CHAPTER 4

# Fats

In comparison to nonvegetarians, on average vegetarians have lower intakes of total fat and saturated fat, and similar or higher intakes of linoleic acid (LA, 18:2n-6) and alpha-linolenic acid (ALA, 18:3n-3).[1] These dietary differences may explain the typically lower serum cholesterol levels of vegetarians. However, concerns have been raised about the lack of long-chain omega-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA, 20:5n-3), and docosahexaenoic acid (DHA, 22:6n-3), found primarily in certain types of cold-water fatty fish, in vegetarian diets. EPA and DHA have potential protective effects against a number of conditions including sudden cardiac death, Alzheimer's disease, and osteoporosis. Studies of neuronal functioning and visual acuity suggest that consumption of DHA may provide some advantage for infants; this may be an important benefit of breastfeeding because breast milk contains more DHA than unfortified infant formula. This chapter focuses on the essential fatty acids LA and ALA, and on EPA and DHA.

## LA AND ALA

### Functions of LA and ALA and Dietary Recommendations

Humans are unable to synthesize omega-6 or omega-3 fatty acids, so the parent fatty compounds for each of these fatty acid categories, LA and ALA, respectively, are considered essential. They function as integral components of phospholipids and modulate cell function by acting as intracellular mediators of signal transduction or modulators of cell–cell interactions. They are required for growth, reproduction, maintenance of skin, and regulation of cholesterol metabolism. Although essential fatty acid deficiency is rarely seen in humans, in animal models deficiency produces reduced growth rate, dermatitis, infertility, depressed inflammatory responses, erythrocyte fragility, and liver and kidney abnormalities.[2] Evidence for ALA's essentiality in humans was first noted $<$30 years ago.[3]

Both LA and ALA appear to play roles in decreased risk of cardiovascular disease. LA consumption in place of saturated fat leads to a reduction in serum total and LDL cholesterol even beyond that which would be expected from simply reducing dietary saturated fat.[4] Higher LA

intakes are associated with lower blood pressure[5] and a reduced risk of diabetes.[6] ALA intake is associated with a reduced risk of coronary artery disease,[7] myocardial infarction,[8,9] and fatal heart disease.[10,11] This risk reduction is due to multiple mechanisms including effects on platelet function, inflammation, endothelial cell function, arterial compliance, and ALA's role in reducing arrhythmia.[12] In the Nurses' Health Study, women in the highest two quintiles of ALA intake (median 0.60% and 0.74% of energy) had a 38–40% reduced risk of sudden cardiac death.[13] ALA intake may be especially important when intakes of EPA and DHA are low.[14]

Although some meta-analyses have reported an increased risk of prostate cancer with higher intakes or blood levels of ALA,[15,16] the relationship has been described as weak with heterogeneity across studies and the possibility of publication bias. Not all studies find this increased risk,[17] with one report[18] finding no greater risk of developing prostate cancer in general but an increased risk of developing advanced prostate cancer with higher ALA intake. To add to the uncertainty, a recent meta-analysis reported a significantly decreased risk of prostate cancer in those consuming >1.5 g/d of ALA compared to those consuming lower amounts.[19] This area requires more investigation, especially in those whose ALA intake is from plant sources. The source of ALA, whether from meat or from plant sources, does not appear to affect risk of prostate cancer.[18]

LA and ALA can be endogenously converted to longer carbon chain PUFA (Figure 4-1). LA, via conversion to arachidonic acid (AA), is the precursor to a variety of eicosanoids (thromboxanes, leukotrienes, prostaglandins, prostacyclins), some of which are proinflammatory, vasoconstrictive, and/or promoters of platelet aggregation,[20–22] whereas others are anti-inflammatory and

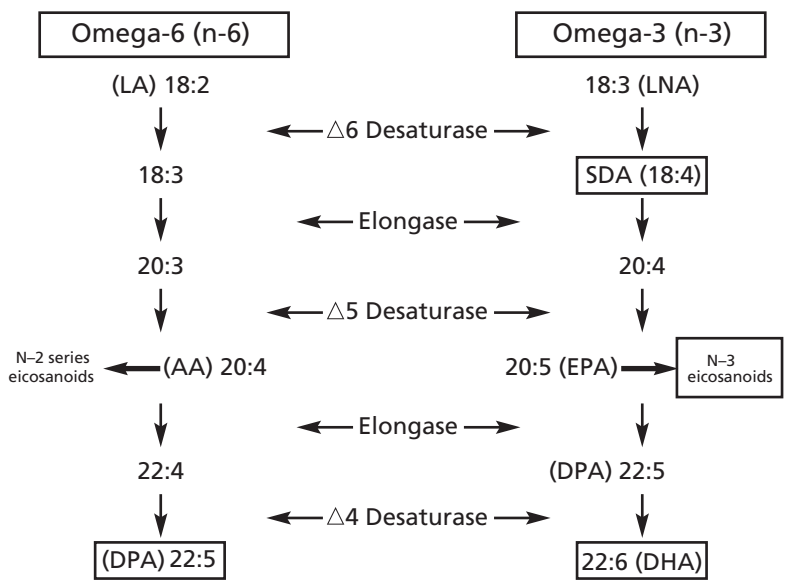


**Figure 4-1** Metabolism of n-6 and n-3 fatty acids and eicosanoid production. Adapted from Arterburn et al.[69]

inhibit platelet aggregation.[23–25] ALA, via conversion to EPA, is the precursor to the n-3 series eicosanoids, which are anti-inflammatory[24] and tend to reduce coronary heart disease (CHD) risk and prevent arrhythmias and thrombosis.[26] EPA can be further modified to produce DHA.

The Institute of Medicine (IOM) has established adequate intakes (AI) for both essential fatty acids. The AI for LA for adults is 12 g/d for women and 17 g/d for men. The AI for ALA is 1.1 g/d for women and 1.6 g/d for men.[27] The IOM has also set an acceptable macronutrient distribution range (AMDR) for LA of 5–10% of energy and for ALA of 0.6–1.2% of energy.[27] Up to 10% of the AMDR for ALA can be from EPA and/or DHA (0.06–0.12% of energy).[27] This recommendation is based on median consumption of EPA and DHA in the United States.

