Commentary

n-3 Fatty Acids: Food or Supplements?

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The practice of good nutrition is guided by a "food-first" approach. Registered dietitians, both in the United States and globally, have long championed a food-based approach for achieving nutrient adequacy and preventing and treating diseases. Consistent with this guiding principle is the position of the American Dietetic Association (ADA) on fortification and nutritional supplements (1). "It is the position of the ADA that the best nutritional strategy for promoting optimal health and reducing the risk of chronic disease is to wisely choose a wide variety of foods. Additional nutrients from fortified foods and/or supplements can help some people meet their nutritional needs as specified by science-based nutrition strategies such as the Dietary Reference Intakes." Inherent to this position is that a variety of nutrient-dense foods be consumed in moderation as the basis for a healthful diet. This is a key message echoed by the *Dietary Guidelines for Americans 2005*, which states, "Consume a variety of nutrient-dense foods and beverages within and among the basic food groups. . . ." and "Meet recommended intakes within energy needs by adopting a balanced eating pattern . . ." (2).

The position of ADA on nutritional supplements is that they can help some individual's meet their nutrient needs when their diet is inadequate because of different circumstances, including being in an "at-risk" life-stage group for a nutrient deficiency (1). For example, because 10% to 30% of the older population is unable to absorb naturally occurring vitamin B-12, the Institute of Medicine advises people 50 years of age and older to meet their Recommended Daily Allowances primarily by consuming foods fortified with vitamin B-12 or by taking a vitamin B-12 supplement (3). Likewise, a prenatal supplement that provides folic acid, iron, zinc, copper, calcium, and other vitamins and minerals typically is recommended for pregnant women, especially those with a compromised nutritional status (4,5). Other circumstances that determine the need for nutrient supplementation include limited variety in food selection, which prevents achieving nutrient adequacy, and the need for medical nutrition therapy for specific diseases or conditions (1).

The ADA position paper on fortification and nutritional supplements (1) emphasizes the importance of bioavailability when considering use of supplements. Relative to this, there are important issues to consider: (a) not all forms of a nutrient function equivalently; (b) natural sources of nutrients may not be the most functionally effective; (c) sources of nutrients in a food matrix may function differently than the isolated form; and (d) nutrient balance must be considered (1). These considerations are germane to the ongoing discussion about n-3 fatty acids and the preferred "delivery system," ie, food vs supplement, to meet current recommendations for plant-derived (α-linolenic acid [ALA; 18:3n-3]) and marine-derived (eicosapentaenoic acid [EPA; 20:5n-3], docosahexaenoic acid [DHA; 22:6n-3], and docosapentaenoic acid [DPA; 22:5n-3]) n-3 fatty acids.

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DIETARY RECOMMENDATIONS FOR n-3 FATTY ACIDS AND FISH

The current n-3 fatty acid recommendations have been issued by the Institute of Medicine of the National Academies (6). The Acceptable Macronutrient Distribution Range for ALA is 0.6% to 1.2% of energy. Up to 10% of total dietary n-3 fatty acids can be provided by EPA and DHA, which represents median consumption for these two fatty acids in the United States. The 2005 Dietary Guidelines promote this position, but also notes the following: "Limited evidence suggests an association between consumption of fatty acids in fish and reduced risks of mortality from cardiovascular disease for the general population. Other sources of EPA and DHA may provide similar benefits; however, more research is needed" (2). The 2005 Dietary Guidelines also note that there is evidence that suggests that consumption of approximately two servings of fish per week (approximately 8 ounces total) can reduce risk of mortality from coronary heart disease, and that consuming EPA and DHA can reduce risk of mortality from cardiovascular disease in people who have already experienced a cardiac event (2). Because of the health benefits associated with EPA and DHA, numerous agencies and organizations worldwide, including ADA, have issued recommendations for EPA and DHA, as well as for fish consumption, for health promotion and decreased risk of many chronic diseases.

