recent report from the Physicians’ Health Study reported an inverse relationship between blood levels of long-chain omega-3 fatty acids and risk of sudden death in men without a history of CVD. The relative risk of sudden death was significantly lower among men with levels in the third quartile (RR=0.28) and the fourth quartile (RR=0.19) compared with men whose blood levels were in the first quartile.

The highest quintile of a-linolenic acid intake in the Nurses Health Study was associated with a 45% reduction in the risk of fatal ischemic heart disease. Similar findings were reported in the Health Professionals' Study where a 1% increase in a-linolenic acid intake was associated with a 0.41 relative risk for acute myocardial infarction.

9) Obesity, excess alcohol intake, diabetes, hypothyroidism, and certain prescription drugs (estrogen, thiazide diuretics, and beta blockers) may contribute to hypertriglyceridemia and should be addressed before initiating drug therapy.

10) Methylmercury is the organic form of mercury that is found naturally in the environment and is released mainly through the burning of fossil fuels and solid wastes. Human exposure to methylmercury occurs almost exclusively from eating fish. Methylmercury reaches its highest levels in large, predatory species such as king mackerel, shark, tilefish (golden bass), and tuna. **Note that salmon, an important source of omega-3 fatty acids, have very low to undetectable mercury concentrations.** Methylmercury is absorbed from the gastrointestinal tract and binds readily with proteins. The highest levels of methylmercury are found in the kidneys. It is slowly transformed into other forms of mercury and excreted mainly in feces, urine, and breast milk, usually within a few weeks to a few months after exposure. Methylmercury may cause tremor, difficulty with concentration, vision deficits, and numbness and tingling. Levels of mercury in fish appear to be increasing.

11) The PCBs are a family of 209 synthetic organochlorine compounds with two linked phenyl rings and variable chlorination used widely in electrical equipment such as transformers and capacitors before 1977 (PCBs were banned in 1979). Of the PCBs produced in the United States, 1.2 billion pounds ended up in rivers, lakes, and oceans, where they accumulate in marine wildlife. Bottom-feeding fish ingest PCBs and the PCBs become more concentrated higher up on the food chain (0.6-20 ppb in edible fish high in the food chain). PCBs are readily absorbed into the body, but are only slowly metabolized and excreted. The PCBs have half-lives ranging from 1-460 days, depending on the level of chlorination. PCBs concentrate in adipose tissue and breast milk and are metabolized in the liver. Chronic effects associated with these compounds include dermatologic manifestations, developmental deficits with exposure in utero, disruption of thyroid or female sex hormones, elevation of liver enzymes, decreased immunity, impaired memory and learning in adults and children, and carcinogenesis. Humans average 1.4 ppb of PCBs in their serum.
Farmed salmon (primarily Atlantic salmon or *Salmo salmar*) are fed ground up fish contaminated with PCBs and are a significant source of PCBs (more than 90% of salmon consumed in the United States are farm-raised, most commonly in Norway and Chile). Wild salmon have much lower levels of PCBs (in one study, the mean concentration of total PCBs in farmed salmon was 51,216 pg/g vs. 5302 pg/g for wild salmon). Wild salmon also contain significantly lower concentrations of related flame retardant compounds (polybrominated diphenylethers or PBDEs) than farmed salmon. Despite these differences, the CHD benefits of salmon consumption (either wild or farmed) outweigh the cancer risks by several hundred-fold. A recent clinical review concluded that per 100,000 individuals, consumption of farmed vs wild salmon would result in 24 vs 8 excess cancer deaths while resulting in 7125 fewer CHD deaths.
Although fish are a major source of PCBs, it is worth noting that virtually all foods contain PCBs and dioxin (an organochlorine by-product of waste incineration, paper bleaching, pesticide production, and production of polyvinyl chloride plastics) and contribute significantly to our total dietary exposure to these compounds. Among adults, major dietary sources of PCBs and dioxin are beef, chicken, and pork (34%), dairy products (30%), vegetables (22%), fish and shellfish (9%), and eggs (5%).