Because of concerns that high intakes of LA may limit conversion of ALA to EPA and DHA, contribute to overproduction of proinflammatory eicosanoids, and increase susceptibility of low-density lipoprotein cholesterol (LDL-C) to oxidation,[12,28] some groups have recommended intakes of omega-6 PUFAs that are lower than current U.S. recommendations.[29] In contrast, the American Heart Association supports an intake of at least 5–10% of energy from omega-6-PUFAs and states that "to reduce omega-6 PUFA intakes from their current levels would be more likely to increase than to decrease risk for CHD."[30] A rationale for this position is that the production of AA from LA is tightly regulated so that even wide variations in dietary LA intake would not markedly alter tissue AA levels, inflammation, or other proatherogenic effects.[31–33] In addition, questions have been raised about the extent and significance of LDL-C oxidation at higher LA intakes.[30] The effect of LA on ALA conversion to EPA is discounted because of the already limited extent of this conversion.[30] This effect, however, may be more significant in populations consuming little or no EPA or DHA.[27]

## Dietary Intakes of LA and ALA

The median daily intake of LA in the United States is approximately 12 to 17 g for men and 9 to 11 g for women.[27] Food sources of LA include nuts, seeds, and vegetable oils such as soybean, corn, safflower, and sunflower oil. LA accounts for 85–90% of dietary omega-6 fatty acid intake.[30]

Median daily ALA intakes in adults in the United States are approximately 1.2 to 1.6 g for men and 0.9 to 1.1 g for women.[27] Sources of ALA include flaxseed, flaxseed oil, canola oil, hempseed oil, soybean oil, and walnuts. Although flaxseed oil is much higher in ALA than soybean oil, the largest source of ALA in the U.S. diet is soybean oil because it is consumed so extensively.[34]

## Vegetarian LA and ALA Intake and Status

LA requirements are easily met even by vegetarians on relatively low-fat diets, as the LA intake of vegetarians is often at or above the AI.[1, 35–40] (Appendix F). Although there are few rich plant sources of ALA, data indicate that vegetarian intake is typically at or above the AI for ALA.[1,35,37,38,40–44]

The proportion of LA in platelets, erythrocytes, and plasma lipid fractions is typically higher in vegetarians and vegans than in nonvegetarians.[39,40,45–49] The proportion of ALA in vegetarians and vegans is higher[39,47,50] or similar to nonvegetarians.[40,49]

## Meeting Recommendations for Essential Fatty Acids with Vegetarian Diets

Table 4-1 provides information on vegetarian sources of LA and ALA and the amounts of each food source that would be needed to meet the AI for ALA. By choosing a variety of foods, including plant oils, nuts, seeds, and vegetables, vegetarians can have adequate intakes of both LA and ALA. Even relatively small amounts of specific foods that are high in ALA can be used to meet the AI for this fatty acid. For example, a little more than half a teaspoon of flaxseed oil or 1¼ tablespoons of canola oil would supply the AI for ALA for an adult man.

**Table 4-1** LA and ALA Content of Foods

| *Food* | *LA Content (g)* | *ALA Content (g)* | *Amount needed to provide 1.6 g ALA** | *Amount needed to provide 1.1 g ALA** |
|---|---|---|---|---|
| **Oils** (1 tbsp) | | | | |
| Almond oil | 2.366 | 0 | | |
| Apricot kernel oil | 3.985 | 0 | | |
| Avocado oil | 1.754 | 0.134 | 12 tbsp | 8 tbsp. |
| Canola oil | 2.61 | 1.279 | 1.25 tbsp | 0.9 tbsp |
| Corn oil | 7.239 | 0.158 | 10 tbsp | 7 tbsp |
| Cottonseed oil | 7.004 | 0.027 | 59 tbsp | 41 tbsp |
| Flaxseed oil | 1.727 | 7.249 | 0.2 tbsp | 0.15 tbsp |
| Grapeseed oil | 9.466 | 0.014 | 114 tbsp | 79 tbsp |
| Hazelnut oil | 1.374 | 0 | | |
| Hempseed oil | 7.98 | 2.24 | 0.7 tbsp | 0.5 tbsp |
| Mustard oil | 2.146 | 0.826 | 1.9 tbsp | 1.3 tbsp |
| Olive oil | 1.318 | 0.103 | 15.5 tbsp | 10.7 tbsp |
| Palm oil | 1.238 | 0.027 | 59 tbsp | 41 tbsp |
| Peanut oil | 4.320 | 0 | | |
| Poppy seed oil | 8.486 | 0 | | |
| Rice bran oil | 4.542 | 0.218 | 7.3 tbsp | 5 tbsp |
| Safflower oil | 1.952 | 0 | | |
| Sesame oil | 5.617 | 0.041 | 39 tbsp | 27 tbsp |
| Soybean oil | 6.857 | 0.923 | 1.7 tbsp | 1.2 tbsp |
| Sunflower oil, high oleic | 0.505 | 0.027 | 59 tbsp | 41 tbsp |
| Walnut oil | 7.194 | 1.414 | 1.1 tbsp | 0.8 tbsp |
| Wheat germ oil | 7.453 | 0.938 | 1.7 tbsp | 1.1 tbsp |
| **Nuts and Seeds** (2 tbsp) | | | | |
| Black walnuts | 5.160 | 0.312 | 0.6 cup | 0.4 cup |
| English walnuts | 5.668 | 1.352 | 2.4 tbsp | 1.6 tbsp |