US AND CANADIAN DIETARY RECOMMENDATIONS FOR LONG-CHAIN n-3 FATTY ACIDS AND FISH

In the position paper on dietary fatty acids, the ADA and Dietitians of Canada recommend two servings of fish per week, preferably fatty fish (7). In addition, 500 mg/day EPA and DHA is recommended. Approximately 8 oz of cooked fatty fish per week is equivalent to 500 mg/day EPA and DHA. Other recommendations for fish and EPA and DHA issued by organizations in the United States are consistent with this guidance. A list of these recommendations includes:

- American Diabetes Association: two or more servings of fish per week (with the exception of commercially fried fish filets) provide n-3 polyunsaturated fatty acids and are recommended (8).
- American Heart Association: two servings of fish (preferably fatty) per week (9,10).
- 2005 Dietary Guidelines Advisory Committee Report: two servings of fish (preferably high n-3 fish) per week (11).
- National Cholesterol Education Program: fish is recommended as a food item for people to choose more often [see Table V.2–6 in (12)].
- National Academies: seafood is part of a healthful diet and can be substituted for other protein sources that are higher in saturated fat (13).

GLOBAL RECOMMENDATIONS FOR LONG-CHAIN N-3 FATTY ACIDS AND FISH

- Australia and New Zealand National Health and Medical Research Council: a suggested dietary target for men and women 19 to older than 70 years of age is 610 and 430 mg/day of DHA/EPA/DPA, respectively (14).
- European Society for Cardiology: oily fish and n-3 fatty acids have particular protective properties for primary cardiovascular disease prevention (15-17).
- International Society for the Study of Fatty Acids and Lipids: a minimum combined intake of 500 mg/day EPA and DHA is recommended for cardiovascular health (18).
- National Heart Foundation of Australia: at least two fish (preferably oily fish) meals per week (19).
- United Kingdom Scientific Advisory Committee on Nutrition: consume at least two portions of fish per week, of which one should be oily, and provide 450 mg per day EPA+DHA (20).
- World Health Organization: regular fish consumption (one to two servings per week; each serving should provide the equivalent of 200 to 500 mg EPA+DHA) (21).

RECOMMENDATIONS FOR SECONDARY PREVENTION OF CORONARY HEART DISEASE AND TRIGLYCERIDE-LOWERING

Recommendations for long-chain n-3 fatty acids for secondary prevention of coronary disease are that patients with documented coronary heart disease consume 1.0 g/day (9), preferably from fatty fish. EPA and DHA in capsule form could be considered in consultation with a physician (9). For patients who need to lower triglyceride levels, 2 to 4 g EPA and DHA per day, as capsules, are recommended under a physician's care (9).

HEALTH RISKS OF N-3 FATTY ACIDS

High intakes of n-3 fatty acids can cause excessive bleeding in some individuals. Thus, patients taking >3 g/day long-chain n-3 fatty acids should do so only under a physician's care (9). The US Food and Drug Administration has set the "generally regarded as safe" level for long-chain n-3 fatty acids at 3.0 g/day (22). Likewise, the Upper Intake Level for DHA/EPA/DPA has been set at 3.0 g/day by the Australia and New Zealand National Health and Medical Research Council (14). Risks (and benefits) of fish consumption have been discussed in detail elsewhere (13,23). Specific concerns have been raised about the presence of environmental toxins, such as mercury, dioxins, and other contaminants. The US Food and Drug Administration and the Environmental Protection Agency acknowledge that some fish and shellfish contain higher levels of mercury, and advise against consumption of shark, swordfish, king mackerel, or tilefish (golden bass) by women who may become pregnant, pregnant women, nursing mothers, and young children (24). In addition, the Advisory indicates that up to 6 oz (one average meal) of albacore tuna per week is acceptable. However, for these high-risk population groups, inclusion of up to 12 oz (two average meals) a week of a variety of fish and shellfish that are lower in mercury as part of a well-balanced diet can contribute to cardiovascular health and children's proper growth and development (24). For all population groups, health professionals and consumers are advised to follow federal, state, and local guidelines for fish consumption.

