The Role of Essential Fatty Acids in Ocular Health

Jeffrey Anshel, OD, FAAO

Omega-3 Fatty Acids

- More than 20,000 scientific papers published
- 2,400 randomized controlled trials in humans (more than 1000 in 2011 alone)
- Affect almost every system in the body
- Global consumer spending on omega-3 food and beverage products (excluding fish), health and beauty care products (including supplements) and pet products expected to reach $13 billion in 2013
Health Claims
Since 2004, omega-3s have been backed by a qualified health claim in the U.S. that states: “Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. One serving of [name of the food] provides [x] gram(s) of EPA and DHA omega-3 fatty acids.”

Global Consumption of EPA/DHA-rich oils (metric tons)

Fatty Acids
- Comprised of carboxylic acids with a long tail (chain), which is either saturated or unsaturated.
- Most naturally occurring fatty acids have a chain of an even number of carbon atoms, from 4 to 28.
- Can be derived from triglycerides or phospholipids.
- When they are not attached to other molecules, they are known as “free” fatty acids.
- Are important sources of fuel because their metabolism yield large quantities of ATP.
- Many cell types can use either glucose or fatty acids for this purpose. In particular, heart and skeletal muscle prefer fatty acids.

Long and short chain fatty acids
- Short-chain fatty acids (SCFA) are fatty acids with tails of fewer than 6 carbons
- Medium-chain fatty acids (MCFA) are fatty acids with tails of 6–12 carbons
- Long-chain fatty acids (LCFA) are fatty acids with tails longer than 12 carbons
- Very Long-chain fatty acids (VLCFA) are fatty acids with tails longer than 22 carbons

Saturation
- Unsaturated fatty acids have one or more double-bonds between carbon atoms.
- The two carbon atoms in the chain that are bound next to either side of the double bond can occur in a cis or trans configuration.

Naming Fatty Acids
- Position of double bonds
- Number of carbons
Fatty Acid Naming

- Docosa-22
- Hexa-6
- Enoic-double bonds
- Docosahexaenoic Acid (DHA) (22:6)

- Eicosa-20
- Penta-5
- Enoic-double bonds
- Eicosapentaenoic Acid (EPA) (20:5)

DHA (Docosahexaenoic Acid)

22:6 (omega-3) or 22:6 n-3

Defining Fatty Acids

- α-linolenic acid (ALA, C18:3; n-3)
- Linoleic Acid (LA, C18:2; n-6)
- Arachidonic acid (ARA, C20:4; n-6)
- Eicosapentaenoic acid (EPA, C20:5; n-3)
- Docosahexaenoic acid (DHA, C22:6; n-3)

Alpha-linolenic acid (ALA)

- A long-chain Omega-3 essential fatty acid
- Is related to a lower risk of cardiovascular disease
- Possible link to prostate cancer, cortical opacities in excess
- Seed oils are the richest sources of α-linolenic acid, notably those of rapeseed (canola), soybeans, walnuts, flaxseed (linseed oil), chia and hemp.

Linoleic acid (LA)

- A long-chain unsaturated Omega-6 fatty acid
- Used in the biosynthesis of arachidonic acid (AA) and some prostaglandins.
- It is found in the lipids of cell membranes.
- It is abundant in many vegetable oils, comprising over half (by weight) of poppy seed, safflower, sunflower and corn oils.

Arachidonic Acid (ARA)

- A polyunsaturated fatty acid that is present in the phospholipids of membranes of the cell, and is abundant in the brain, muscles and liver.
- Necessary for the repair and growth of skeletal muscle tissue.
- One of the most abundant fatty acids in the brain, and is present in similar quantities to DHA
- Activates a protein involved in the growth and repair of neurons. Is also a key inflammatory intermediate.
- Sources: usually comes from dietary animal sources—meat, eggs, dairy—or is synthesized from linoleic acid.
Eicosapentaenoic Acid (EPA)
- A polyunsaturated fatty acid (PUFA) that acts as a precursor for anti-inflammatory prostaglandin-E3
- A precursor for DHA
- It is obtained in the human diet by eating oily fish or fish oil
- It is also found in human breast milk.