*(Table 4-1. continued)*

*(Table 4-1 Continued)*

| Food | LA Content (g) | ALA Content (g) | Amount needed to provide 1.6 g ALA* | Amount needed to provide 1.1 g ALA* |
|---|---|---|---|---|
| Flax seeds, ground | 0.826 | 3.194 | 1 tbsp | 0.7 tbsp |
| Flax seeds, whole† | 1.216 | 4.700 | 0.7 tbsp | 0.5 tbsp |
| Pumpkin seeds | 2.862 | 0.016 | 12.5 cups | 8.6 cups |
| **Fruits and Vegetables** | | | | |
| Avocado, ½ cup | 1.248 | 0.080 | 10 cups | 7 cups |
| Broccoli rabe, cooked, 1 cup | 0.034 | 0.221 | 7,2 cups | 5 cups |
| Broccoli, Chinese, cooked, 1 cup | 0.067 | 0.227 | 7 cups | 4.8 cups |
| Broccoli, cooked, 1 cup | 0.080 | 0.186 | 8.6 cups | 5.9 cups |
| Collards, cooked, 1 cup | 0.133 | 0.177 | 9 cups | 6.2 cups |
| Kale, cooked, 1 cup | 0.103 | 0.134 | 11.9 cups | 8.2 cups |
| **Soy Products** | | | | |
| Soy burger, 1 patty | 1.358 | 0.057 | 28 patties | 19 patties |
| Soybeans, 1 cup | 7.680 | 1.029 | 1.6 cup | 1.1 cups |
| Soy nuts, 2 tbsp | 2.610 | 0.350 | 9 tbsp | 6 tbsp |
| Tempeh, ½ cup | 2.981 | 0.183 | 4.4 cups | 3 cups |
| Tofu, firm, ½ cup | 2.013 | 0.228 | 3.5 cups | 2.4 cups |
| **Animal Products** | | | | |
| Egg, 1 large | 0.574 | 0.017 | 94 eggs | 65 eggs |
| Milk, 1 cup | 0.066 | 0.010 | 160 cups | 110 cups |
| **Fortified Foods** | | | | |
| Flax cereal, ¾ cup | 1.300 | 0.091–1.000 | 2–23 cups | 1.5–16 cups |
| Margarine with flaxseed oil, 1 tbsp | 1.952 | 0.474 | 3.4 tbsp | 2.3 tbsp |
| Mayonnaise with flaxseed oil, 1 tbsp | 1.1 | 0.500 | 3.2 tbsp | 2.2 tbsp |
| Peanut butter with flaxseed oil, 1 tbsp | 0.650 | 0.500 | 3.2 tbsp | 2.2 tbsp |

*1.6 g and 1.1 g are the AI for ALA for men and women, respectively.

†Whole flaxseeds are not well digested; their alpha-linolenic acid has low bioavailability.[153]

*Source*: Data from USDA National Nutrient Database for Standard Reference, Release 22, 2009 and manufacturers' information.

Animal studies suggest that LA can actually be synthesized in humans from the fatty acid hexadecadienoate (16:2 n-6), which represents 1–2% of total fatty acids in common edible green vegetables including broccoli and spinach, and ALA can be synthesized from the fatty acid hexadecatrienoate (16:3 n-3), which is present in edible green vegetables at up to 14% of total fatty acids.[51] The endogenous synthesis of these essential fatty acids could play a role in populations consuming vegetarian diets,[52] although no information is available on rates of synthesis in humans.

## ARACHIDONIC ACID

Arachidonic acid (AA) can be endogenously produced through the desaturation and elongation of LA, similar to the way that EPA is made from ALA. Rates of conversion of LA to AA are very low; <0.1% of dietary LA is converted to AA.[53] Typical intake of AA by nonvegetarians is limited (approximately 150 mg/d) and mainly comes from meat, eggs, and some fish.[30] Although plant foods do not contain AA and intakes of AA by vegans have been reported as nondetectable,[37] it is not clear that AA tissue or serum content in vegetarians is different from that of nonvegetarians. Some studies show that tissues or cells from vegetarians and vegans contain a lower proportion of AA,[39,45,47,50] whereas others show little or no difference between vegetarians or vegans and nonvegetarians.[39,40,49]

Two intervention studies demonstrate the conflicting nature of this literature; in one, AA levels were reduced significantly when omnivore subjects were placed on a vegan diet for 3 to 5 months after an initial 7- to 10-day fast, but levels returned to their initial values when subjects consumed a lacto vegetarian diet.[54] In the other study, when meat eaters were placed on a vegetarian diet, AA levels increased.[55]

## EPA AND DHA

Recently, calls have been made for the IOM to establish specific recommendations for the individual long-chain omega-3 fatty acids DHA and EPA.[56,57] New evidence of DHA and EPA's effects on risk of fatal CHD as well as limited conversion of ALA to DHA and EPA have been proposed as a rationale for establishing Dietary Reference Intakes (DRIs) for these fatty acids.[56]

In 2002, the IOM concluded that only limited data were available to define a DRI for EPA and DHA. EPA and DHA are not currently considered essential nutrients because EPA can be synthesized from ALA, and DHA from EPA (DHA can be retroconverted into EPA)[52,58–60] (Figure 4-1). DHA is believed to be important for brain development and retinal function[61–63] and possibly for reproduction.[64] EPA and DHA reduce the risk of cardiac mortality.[56] Depressed DHA levels have been seen in those with Alzheimer's disease,[65] depression,[66] attention deficit disorder,[67] and schizophrenia.[68] DHA is found in low levels in most cells of the body, in higher levels in sperm and testes, and in very high levels in the brain and retina.[69] Adipose tissue stores of EPA and DHA are very low, suggesting a limited storage of these fatty acids and a need for a regular dietary supply.[69]

### Effects of EPA and DHA on CHD

Initial speculation about the cardiovascular benefits of omega-3 fatty acids stemmed from the observation that Eskimos, who consume a diet that is high in omega-3 fatty acids, have a very

low rate of CHD despite high total fat intakes.[70] The Greenland Eskimos consume as much as 10 to 11 g of omega-3 fatty acids per day,[71] much more than the 0.8 g/d, and 0.1 to 0.2 g/d consumed by Danish whites [71] and persons in the United States, respectively. [72] Cardioprotective effects of DHA and EPA include decreased risk of arrhythmia,[73] lower plasma triglyceride levels,[74] reduced inflammatory responses,[75] improved endothelial function,[76] reduced heart rate,[77] and reduced platelet aggregation.[78,79] EPA and DHA supplementation has reduced blood pressure in hypertensive individuals.[75] High doses of EPA + DHA (3 to 4 g/d) appear effective in treatment of severe and moderate hypertriglyceridemia.[74] These mechanisms, especially the reduction in cardiac arrhythmias, are likely to account for the reduced risk of sudden cardiac death associated with higher intakes of DHA and EPA.[12,56] Other roles of DHA + EPA in cardiovascular disease such as effects on atherosclerosis progression and a reduction in risk of nonfatal events and stroke are less definitive compared with EPA and DHA's effects on cardiac mortality.[56,80]