N-3 FATTY ACID INTAKE AND FISH INTAKE

According to the National Health and Nutrition Examination Survey, 1999-2000, for the US population, mean intake of EPA and DHA is 100 mg/day (25). Based on data from the Continuing Survey of Food Intakes by Individuals 1994-96, fish and shellfish consumption is 10 g/day (or about 2.5 oz per week) for males and females of all ages (n=16,103) (26). Based on National Health and Nutrition Examination Survey 1999-2000 data, mean intake of fish is 2.92 oz per week (11). Moreover, much of the seafood consumed in the United States comes from fish not high in n-3 fatty acids (ie, shrimp and other shellfish and whitefish) (13). In addition, estimates are limited by the "all or none" phenomenon seen with fish and shellfish consumption; the number of individuals who regularly eat fish and shellfish is small, but consumption within this group is high (27). Thus, it appears that a large proportion of the population is not meeting current recommendations for n-3 fatty acid intake, which is consistent with US population intake data for EPA and DHA (≈100 mg/day).

Relative to the question of food providing sufficient n-3 fatty acids to meet current recommendations is whether fish production and consumption globally is adequate. Data from the Food and Agriculture Organization of the United Nations indicate that in 2003, average apparent per capita consumption of fish (and crustaceans and mollusks) was estimated to be 16.5 kg/year, which corresponds to about 45 g/day (1.5 oz/day) (28). The latter estimate conveys that seafood consumption meets current guidelines for fish consumption (ie, 10.5 oz/week, or about two servings per week). However, the Food and Agriculture Organization estimate includes nonfish seafood and an unknown proportion of nonfatty fish. Based on fish consumption data for the United States, it is apparent that intake does not meet recommendations for

Table. Fatty acid profile[a] (per amount [g] of fish or supplement to achieve 600 mg docosahexaenoic acid)

Lipids (1-g unit)	Atlantic farmed	Atlantic wild	Coho farmed	Coho wild	DHASCO-T[b]
Amount of product (g)	41.5	42.4	69.4	91.7	1.5
Fatty acids, total saturated	1.039	0.533	1.349	0.967	0.449
4:0					
6:0					
8:0					0.013
10:0					0.015
12:0					0.040
14:0	0.237	0.075	0.214	0.138	0.182
16:0	0.620	0.343	0.815	0.626	0.192
18:0	0.131	0.115	0.229	0.145	
20:0					
22:0					0.003
24:0					0.002
Fatty acids, total monounsaturated	1.839	1.144	2.511	1.450	0.338
14:1 undifferentiated					0.002
16:1 undifferentiated	0.318	0.137	0.335	0.249	0.020
18:1 undifferentiated	0.849	0.734	1.280	0.789	0.314
20:1	0.568	0.121	0.382	0.252	
22:1 undifferentiated		0.152	0.462	0.140	
Fatty acids, total polyunsaturated	1.837	1.381	1.362	1.167	0.634
18:2 undifferentiated	0.276	0.093	0.259	0.051	0.018
18:3 undifferentiated	0.047	0.160	0.053	0.050	
18:4	0.076	0.045	0.082	0.048	
20:4 undifferentiated	0.528	0.145	0.065	0.020	
20:5 n-3 (EPA[c])	0.286	0.174	0.283	0.368	
22:4 n-6					
22:5 n-3 (DPA[d])		0.156			0.003
22:5 n-6					
22:6 n-3 (DHA[e])	0.605	0.606	0.604	0.603	0.605

[a]Sources for fatty acid profiles: US Department of Agriculture National Nutrient Database (fish); (32) algal oil (DHASCO-T).
[b]DHASCO-T=Docosahexaenoic Acid Single Cell Oil (Martek Biosciences Corp, Columbia, MD).
[c]EPA=eicosapentaenoic acid.
[d]DPA=docosapentaenoic acid.
[e]DHA=docosahexaenoic acid.

either fish or EPA and DHA. Consequently, to meet recommendations for long-chain n-3 fatty acids in the United States, fatty fish intake must increase, which corresponds to increasing availability in the marketplace. This translates to a pressing question, which is: Are fatty fish stocks and production capacity sufficient to do this? If not, the question looms as to what are the alternatives for meeting EPA and DHA recommendations.