Docosahexaenoic Acid (DHA)
- Is the most abundant omega-3 fatty acid in the brain and retina
- Comprises 40% of the PUFAs in the brain and 60% of the PUFAs in the retina
- Fifty percent of the weight of a neuron’s plasma membrane is composed of DHA
- Is either present in the diet or derived from EPA
- Commercially manufactured from microalgae-a vegetarian source or from fish oils

Fatty Acid Forms
<table>
<thead>
<tr>
<th>Trans (Elaidic acid)</th>
<th>Cis (Oleic acid)</th>
<th>Saturated (Stearic acid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elaidic acid is the principal trans unsaturated fatty acid often found in partially hydrogenated vegetable oils.</td>
<td>Oleic acid is a cis unsaturated fatty acid that comprises 55-80% of olive oil.</td>
<td>Stearic acid is a saturated fatty acid found in animal fats and is the intended product in full hydrogenation. Stearic acid is neither cis nor trans because it has no double bonds.</td>
</tr>
</tbody>
</table>

Omega-9
- The family of unsaturated fatty acids which have in common a final carbon–carbon double bond in the n-9 position;
- Unlike n-3 and n-6 fatty acids, n-9 fatty acids are not classified as essential fatty acids (EFA).
- They can be created by the human body from unsaturated fat, and are therefore not essential in the diet.
- They lack of an n-6 double bond keeps them from participating in the reactions that form the eicosanoids.

EFAs in Infancy
- The amount of DHA in the brain increases approximately 30-fold from about 24 weeks gestation to about two years of age
Effects of n-3 long chain polyunsaturated fatty acid supplementations on visual and cognitive development throughout childhood: A review of human studies

“...supplementing term infants with daily doses of 100 mg DHA plus 200 mg ARA improves visual developments as measured by electrophysiological tests”


A Docosahexaenoic Acid-Functional Food During Pregnancy Benefits Infant Visual Acuity at Four but not Six Months of Age

“Based on our results, we conclude that DHA supplemented during pregnancy plays a role in the maturation of the visual system.”

M. Judge, O. Harel, and C. Lammi-Keefe, University of Connecticut Department of Nutritional Sciences Lipids 2007; 42: 117-122

Long-term effects of prenatal omega-3 fatty acid intake on visual function in school-age children

Objective: To assess the long-term effect on visual development of omega-3 polyunsaturated fatty acid intake during gestation.

Conclusion: This study demonstrates beneficial effects of DHA intake during gestation on visual system function at school age. DHA is particularly important for the early development and long-term function of the visual parvocellular pathway.

Jacques et al., J Pediatrics Volume 158, Issue 1, Pages 83-90.e1, January 2011

European Health Claim

Article 14:
DHA intake contributes to the normal visual development of infants up to 12 months of age (100 mg/day of DHA);

Article 13 (awaiting approval):
Maintenance of normal vision (250 mg DHA/1 or more servings)

Comparison of DHA Levels in Breast Milk Among Various Countries

Fish Intake in U.S. Children

16% of U.S. children consumed no fish or shellfish during a 12-month period and the average consumption rate among those who ate fish (the remaining 84%) was <1 meal per week.


Children: Recommended Intake

- In children (<18 months) Omega-3 fatty acids are used in some infant formulas, although effective doses are not clearly established.
- Ingestion of fresh fish should be limited in young children due to the presence of potentially harmful environmental contaminants.
- Fish oil capsules should not be used in children except under the direction of a physician.

Dry Eye Syndrome

Randomized Clinical Trials on Omega-3 Treatment of Dry Eyes

1. Pilot, Prospective, Randomized, Double-masked, Placebo-controlled Clinical Trial of an Omega-3 Supplement for Dry Eye
   Wojtowicz, J.C., et al., Cornea. ePub 28 Oct 2010

Patients with dry eye received a daily dose of fish oil, containing 450 mg of EPA, 300 mg of DHA and 1000 mg of flaxseed oil for 90 days.

Dietary supplementation with omega-3 fatty acids in dry eye showed no significant effect in meibum lipid composition or aqueous tear evaporation rate. On the other hand, the average tear production and tear volume was increased in the omega-3 group as indicated by both Schirmer testing and fluorophotometry.