Several intervention studies have demonstrated the benefits of omega-3 fatty acids for reducing chronic disease risk.[81–83] For example, in the GISSI Prevenzione trial, patients suffering a previous myocardial infarction who were given 1 g of omega-3 PUFAs (EPA + DHA from fish oil) per day experienced a 45% reduced risk of sudden cardiac death over a 3.5-year period in comparison to the placebo group.[81]

One group estimates that cardiac mortality is reduced by approximately 35% from moderate EPA and DHA consumption in the range of 250 to 500 mg/d.[56] Intakes of approximately 500 mg/d appear to provide the greatest protection according to a recent meta-analysis limited to prospective studies in the United States.[84]

## Other Health Effects of EPA and DHA

A number of studies and a recent meta-analysis have found that fish and foods rich in omega-3 fatty acids were associated with a reduced risk of age-related macular degeneration.[85] Some studies suggest that this association is strongest in those consuming lower amounts of LA.[86,87] At this point, results, although promising, do not provide enough evidence to develop recommendations for EPA and DHA based on their potential role in preventing age-related macular degeneration.[85]

Chapter 11 provides information on DHA's role in pregnancy outcome, cognitive development, and visual development.

Interest in DHA's role in reduction of the risk of dementia and Alzheimer's disease arose because DHA is concentrated in many of the most active areas of the brain, and DHA content of the brain decreases with age in animals.[56] Epidemiologic studies have found that higher DHA intakes are associated with a lower risk of Alzheimer's disease,[88] and higher DHA + EPA intakes were associated with a postponement of cognitive decline in elderly men.[89] Higher plasma EPA and DHA levels or EPA levels alone have been associated with a marked reduction in risk of developing dementia and a lower decline in verbal fluency.[65,90,91] One randomized controlled trial found some positive effects of supplemental EPA and DHA in patients with very mild Alzheimer's disease, although overall little effect was seen.[92] Additional trials are being conducted.[56]

Omega-3 fatty acids may play a role in treatment of depressive illness, although study results are inconsistent. For example, a meta-analysis of 12 randomized trials of omega-3 fatty acids in treatment of depression found little evidence of benefit.[93] Another meta-analysis of 10 double-

blind, placebo-controlled trials of omega-3 fatty acid in treatment of mood disorders found a significant antidepressive effect.[94] Weighted analysis of omega-3 status in those with mental health problems found no significant differences from controls.[95]

Omega-3 fatty acids, mainly DHA, also appear to play a role in osteoporosis prevention, although there have only been limited studies in this area.[96]

## Recommendations for EPA and DHA

The DRI report published in 2002 did not include a recommended dietary allowance for EPA or DHA but did state that up to 10% of the AMDR for ALA can be from EPA and/or DHA (0.06–0.12% of energy).[27] This range was based on median consumption of EPA and DHA in the United States.

Many expert groups and health agencies have issued recommendations for these omega-3 fatty acids or for fish intakes to provide EPA and DHA. Table 4-2 provides examples of these recommendations. Typically, recommendations are near 500 mg/d with higher amounts sometimes recommended for secondary prevention of CHD.[97]

## Dietary Intakes of EPA and DHA

The median intake of EPA by adults in the United States ranges from 4 mg/d to 7 mg/d; median DHA intakes are between 66 mg/d and 93 mg/d for men and 52 mg/d to 69 mg/d for women.[27]

**Table 4-2** Examples of Recommendations for Omega-3 and Omega-6 Fatty Acid Intakes for Healthy Adults

| | *ALA* | *EPA + DHA* | *Total Omega-3 Fatty Acids* | *Total Omega-6 Fatty Acids* |
|---|---|---|---|---|
| U.S. Dietary Reference Intakes[27] | 1.6 g/d Men<br>1.1 g/d Women | 0.06–0.12% of calories | 0.6–1.2% of calories | 5–10% of calories |
| American Heart Association[154] | | 450–500 mg* | | At least 5–10% of calories[30] |
| American Dietetic Association and Dietitians of Canada[12] | 0.6–1.2% of calories | 500 mg/d | | 3–10% of calories |
| United Kingdom[155] | | 450–500 mg* | | |
| Australia and New Zealand[156] | 1.3 g/d men<br>0.8 g/d women | 610 mg/d men<br>430 mg/d women | | 4–10% of calories |
| The Netherlands[157] | | 450–500 mg* | | |
| FAO/WHO[158] | | 450–500 mg* | 1–2% of calories | 5–8% of calories |

*Estimated amount of EPA + DHA in 2 servings of fish, preferably fatty fish, per week

**Table 4-3** DHA and EPA Content of Vegetarian Foods

| | *EPA (mg)* | *DHA (mg)* |
|---|---|---|
| **Animal Products** | | |
| Egg, 1 large | 2 | 0 |
| Eggs from chickens fed flax,[120] 1 egg | | 60–100 |
| Eggs from chickens fed microalgae,[120] 1 egg | | 100–150 |
| **Sea Vegetables** | | |
| Dulse, dried, 8 g[159] | 86.8 | |
| Kelp, dried, 8 g[159] | 63.4 | |
| Kelp, raw, 1/2 cup | 0.2 | 0 |
| Nori, dried, 8 g[159] | 198.2 | |
| Nori, raw, 1 sheet | 0.2 | 0 |
| Sea lettuce, dried, 8 g[160] | 2.4 | 7.1 |
| Sea spaghetti, dried, 8 g[159] | 42.7 | |
| Wakame, dried, 8 g[159] | 79.2 | |
| Wakame, raw, ¼ cup | 74 | 0 |
| **Foods fortified with microalgae-derived DHA** | | |
| DHA-fortified cheese, 1 ounce | 0 | 32 |
| DHA-fortified energy bar, 1 | 0 | 50 |
| DHA-fortified juice, 1 cup | 0 | 50 |
| DHA-fortified kefir beverage (dairy), 1 cup | 0 | 32 |
| DHA-fortified milk (dairy), 1 cup | 0 | 32 |
| DHA-fortified canola or olive oil, 1 tbsp | 0 | 25–32 |
| DHA-fortified powdered drink mix, 1 packet | 0 | 100 |
| DHA-fortified soymilk, 1 cup | 0 | 32 |
| DHA-fortified yogurt (dairy), 6 oz | | 32 |
| **Vegan Supplements** | | |
| Vegan DHA supplement, 1 capsule or soft gel | | 200–300 |
| Vegan DHA supplement, liquid, 1 dropper | | 300 |
| Vegan EPA + DHA supplement, 1 soft gel or capsule | 10–50 | 300–350 |

*Source*: Data from USDA National Nutrient Database for Standard Reference, Release 22, 2009 and manufacturers' information except where otherwise identified.