There is an expanding list of fortified foods and supplements that provide long-chain n-3 fatty acids. Such products are making it easier to meet long-chain n-3 fatty acid targets (29). Fortified foods contain varying amounts of EPA and DHA, depending on the source of these fatty acids. If ALA is used to fortify rations fed to nonruminants (ie, chickens and pigs), the meat and eggs produced by these animals will be enriched with this fatty acid (30). Obviously, if fish oil is used as a source, the fortified food will provide long-chain n-3 fatty acids (31). If algae are the source, then the fortified foods will be high in DHA (as algae are a rich source of DHA) (32,33).

In a carefully conducted study by Hoffman and colleagues (34), published in this issue of the *Journal of the American Dietetic Association*, nutrient (ie, DHA) availability of algal-oil capsules was compared with cooked salmon. Fatty acid analyses of plasma erythrocytes and phospholipids demonstrated substantial and equivalent increases in DHA in healthy individuals fed 600 mg/day DHA from salmon or algal oil. Bioavailability assessments concluded that equivalent amounts of DHA were available from both sources for incorporation into plasma erythrocytes and phospholipids. While this is a key physiological observation, it is necessary to highlight that plasma erythrocyte and phospholipid EPA and DPA levels increased in the salmon group only, an effect reflective of the fatty acid profiles of salmon (both farmed and wild) vs algal oil (Table). This is important when choosing a source of n-3 fatty acids to consume. The nutrient profile of a food vs a supplement should also be considered when making a decision about how to include a target nutrient in the diet. Along these lines, fish is an excellent source of protein, vitamins, and minerals, which are not present in algae. Moreover, fish is recommended as an alternative protein source for fatty red meats that are high in saturated fat. Thus, in addition to serving as "food vehicle" for meeting current recommendations for long-chain n-3 fatty acids, substituting fish for high saturated fat pro-