12) Organochlorine (OC) pesticides include chlordane, dieldrin, DDT, aldrin, endrin, heptachlor, hexachlorobenzene, mirex, and toxaphene. These compounds persist in the environment and are resistance to degradation with half-lives ranging from months to years. Organochlorine pesticides concentrate over 1000-fold in fish and marine mammals. Because of their neurotoxic properties, OC pesticides were banned in 1973. Despite this ban, 99.5% of the population has an average of 1.8-12.6 ppb of DDT in their serum from persistent nutritional and environmental exposure. DDT and its metabolite DDE concentrate in adipose tissue (123-567 ppb) and breast milk (24-202 ppb). DDT is found in all types of food including fish. Fish contain 37-373 ppb of DDT and DDE and constitute a significant contribution to a person's daily intake of these compounds. Again, wild salmon have been found to have lower levels of organochlorine pesticides than farmed salmon.

13) Due to concerns about methylmercury contamination, the **U.S. Environmental Protection Agency** recommends that women who might become pregnant, women who are pregnant, nursing mothers, and young children adhere to the following recommendations for selecting and eating fish or shellfish. Note that the U.S. Environmental Protection Agency and FDA are *not* recommending that these populations avoid fish. In fact, DHA appears to be important for early neurodevelopment and is preferentially incorporated into the rapidly developing brain (gray matter and retina) during gestation and the first 2 years of childhood. There is evidence that increased maternal DHA intake during pregnancy and lactation improves a child's visual acuity and a variety of cognitive measures.
    - Do not eat shark, swordfish, king mackerel, or tilefish (golden bass) because they contain high levels of mercury.
    - Eat up to 12 ounces (2 average meals) per week of a variety of fish and shellfish that are lower in mercury. Five of the most commonly eaten fish that are low in mercury are shrimp, canned light tuna, pollock, and catfish. Another commonly eaten fish, albacore ("white") tuna has more mercury than canned light tuna. Therefore, up to 6 ounces (one average meal) of albacore tuna may be consumed per week.

The **Minnesota Department of Health** has also issued safe eating guidelines for fish consumption. For pregnant women, women who may become pregnant, and children under age 15 years, the MDH recommends:

- Do not eat shark, swordfish, king mackerel, and tilefish (golden bass).
- Limit canned "white" tuna, tuna steak, halibut, and lobster to 2 meals per month.
- Limit salmon, cod, pollock, canned "light" tuna, catfish, tilapia, herring, sardines, shrimp, crab, scallops, and oysters to 2 meals per week.

Although not fatty/oily fish, the MDH also makes that following recommendations regarding the consumption of freshwater fish from Minnesota waters:

- Limit sunfish, crappie, yellow perch, and bullheads to 1 meal per week.
- Limit walleyes shorter than 20 inches, northern pike shorter than 30 inches, smallmouth bass, largemouth bass, channel catfish, flathead catfish, white sucker, drum, burbot, sauger, carp, lake trout, white bass, rock bass, whitefish, and other species to 1 meal per month.
- Do not eat walleyes larger than 20 inches, northern pike longer than 30 inches, and muskellunge.

The **Institute of Medicine** has recently published recommendations regarding the consumption of seafood by different population groups:

1) Females who are or may become pregnant or who are breastfeeding:

- May benefit from consuming seafood, especially those with relatively higher concentrations of EPA and DHA;
- Can reasonably consume two 3-ounce (cooked) servings but can safely consume 12 ounces per week;
- Can consume up to 6 ounces of white (albacore) tuna per week;
- Should avoid large predatory fish such as shark, swordfish, tilefish, or king mackerel;

2) Children up to 12 years of age:

- May benefit from consuming seafood, especially those with relatively higher concentrations of EPA and DHA;
- Can reasonably consume two 3-ounce (cooked) or age-appropriate servings but can safely consume 12 ounces per week;
- Can consume up to 6 ounces of white (albacore) tuna per week;
- Should avoid large predatory fish such as shark, swordfish, tilefish, or king mackerel;

3) Healthy adolescent and adult males and females (who will not become pregnant):

- May reduce their risk for future cardiovascular disease by consuming seafood regularly (as suggested by the Dietary Guidelines for Americans);
- Who consume more than two servings a week should ensure that they select a variety of seafood to reduce the risk for exposure to contaminants from a single source;

4) Adult males and females who are at risk of coronary heart disease:

- May reduce their risk for cardiovascular disease by consuming seafood regularly;
- May additionally benefit from including high EPA/DHA seafood selections (although supporting evidence is limited);
- Who consume more than two servings a week should ensure that they select a variety of seafood to reduce the risk of exposure to contaminants from a single source.

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