These intakes are based on dietary records and do not include supplements of EPA, DHA, or fish oil. Typically fish oil supplements are higher in EPA, whereas fish provides more DHA.[56] DHA and EPA both appear to be beneficial in terms of reductions of risk; it is not possible at this time to conclude whether the effects are due to primarily to DHA or to EPA or to a specific ratio of these two fatty acids. A ratio of EPA to DHA between 1:2 and 2:1 has been suggested.[56]

### Vegetarian DHA and EPA Sources and Intake

Mann et al reported mean daily DHA intakes by moderate meat eaters, lacto-ovo vegetarians, and vegans in Australia to be 70 mg, 10 mg, and 0 mg, respectively, and EPA intakes among these same groups to be 40 mg, 0 mg, and 0 mg.[39] Lacto-ovo vegetarian DHA intake was mainly from eggs. Several other studies including those in the United Kingdom[1,37] and Austria[40] have reported that vegans have very low or no detectable dietary EPA or DHA. DHA intakes of lacto-ovo vegetarians are slightly higher, but EPA intakes are often undetectable.

Vegetarian food sources of DHA and EPA typically contain limited amounts of these fatty acids and include sea vegetables, eggs, and foods fortified with microalgae-derived DHA. (Table 4-3). Sea vegetables mainly provide EPA; there is little information available on their DHA content. Foods fortified with microalgae-derived DHA typically contain 30 to 50 mg of DHA per serving. Microalgae-derived DHA is vegan, although it may be added to nonvegan as well as nonvegetarian foods.

### Vegetarian EPA and DHA Status

Most studies have found the proportion of EPA and DHA in blood and/or tissues to be lower in both lacto-ovo vegetarians and vegans compared to nonvegetarians[1,39,40,45–49] DHA proportions in erythrocytes, plasma, serum, platelet phospholipids, and erythrocyte phosphatidyl ethanolamine are typically $\geq$50% lower in vegans than in nonvegetarians.[1] DHA proportions in nonvegan vegetarians are also lower than in nonvegetarians although typically not as low as in vegans.[1]

Harris and von Schacky[98] proposed an "omega-3 index" based on the proportion of erythrocyte fatty acids as EPA + DHA. An omega-3 index of $\geq$8% was designated a cardioprotective target level, and an index of $\leq$4% was associated with the greatest risk of death from CHD. Two studies suggest that the estimated omega-3 index in vegans is >4%, whereas that of nonvegetarian controls is >4% but not at the cardioprotective target.[46,99]

Limited research suggests that DHA levels are lower in pregnant vegetarian women and in cord blood than in nonvegetarians.[41,48] Reddy et al found lower levels of DHA in breast milk of vegetarian women compared to omnivore women, although levels were higher than in unfortified infant formula.[48]

## ENDOGENOUS SYNTHESIS OF LONG-CHAIN PUFA

As Figure 4-1 indicates, EPA and DHA can be endogenously produced from ALA. A key question is whether or not this endogenous conversion is sufficient to meet needs. Nearly 20 studies of ALA conversion to EPA and DHA indicate that, generally, only about 5% of ALA is converted to EPA and <0.5% of ALA is converted to DHA.[53,100] Premenopausal women have

been shown to convert more ALA to EPA (2.5-fold more) and DHA (>200-fold more) than similarly aged men.[101] This is believed to be due to estrogen's effect on increasing the activity of the pathway and may help to explain the higher conversion rates seen in pregnancy.[100] During lactation, ALA supplementation does not appear to increase breast milk DHA levels, suggesting that conversion rates are not increased in lactation.[102]

Vegan diets are devoid of DHA, so the DHA found in blood and tissue of long-term vegans must be produced from dietary ALA. Based on the low endogenous synthesis rates of DHA that have been reported in nonvegetarians, vegans might be expected to have clinical symptoms of DHA deficiency; however, this does not seem to occur.[53] Vegans have low but stable plasma levels of DHA[49,50] that do not appear to fall according to the duration of a vegan diet,[49] suggesting there is some basal rate of conversion of ALA to DHA.[1] Additionally, vegans do not seem to markedly increase DHA production in response to ALA supplementation.[103] A lower rate of beta-oxidation of DHA in vegans has been proposed as one possibility to help explain their relative resistance to DHA deficiency.[53] This is certainly an area where additional research is needed.

The synthesis of EPA and DHA is affected by a number of dietary and metabolic factors. A major factor may be either total LA intake or the LA-to-ALA ratio in the diet. This will be discussed in later sections. Inadequate intakes of zinc, iron, and pyridoxine[104] may impair the synthesis of EPA and DHA. In addition, gestational diabetes appears to affect maternal synthesis of omega-3 fatty acids.[41,105]

## ENHANCEMENT OF VEGETARIAN DHA AND EPA STATUS

Vegetarians have been shown to have intakes of DHA and EPA that are typically lower than the amounts being recommended for optimal health and to have lower proportions of these fatty acids in blood and tissue than nonvegetarians. A number of possible alternatives could potentially increase vegetarians' blood and tissue concentrations of DHA and EPA. These include indirect supplementation through increased intake of ALA, enhanced endogenous synthesis through a reduction in trans-fat intake along with reduced total LA intake or an altered ratio of LA to ALA, and direct supplementation.