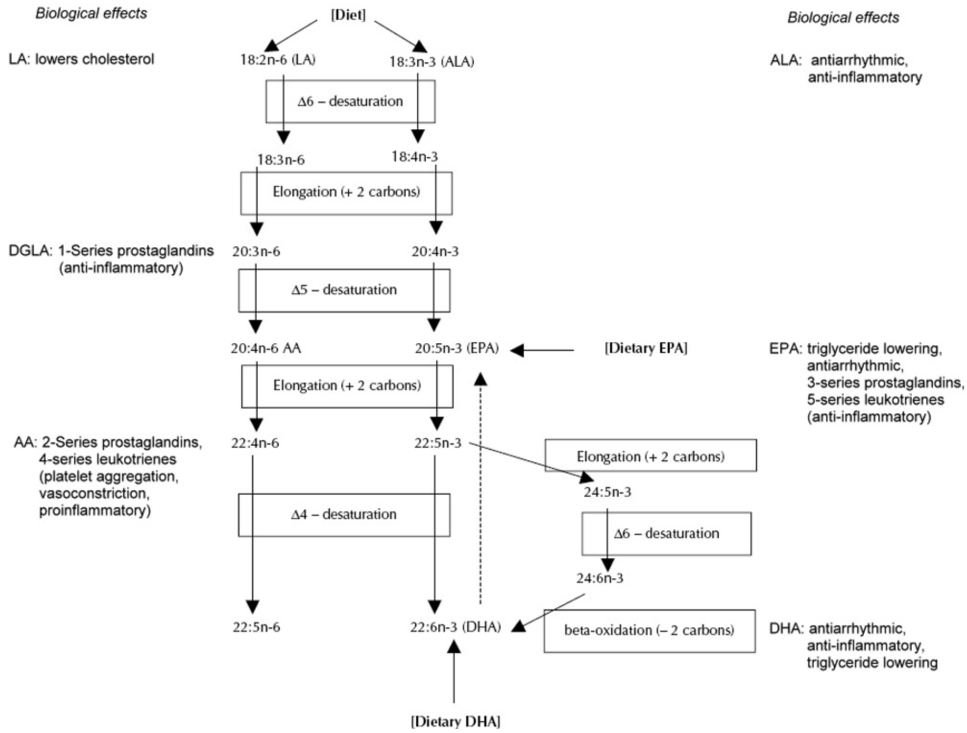

Figure. Metabolic conversion and biological effects of n-6 and n-3 polyunsaturated fatty acids. Dashed line indicates retroconversion. AA=arachidonic acid. ALA=α-linolenic acid. DGLA=dihomo-γ-linolenic acid. DHA=docosahexaenoic acid. EPA=eicosapentaenoic acid. LA=linoleic acid. Modified from Holub (41): "Clinical nutrition: 4. Omega-3 fatty acids in cardiovascular care"—Reprinted from *CMAJ* 05-Ma-02; 166(5), Page(s) 608-615 by permission of the publisher. © 2002 Canadian Medical Association.

tein foods can facilitate meeting dietary recommendations for saturated fat. Consequently, fish "brings to the table" more than just n-3 fatty acids, which is the underpinning of achieving nutrient adequacy with nutrient-dense foods.

n-3 FATTY ACIDS AND HEALTH BENEFITS

Current dietary recommendation of two servings of fish, preferably fatty fish, per week, or 500 mg/day EPA+DHA (7) is based on evidence from epidemiologic and clinical studies demonstrating cardiovascular health benefits from regular fish or fish-oil consumption. Collective analyses of prospective cohort studies and randomized clinical trials clearly demonstrate that modest consumption of n-3 fatty acids (ie, <500 mg/day EPA+DHA) lowers risk of death from coronary heart disease (23). Both EPA and DHA improve numerous cardiovascular risk factors and these have been the subject of several comprehensive scientific reviews (9,23,35). Briefly, EPA+DHA in a dose-dependent manner can lower plasma triglycerides, heart rate, and blood pressure, and have antiarrhythmic and antithrombotic effects (23).

In addition to cardiovascular health, several studies have shown that supplementation with EPA and/or DHA can have antidepressant and mood-stabilizing effects, prompting recommendations for clinical use of n-3 fatty acids in the prevention and/or treatment of psychiatric disorders. The American Psychiatric Association has approved recommendations for supplementation in depressed individuals of 1 g/day EPA+DHA, but advises against substitution of n-3 fatty acids with antidepressants (36). There also is increasing interest in the role of n-3 fatty acids in the treatment and prevention of behavioral disorders, such as attention deficit hyperactivity disorder (37), and onset of age-related neurodegenerative diseases (38). While research in these areas is promising, there is uncertainty as to the mechanism of action of n-3 fatty acids with respect to mental health, and whether EPA or DHA is responsible for these effects. In comparison, clear evidence exists for the role of DHA in neural and visual development and function, especially during pregnancy, lactation, and infancy. Low levels of DHA are associated with impaired visual acuity and brain development in infants (39).

SPECIFIC POPULATION CONSIDERATIONS: THE VEGAN

It is evident that current consumption of long-chain n-3 fatty acids and fish is markedly less than current recommendations for optimal health. Thus, the question arises as to how to close this intake "gap." For individuals with a low intake of EPA and DHA, algal supplements can be a suitable alternative, and for vegans they are ideal. Individuals who consume a vegan diet are the most obvious population to benefit from algal supplements because of their unique dietary pattern, which restricts all animal products, including dairy and eggs. This raises questions about the fatty acid intake in this population and how best to achieve an optimal essential fatty acid status (40).

There are several issues to consider before recommendations for use of these supplements can be made.