Wojtowicz, J.C., et al., Cornea. ePub 28 Oct 2010
**Prostaglandins**

**PGE1**
- Reduce inflammation and inhibit blood clotting.
- Capable of reducing pain, swelling and redness associated with inflammation, particularly in mucosal tissues, which includes the eyes.
- Can only be produced by **Omega-6** fatty acids

**PGE2**
- Are opposite of PGE1s but can only be produced by Omega-6 fatty acids, as well.
- Are pro-inflammatory mediators that constrict blood vessels, increase body temperature, and encourage blood clotting.
- These events are lifesaving when the body suffers a wound or injury, for without PGE2s, a person could bleed to death.
- However, **in excess**, this type of prostaglandin is harmful because it sets up a chronic inflammatory condition in the body.

**PGE3**
- Are available from Omega-3 fatty acids
- The Omega-3 fatty acid, EPA, also plays an important anti-inflammatory role.
- It appropriately blocks the release of Omega-6 arachidonic acid, so without sufficient Omega-3s in the diet, chronic inflammation becomes one of the problems now linked to many degenerative diseases of the eye.

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**Sources of EFAs**

<table>
<thead>
<tr>
<th>Oil</th>
<th>Omega-3</th>
<th>Omega-6</th>
<th>Gamma-Linolenic Acid (GLA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLAX</td>
<td>85%</td>
<td>15%</td>
<td>NONE</td>
</tr>
<tr>
<td>EPO</td>
<td>NONE</td>
<td>75%</td>
<td>9%</td>
</tr>
<tr>
<td>Borage</td>
<td>75%</td>
<td>NONE</td>
<td>23%</td>
</tr>
<tr>
<td>Black Currant Seed Oil</td>
<td>15%</td>
<td>65%</td>
<td>18%</td>
</tr>
</tbody>
</table>
**Chia Seed**
- *Salvia hispanica*, a species of flowering plant in the mint family, native to central and southern Mexico and Guatemala.
- Contains protein (4g), fat (9g) (57% of which is ALA) and dietary fiber (11g) in 28 g (1 oz.)
- Seeds also contain essential minerals phosphorus, manganese, calcium, potassium and sodium.
- Although some research indicates potential for dietary health benefits in certain disease conditions, this work remains sparse and inconclusive.

**Hemp Seed**
- Low tetrahydrocannabinol (THC) strains of the plant *Cannabis sativa*.
- Although hemp is commonly associated with marijuana (hemp's THC rich cousin), since 2007 the commercial success of hemp food products has grown considerably.
- Approximately 44% of the weight of hempseed is edible oils, containing about 80% essential fatty acids (EFAs); e.g., LA, 55%, ALA, 22%, GLA, 1–4% and SDA, 0–2%.
- Proteins are the other major component (33%), second only to soy (35%).

<table>
<thead>
<tr>
<th>Fish/Seafood</th>
<th>mg DHA/100g (3.5 oz)</th>
<th>Servings/Week*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlantic Mackerel</td>
<td>1600</td>
<td>0.9</td>
</tr>
<tr>
<td>Atlantic Salmon</td>
<td>900</td>
<td>1.6</td>
</tr>
<tr>
<td>Atlantic Herring</td>
<td>900</td>
<td>1.6</td>
</tr>
<tr>
<td>Rainbow Trout</td>
<td>400</td>
<td>3.5</td>
</tr>
<tr>
<td>Pacific Halibut</td>
<td>300</td>
<td>4.7</td>
</tr>
<tr>
<td>Red Snapper</td>
<td>200</td>
<td>7</td>
</tr>
<tr>
<td>Atlantic Cod</td>
<td>200</td>
<td>7</td>
</tr>
<tr>
<td>Pacific Oyster</td>
<td>200</td>
<td>7</td>
</tr>
<tr>
<td>Haddock</td>
<td>100</td>
<td>14</td>
</tr>
<tr>
<td>Alaska King Crab</td>
<td>100</td>
<td>14</td>
</tr>
</tbody>
</table>

*to achieve an average intake of 200 mg DHA day (1400 mg/week)
Option 2: supplement at 200-300 mg DHA / day.