### ALA supplementation

One possible way to increase DHA and EPA synthesis is to provide more of the precursor fatty acid, ALA. It may not be possible, however, to ingest sufficient ALA to achieve blood and tissue levels of DHA + EPA at a cardioprotective target level. In observational studies of both vegetarians and nonvegetarians, intakes of ALA ranging from <1 g/d to >18 g/d result in larger proportions of EPA in plasma and cell lipids but no higher DHA proportions.[69,100,106,107]

Supplementation studies in which vegetarian diets are supplemented short term with ALA show some effect on EPA but not on DHA concentrations. For example, Li et al found that in response to a high-ALA diet in which vegetarian subjects consumed 15.4 g ALA/d for 6 weeks, the proportion of EPA in platelet phospholipids, plasma phospholipids, and plasma triacylglycerols increased while DHA remained unchanged.[43] Specifically, platelet phospholipid EPA increased from 0.2% to 0.5% of total fatty acids, plasma phospholipid EPA increased from 0.4% to 1.4%,

and plasma triacylglycerol EPA increased from 0.1% to 0.4%.[43] Sanders and Younger gave vegan subjects 6.5 g/d of ALA from flaxseed oil for 2 weeks and found an increase in plasma EPA but no effect on plasma DHA or platelet EPA or DHA.[108] Fokkema et al gave vegans 2 g of ALA from flaxseed oil for 4 weeks. No significant effect on EPA or DHA levels was seen.[103]

These limited results may be due to a buffering effect of the comparatively high stores of LA in adipose tissue that limit the efficacy of short-term manipulation of the relative amounts of LA and ALA.[1] In addition, due to the larger size of the plasma DHA pool compared to that of EPA, a longer time may be needed to detect changes in DHA levels following ALA supplementation.[107] Sanders concludes that longer-term, randomized controlled studies with a diet reduced in LA are needed in vegetarians.[1] At this point, however, ALA supplementation does not appear to markedly increase DHA and EPA levels.

An additional consideration is that, at an estimated conversion rate of 0.5% for ALA to DHA, even with a daily intake of 1000 mg of ALA, only about 5 mg/d of DHA would be produced, considerably below intakes that are recommended.[53] Even with conversion rates of 10%, a rate higher than has been seen in published studies, a daily intake of ALA of 2000 mg would be needed to produce even 200 mg of DHA.[53]

ALA supplementation, although apparently not effective at increasing DHA levels, may offer other benefits. In the Health Professionals Follow-up Study, in men with little or no EPA or DHA intake, each 1 g/d of ALA intake was associated with a 58% lower risk of nonfatal myocardial infarction and a 47% lower risk of total heart disease and of sudden death. These benefits were not seen in men with higher EPA and DHA intakes.[14] These results may be particularly relevant for those eating vegetarian diets.

Despite some positive findings, randomized controlled trials of ALA in cardiovascular disease[10,81,109] are limited in number and in quality, leaving many questions about ALA's ability to replace DHA + EPA in reducing risk of cardiac death.[110]

In addition, ALA may not duplicate all of the biologic effects of the longer chain omega-3 fatty acids. For example, ALA does not lower triglyceride levels, whereas long-chain omega-3 fatty acids do.[111] Also, fish intake and DHA and EPA intake were found to be associated with a reduced risk of developing macular degeneration,[85] whereas ALA intake was associated with an increased risk.[112] However, this may be because dairy and animal products are often the biggest contributors of ALA to the diet.[113,114] Finally, ALA does not appear as effective as DHA and EPA in terms of anti-inflammatory effects.[115]

Reports of a link between higher intakes or higher blood levels of ALA and prostate cancer[15,16] are concerning and suggest that further research is required before making strong recommendations, especially for those at risk of prostate cancer, to increase ALA intakes.

## Altered LA Intake

Dietary modifications have been proposed as a means to increase the rate of conversion of ALA to DHA and EPA. The rate-limiting step in the conversion of ALA to EPA and DHA is the reaction involving Δ6-desaturase (Figure 4-1). The affinity of this desaturase is greater for ALA than for LA, but higher concentrations of LA result in more conversion of LA to AA and a reduced conversion of ALA to EPA and DHA.[100] Proposed dietary modifications center on a

reduced dietary ratio of LA to ALA (achieved by decreasing LA intake or increasing ALA intake or both) and a reduced total intake of LA (with less focus on the LA-to-ALA ratio).

Some studies argue that a lower LA intake or a lower LA-to-ALA ratio will enhance synthesis of DHA and EPA from ALA. For example, Ezaki et al found that when elderly Japanese subjects switched from soybean oil to perilla oil (high in ALA), causing the LA-to-ALA ratio to go from 4:1 to 1:1, serum EPA, but not DHA increased after 3 months. Ten months were needed to see a 21% increase in DHA.[116] This study was rather unique because the LA-to-ALA ratio was so low and because of its long duration. Goyens et al[117] decreased the LA-to-ALA ratio of a control diet from 19:1 to 7:1 by either reducing LA while keeping ALA constant or by increasing ALA while keeping LA constant. The rate of conversion of ALA to EPA and DHA increased compared to the control diet when dietary ALA was increased while keeping LA constant but did not change when LA was reduced but ALA was kept constant. These results suggest that the amount of ALA and LA influence ALA conversion to EPA and DHA rather than the ratio of LA to ALA.

Other studies only find positive effects on the conversion of ALA to EPA but not on conversion to DHA with lower intakes of LA. Hussein et al reported increased phospholipid EPA but no change in DHA when the LA-to-ALA ratio went from 27.9:1 to 0.5:1.[118] In addition, Liou et al found that while plasma EPA content was reduced when dietary LA was increased from 3.8% to 10.5% of energy and the ratio of LA-to-ALA went from 4:1 to 10:1, DHA was unaffected.[119]

Although some have downplayed the reduction of dietary LA as a strategy to promote increased EPA and DHA production from ALA,[30] this reduction may offer benefits in those with few or no dietary sources of EPA and DHA,[27] as is typical of both vegetarian and vegan diets. Because of the need for enhanced conversion of ALA to DHA and EPA, vegetarians and vegans may benefit from an LA-to-ALA ratio that is toward the lower end of recommended ranges (5:1 to 10:1 are often suggested as reasonable ranges). Davis and Kris-Etherton[120] have suggested a ratio of 2:1 to 4:1 as optimal for vegetarians and others not consuming preformed EPA and DHA. As shown in Appendix F, the LA-to-ALA ratio in vegetarian diets is frequently higher than most recommendations.