The fatty acids, linoleic acid and ALA, are essential nutrients for human health. Linoleic acid and ALA undergo a series of elongation and desaturation steps to produce arachidonic acid and EPA, respectively [Figure; (41)]. EPA is then elongated to DHA, however, this occurs at a very low rate (42,43). In humans, conversion of linoleic acid to arachidonic acid is more efficient than that of ALA to EPA and DHA. Production of arachidonic acid and EPA is further regulated by competition between linoleic acid and ALA for desaturase enzymes that catalyze their conversion to these long-chain fatty acids. Additional competition between arachidonic acid and EPA for cyclooxygenases and lipoxygenases can substantially impact eicosanoid production. Eicosanoids derived from arachidonic acid are proinflammatory and proaggregatory, and promote vasoconstriction and cell proliferation. By comparison, EPA-derived eicosanoids are less inflammatory and less proaggregatory. Thus, a diet higher in ALA and EPA (as provided by fish) can limit overproduction of proinflammatory and aggregatory eicosanoids.

EPA can directly influence arachidonic acid biosynthesis from linoleic acid by inhibiting $\Delta 6$ desaturase activity (the rate-limiting enzyme for metabolism of linoleic acid), although this effect is blunted with high intakes of linoleic acid (44). In addition, DHA has been shown to reduce arachidonic acid levels via the same mechanism (45). This is important in the context of whether tissue arachidonic acid levels are linked to risk of coronary disease, because arachidonic acid is the parent molecule for many inflammatory cytokines. However, a recent study conducted by Harris and colleagues (46) that evaluated tissue levels of arachidonic acid and risk for coronary heart disease events reported that there was no consistent relationship between risk and arachidonic acid levels.

While vegan diets do not differ from omnivorous and vegetarian diets with respect to quantity of linoleic acid and ALA, they are essentially devoid of EPA and DHA (47). Thus, long-chain n-3 fatty acid (EPA and DHA) levels are reduced in plasma phospholipids and erythrocytes from vegans compared to vegetarians and omnivores (48,49). This has significant implications for pregnant women and nursing mothers who must deliver these fatty acids to their developing fetus or child. Algal supplements that are rich in DHA also will provide some EPA via retroconversion of DHA to EPA. However, this metabolic pathway is highly inefficient; <10% to 11% of DHA is retroconverted to EPA (47). Therefore, in addition to a DHA source, registered dietitians should encourage individuals following a vegan diet to consume foods that are rich in ALA. However, for vegans who do not consume any preformed sources of EPA and DHA, further research is needed before specific recommendations can be made specifically for DHA (ie, that would be delivered as an algal supplement). In particular, it will be important to establish the health benefits associated with DHA supplementation in this population.

SUMMARY

In summary, for all fatty acids, a food-based approach is recommended. For individuals who do not eat fish, other options can be pursued, such as "designer" foods high in these long-chain n-3 fatty acids, foods fortified with these fatty acids, or even supplements (29,50). DHA-rich algal supplements are an alternative source of DHA vs fish or fish oil, especially for vegans, and as Hoffman and colleagues (34) have shown, are equivalent with respect to bioavailability. This is one criterion that should be assessed for supplements per guidance given in the ADA position paper on fortification and nutritional supplements (1). Although it would seem that because bioavailability is similar between DHA supplements and food sources of DHA, functionality also would be comparable, but this needs to be evaluated. Another important consideration relates to nutrient (ie, fatty acid) balance. Specifically, high doses of DHA have been shown to inhibit elongases and desaturases, which in turn affect the metabolism of other n-3 and n-6 fatty acids. Important questions remain about the optimal amount of DHA that should be recommended and, notably, how DHA affects the metabolism of C18 and longer n-6 and n-3 fatty acids, and whether this might result in any adverse health outcomes. Based on the available evidence, a DHA supplement provided in the appropriate dose (for which there currently are no recommendations) would be expected to confer health benefits, especially in individuals who do not eat fish. The expertise of registered dietitians is needed to communicate sound nutrition information about fatty acid recommendations, and to help people achieve these through a food-based approach or via supplements, if warranted. However, in the absence of specific recommendations for EPA and DHA individually at the present time, this is challenging. Thus, in the meantime, registered dietitians should play a key role in assuring that individuals do not overconsume DHA from algal supplements.

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