**Macular Degeneration**

- 50% of brain weight is EFA, and half of that is DHA
- 93% of Omega-3 in retina is DHA
Fat Consumption and Its Association with Age-Related Macular Degeneration

6,734 participants (58-69 yrs) in 1990-1994 had fatty acid intakes determined by FFQ followed in 2003-2006 with evaluation for early and late AMD by digital macula photographs of both eyes.

CONCLUSION: A diet low in trans-unsaturated fat and rich in O-3 fatty acids and olive oil may reduce the risk of AMD.


Fish Consumption and AMD

- 60% reduced risk to advanced AMD for people with highest fish consumption (>2x/wk):
  Seddon, et al., Ophthalmology, 2004
- US Twin Study showed that fish consumption and Omega-3 intake reduced risk of AMD:
  Arch Ophthalmology, July 2006
- A diet high in Omega-3 EFA, especially from fish suggests protection against early and late AMD in Australian patients:
  Arch Ophthalmology, July 2006

Prospective Study of Dietary Fat and Risk of Cataract Extraction among U.S. Women

Nurses’ Health Study:
71,083 women followed prospectively for up to 16 years.

Results:
Women in highest quintile for EPA/DHA omega-3 intakes had
12% lower risk for cataract extraction (any type).

Less than 3 fish servings/wk (vs. < 1/mo.) was associated with 19% 1 risk.

Diabetes

- The Delta-6 desaturase enzyme is greatly impaired in diabetic patients.
- The addition of GLA (from EPO) to the diet can stop and even reverse diabetic neuropathy by speeding up nerve conduction velocity.


Protein vs. Fat Energy Source

- The n-3 fatty acids, EPA and DHA regulate hepatic lipid and glucose metabolism; however, they are naturally present in human diets in foods of animal origin, which are generally high in protein with variable triglycerides and uniformly low amounts of carbohydrate.
- Recommendations regarding EPA and DHA intake should focus on protein sources, rather than diet fat, and consider their potential roles in amino acid and protein metabolism.

Dietary long chain n-3 fatty acids are more closely associated with protein than energy intakes from fat

American Heart Association
Summary of Recommendations for Omega-3 Fatty Acid Intake (as of May 7, 2009)

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without CVD</td>
<td>Eat a variety of fatty fish at least twice a week</td>
</tr>
<tr>
<td>Patients with documented CVD</td>
<td>Consume about 1 gram of EPA+DHA per day, preferably from fatty fish.</td>
</tr>
<tr>
<td>Patients who need to lower triglycerides</td>
<td>2 to 4 grams of EPA+DHA per day, provided as fish oil capsules, under a physician's care.</td>
</tr>
</tbody>
</table>

Fish Oils vs. EPA/DHA

Dietary long chain n-3 fatty acids are more closely associated with protein than energy intakes from fat

Fish Oil Pills

- Standard 1000mg pill: 180mg EPA / 120mg DHA
**Lovasa**
- Only prescription form
- Ethyl Ester form
- Each 1-gram capsule is 47% EPA, 38% DHA and 17% other fish oils.
- Indicated for reduction in triglycerides

**Bioavailability/Absorption of Different Forms of EPA/DHA**
- The absorption of EPA/DHA in TG (triglyceride) form was found to be better than the EE (ethyl ester) form on a high-fat or low-fat meal. (Lawson and Hughes, BBRC, 156:960-963 (1988)).
- PL (phospholipid) form of DHA did not yield greater rise in blood plasma DHA levels when compared to TG form. (Mathews et al., J. Nutr., 132:3081-3089 (2002)).
- Bioavailability of (EPA+DHA) via TG (re-esterified) form reported to be significantly better than EE form in recent human study. (Dyerberg et al., Prost., Leuk., and EPA, 83:137-141 (2010)).
- Most of the studies done from 1992-2005 that demonstrated the positive effects of Omega-3 fish oil were done with EE.

**Omega-3 fatty acids, oxidative stress, and leukocyte telomere length: A randomized controlled trial**
- Changes in the n-6:n-3 PUFA plasma ratios helped clarify the intervention’s impact: telomere length increased with decreasing n-6:n-3 ratios.
- The data suggest that lower n-6:n-3 PUFA ratios can impact cell aging.