To achieve a lower ratio of LA to ALA, vegetarians can strive for an intake of $<$1.5% to 2% of calories from ALA and 5.5–8% of calories from LA.[120] Several dietary modifications can help to achieve a lower LA-to-ALA ratio. These include choosing primary cooking oils that are rich in monounsaturated fats and consuming adequate amounts of ALA. Monounsaturated fats by themselves do not affect the LA-to-ALA ratio and, if substituted for oils high in LA, will result in a lower ratio. Foods high in monounsaturated fats include olive oil, canola oil, high-oleic sunflower oil, high oleic-safflower oil, nuts (except walnuts), peanuts, olives, and avocados.[120] Cooking oils that are high in LA, including safflower oil, grapeseed oil, sunflower oil, corn oil, cottonseed oil, and soybean oil (Table 4-1), should not be used as primary cooking oils.

Because of the importance of the question of the efficacy of alteration of LA intakes on EPA and DHA production in those with no dietary EPA or DHA, additional research on vegans and vegetarians is needed before conclusions can be made as to amounts of LA and ALA to recommend for this population.

## Dietary Trans-Fatty Acids

Dietary trans-fatty acids (TFA) may interfere with the conversion of ALA to EPA.[120,121] There are few data on the TFA intake of vegetarians. Draper et al reported that the daily intake of TFA by British male and female lacto-ovo vegetarians was 5.4 and 3.4 g, respectively, and for vegan males and females, it was 2.7 and 2.8 g.[42] In comparison, British male and female nonvegetarians reportedly consume 5.5 and 3.9 g of TFA/d, respectively.[42] In a Swedish study involving small numbers of subjects, nonvegetarian, lacto-vegetarian, and vegan diets reportedly contained 2.0%, 1.3%, and 0.5%, respectively, of their calories as TFA (only trans-octadecanoic acids were determined).[122] The level of TFA (18:n-9) in the subcutaneous fat of lacto-ovo vegetarians was reported by Crane et al to be about a third lower than that of nonvegetarians.[123] Finally, lacto-ovo vegetarians in Hong Kong had lower serum trans-fatty acids than nonvegetarians (0.03% compared with 0.5%).[47] Dietary TFA content is expected to decrease due to a reduction in TFA use by the food industry and to greater consumer awareness of health risks of TFA.[124,125]

## Direct Supplementation

Some researchers have recommended that vegans use a supplement or fortified foods to supply DHA and EPA because of limited conversion of ALA and because of EPA and DHA's many benefits,[57] although others question the benefit of EPA and DHA supplementation in vegetarians and vegans.[126]

Direct supplementation with DHA-rich microalgae has been suggested as a means to increase blood and tissue DHA and EPA content of vegetarians. Five studies have been reported in which preformed DHA from microalgae was provided to vegetarians. Geppert et al compared the effect of 940 mg of DHA and a placebo for 8 weeks.[127] The proportion of DHA in plasma phospholipids increased from 2.8% to 7.3% and EPA increased from 0.58% to 0.77%.[127] In another report from the same study, erythrocyte lipid DHA proportion increased from 4.4% to 7.9%.[44] Conquer and Holub gave vegetarian subjects 1620 mg of microalgal-derived DHA daily for 6 weeks. Serum phospholipid DHA proportion increased from 2.4% to 8.3% and platelet phospholipid DHA proportion increased from 1.2% to 3.9%. EPA levels also increased.[59] Postmenopausal vegetarian women who received 2.14 g of DHA daily for 6 weeks had higher plasma LDL EPA and DHA.[128] Most of these studies have used amounts of DHA higher than those typically recommended. A single study has reported, in abstract form, use of a lower dose of DHA. In a study of vegans, 200 mg/d of DHA for 3 months increased the proportion of DHA in plasma by 50%.[129] In nonvegetarians, DHA supplementation at doses above approximately 2 g/d produces little additional increase in plasma phospholipid DHA concentration.[69] When DHA is provided in combination with EPA, the DHA saturation dose appears to be 1.2 g/d.[69]

DHA supplementation appears to increase both the DHA and EPA content of blood and tissues. The production of EPA following DHA supplementation appears to be due to retroconversion.[53] EPA concentrations increase by approximately 0.4 g/100 g fatty acid for each 1 g of DHA intake.[69]

Microalgal-derived DHA supplements are available in liquid form and in vegan gelatin capsules. Foods fortified with microalgae-derived DHA include soymilk, energy bars, olive oil, and cow's milk. Table 4-3 provides information on vegetarian sources of DHA and EPA. In addition,

microalgal-derived DHA is used to fortify some cow's milk-based and soy-based infant formulas. DHA, whether provided as a supplement (oil in capsules) or in DHA-fortified foods, is bioavailable and well tolerated.[130]

Specific recommendations for amounts of DHA and EPA for vegetarians have not been developed. Guidelines developed for the general public (Table 4-2) may be helpful to vegetarians who opt to use microalgal sources of DHA (or DHA + EPA). Intakes of EPA + DHA up to 1 g/d and of 1.8 g/d of EPA have been used in large studies with no adverse effects.[81–83]

The creation of new plant cultivars that contain fatty acids that are more readily converted to EPA and DHA than ALA is or that contain plant-derived EPA and DHA is being studied,[131–133] suggesting the possibility of new sources of EPA and DHA for vegetarians. Stearidonic acid (SDA, 18:4 n-3) is one such fatty acid. SDA is a metabolic intermediate in the conversion of ALA to EPA. Compared to ALA, SDA was more efficiently converted to EPA, although it did not increase EPA concentrations as much as direct EPA supplementation did.[134,135] Limited research suggests that SDA offers promise as a surrogate for EPA in terms of some physiologic effects.[134]

## WOULD VEGETARIANS BENEFIT FROM EATING FISH?

The inefficient conversion of ALA into EPA and DHA, possible differences in biologic effects between ALA and the long-chain omega-3 PUFAs, and the difficulty of ingesting sufficient ALA have led to speculation that the addition of fish to a vegetarian diet might confer health benefits beyond those associated with vegetarian diets alone. The development of microalgae-derived DHA and EPA supplements and fortified foods would seem to eliminate any calls for vegetarians to eat fish or use fish oil. In addition, even if one assumes that fatty fish intake is associated with health benefits in omnivores, this does not imply that vegetarians will have similar benefits because factors common to vegetarian diets may result in similar outcomes even though they do not eat fish. One review of dietary fatty acid requirements states, "For vegans who do not consume any preformed sources of EPA and DHA, additional research is needed before recommendations can be made for these fatty acids, including supplements. It is important to note the absence of reported adverse health effects in this population that consumes no fish."[12]

Numerous observational studies suggest that vegetarians live longer than nonvegetarians and have ≤25% lower death rates from cardiovascular disease.[126,136,137] For example, an analysis of five studies involving >75,000 adults found that mortality from ischemic heart disease was 24% lower in vegetarians than in nonvegetarians.[137] Specifically, compared to regular meat eaters, lacto-ovo vegetarians had a 34% lower risk of death and vegans a 26% lower risk. The number of vegan subjects was quite small, which may have affected results. Subjects who ate fish but not meat had death rates similar to those of vegetarians suggesting that vegetarians do not need to eat fish to reduce risk of death from ischemic heart disease. Fraser et al did not find protective effects of fish consumption against CHD in the Adventist Health Study[138] or in a subset of older vegetarians (≥84 years of age).[139]

Factors in vegetarians that may reduce risk of CHD death include lower rates of overweight and obesity,[140,141] lower blood pressure and lower rates of hypertension,[140] and lower total and LDL cholesterol levels.[142,143]

Protective effects of fatty acids from fish on risk of dementia have also been suggested, although there is not enough evidence to make specific recommendations.[56] Only limited research has been done on the incidence of Alzheimer's disease or dementia in vegetarians. Existing studies find no increased risk of dementia or cognitive impairment in vegetarians or in vegan men.[1,144,145] The Oxford Vegetarian Study found a higher mortality from mental and neurologic disease in vegetarians compared to nonvegetarians, although there were, overall, a small number of deaths from this condition.[146]

In addition, concerns have been raised about the potential environmental and societal impact of the increased fish consumption that is being recommended by some health authorities.[147] Overfishing has led to the extinction of some types of fish and to limited availability of other types.[148] Loss of species has a number of harmful environmental effects.[149,150] Fish farming, although sometimes proposed as a solution, has also been associated with environmental damage.[151] Food security of developing nations is jeopardized by increased exporting of fish.[152] Use of more sustainable vegetarian sources of DHA and EPA, such as microalgae, reduces the environmental and societal impacts of increasing consumption of these long-chain fatty acids.

## CONCLUSION

There are many questions about ALA, LA, EPA, and DHA needs for vegetarians that are not resolved. Although we know that ALA and LA are essential fatty acids, we do not know the optimal ratio of these nutrients for vegetarians. Additional research is needed to determine if dietary manipulations such as increased ALA, decreased LA, and/or an altered ratio of LA to ALA can promote EPA and DHA synthesis by vegetarians so that blood and tissue content of these fatty acids are similar to those seen in fish eaters. With the availability of supplemental DHA and EPA derived from microalgae and foods fortified with DHA, there is no need for vegetarians to eat fish or use fish oil to obtain DHA or EPA. Vegetarians can improve their EPA and DHA status by using direct sources of these fatty acids and possibly by increasing dietary ALA and replacing some dietary LA with carbohydrates or monounsaturated fats.

## COUNSELING POINTS: MEETING NEEDS FOR KEY FATS

- There are two essential fatty acids: linoleic acid and linolenic acid.
- Linoleic acid is found in whole grains, nuts, seeds, soybeans, and in many vegetable oils. Dietary recommendations for linoleic acid are 12 g/d for adult women and 17 g/d for adult men. Because it is widely available in foods, most people have high intakes of linoleic acid.
- Needs for alpha-linolenic acid can be met by choosing daily servings of ground flaxseed or flaxseed oil, walnuts, hempseed products (such as veggie burgers or cheese made from hemp), canola oil, soybeans, and generous quantities of leafy green vegetables. Dietary recommendations are 1.1 g/d for adult women and 1.6 g/d for adult men. Higher intakes may be beneficial for those with low or no dietary DHA and EPA.
- Due to concerns about an increased risk of prostate cancer in those with higher intakes of alpha-linolenic acid, excessive intakes should be avoided especially by those in risk groups for prostate cancer.

- A lower ratio of linoleic acid to alpha-linolenic acid may be beneficial. Foods high in monounsaturated fat such as olive oil, canola oil, high-oleic sunflower oil, high-oleic safflower oil, nuts, peanuts, olives, and avocados should be used judiciously in place of overreliance on oils high in linoleic acid such as safflower oil, grapeseed oil, sunflower oil, corn oil, cottonseed oil, and soybean oil. Complex carbohydrates can also be used to replace some linoleic acid.
- EPA and DHA are long-chain fats found in fish oils and in limited amounts in some sea vegetables. The body can make some EPA and DHA from other fats, but production is limited. Vegetarians can use nonanimal sources of DHA and EPA by selecting foods fortified with DHA derived from microalgae or by using vegan supplements of DHA or DHA + EPA derived from microalgae. The DHA or DHA + EPA in supplements or fortified foods may offer health advantages to some individuals. Their use should be assessed in view of other risk factors for chronic diseases.
- Microalgae-derived DHA and EPA are vegan sources of DHA and EPA, although they may be added to nonvegan or nonvegetarian foods. Some foods contain added DHA and EPA from fish oil, so label reading is important to determine the source of these fatty acids and to identify nonfish sources for vegetarians.
- Trans-fatty acids may interfere with the synthesis of EPA and DHA. Limit consumption of foods rich in trans-fatty acids such as foods containing partially hydrogenated oils.

**Case Study**

Dorothy is a 58-year-old woman with a family history of CHD. About 5 years ago she became vegan, with a goal of reducing her risk of heart disease. She eats a generally healthy diet but would like advice on omega-3 fats. After discussing various strategies with Dorothy, she tells you that she wants to modify her diet so that the LA-to-ALA ratio is closer to 4:1 while maximizing her intake of ALA. Her cardiologist has recommended a total fat intake of ≤30% of calories. Dorothy's recommended calorie intake is 2000 calories per day. Develop 2 days of menus for Dorothy that meet her objectives while staying within her fat and calorie limits.

Should Dorothy take supplemental DHA? Why or why not?

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