**Krill Fish**
- Krill is considered by many scientists to be the largest biomass in the world.
- Main source of food for whales, seals, penguins, squid and fish.
- Three of the most important nutrients in krill oil are:
  - Omega-3 fatty acids similar to those of fish oil,
  - Omega-3 fatty acids attached to phospholipids, known as marine lecithin.
  - Astaxanthin, a powerful antioxidant (not normally found in eye)
**EPA/DHA Levels in Krill Oil and Selected Omega 3 Supplements Derived from Marine Oil**

**Krill Metabolism**
Metabolic effects of krill oil are essentially similar to those of fish oil but at lower dose of EPA and DHA, in healthy volunteers.

Ulven, SB; Karkhus, B, et al

**Krill Oil (the hype)**
- Reduce risk of a cardiovascular "event" by up to 45%...
- Vanquish artery-clogging LDL "bad" cholesterol by up to 55%...
- Reduce harmful triglycerides by up to 27%...
- Slash heart-damaging inflammation by as much as 29%...
- Raise HDL "good" cholesterol by as much as 43.92%...
- Soothe the pain and discomfort of stiff joints by up to 29%...
- Boost your memory and mental focus by as much as 48%...
- Reduce facial wrinkles by up to 51%...
- Increase your energy by over 50%...
- Decreases the physical and emotional effects of PMS by up to 57%...
- Increase your sex appeal by 37%... WHAT???

**Standard American Diet and EFAs**
- Average Americans dietary intake of omega-3/omega-6 fatty acids for adults (>18 years): Approx. 1.6 grams of omega-3 fatty acids each day, of which about 1.4 grams (~90%) comes from α-linolenic acid, and only 0.1-0.2 grams (~10%) from EPA and DHA.
- In Western diets, people consume roughly 10 times more omega-6 fatty acids than omega-3 fatty acids.
- These large amounts of omega-6 fatty acids come from the common use of vegetable oils containing linoleic acid (for example: corn oil, evening primrose oil, canola oil, safflower oil, sesame oil, soybean oil, sunflower oil, and wheatgerm oil).
- Because omega-6 and omega-3 fatty acids compete with each other to be converted to active metabolites in the body, benefits can be reached either by decreasing intake of omega-6 fatty acids, or by increasing omega-3 fatty acids.

**Omega-6:Omega-3 ratio**

<table>
<thead>
<tr>
<th>Dietary Source</th>
<th>Omega-6</th>
<th>Omega-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soybean, Cottonseed, Canola Oil (96%)</td>
<td>12-21</td>
<td>1</td>
</tr>
<tr>
<td>Corn</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
<td>Olive Oil</td>
<td>13.1</td>
<td>1</td>
</tr>
<tr>
<td>Walnuts</td>
<td>10.2</td>
<td>1</td>
</tr>
<tr>
<td>Butter</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td>Soybeans</td>
<td>4.3</td>
<td>1</td>
</tr>
<tr>
<td>Pumpkin seeds</td>
<td>7.3</td>
<td>1</td>
</tr>
<tr>
<td>Free Range Chicken egg</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Corn-Fed Chicken egg</td>
<td>19.4</td>
<td>1</td>
</tr>
<tr>
<td>Recommended</td>
<td>3.4</td>
<td>1</td>
</tr>
</tbody>
</table>

**Omega-3 EFA in Meat**

<table>
<thead>
<tr>
<th>Total O-3 Fatty Acids in Animal Muscle Meat (mg per 100g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elk</td>
</tr>
<tr>
<td>178</td>
</tr>
<tr>
<td>Deer</td>
</tr>
<tr>
<td>276</td>
</tr>
<tr>
<td>Antelope</td>
</tr>
<tr>
<td>61</td>
</tr>
<tr>
<td>Pork Fat Cut</td>
</tr>
<tr>
<td>40</td>
</tr>
</tbody>
</table>

Recommendations

- “Balance” Omega EFAs in the diet
- Reduce/eliminate “junk” food and excessive sugar
- Eat fatty fish at least twice a week
- Supplement on days you don’t
- Join the ONS to help your patients!

The Role of Essential Fatty Acids in Ocular Health

Thank you

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