Omega 3 Update
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Objectives

- Understand which fatty acids (FA) are essential and the associated pathology/physiology
- Be able to explain how diet impacts eicosanoid metabolism
- Understand EFA requirements and the relationship between n3/n6 ratios.
- Know the n3 Index and its importance
- Understand the disease conditions in which n3 fatty acids might be beneficial and the dietary amounts needed
Fatty Acid Structure

- Omega end
- Methyl end
- Degree of saturation
- Alpha end
- Carboxyl end
Monounsaturated Fatty Acid Structure

One double bond

omega end
alpha end

One double bond
Polyunsaturated Fatty Acid Structure

H H H H H H H H H H H H H H H
H-C-C-C-C-C-C=C-C=C-C-C-C-C-C-C-C-C-OH

omega end

> 2 double bonds

alpha end
Chain Length of Fatty Acids

• Very long chain fatty acid
  – $\geq 20$ Carbons
• Long chain FA
  – $\geq 12$ Carbons
• Medium chain FA
  – 6 - 10 Carbons
• Short chain FA
  – $< 6$ Carbons

Volatile Fatty Acids
- 1-3 Carbons
Function of EFAs

• Formation of healthy cell membranes
• Proper development and functioning of the brain and nervous system
• Production of hormone-like substances called Eicosanoids
  – Thromboxanes/Prostacylin
  – Leukotrienes
  – Prostaglandins

Responsible for regulating blood pressure, blood viscosity, vasoconstriction, immune and inflammatory responses.
Essential Fatty Acid Deficiency Symptoms

- hemorrhagic dermatitis
- scaly dermatitis
  - Flaky, itchy skin
- weakness
- impaired vision
- edema
- diarrhea
- fatty liver

- high blood pressure
- high triglycerides
- hemotologic disturbances (ex: sticky platelets)
- immune and mental deficiencies
- impaired growth & reproduction
- increased water consumption
  - Increased IWL
## Differing Characteristics ω-3 and ω-6 Essential Fatty Acid Deficiencies

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Omega-3 (α-Linolenic Acid)</th>
<th>Omega-6 (Linoleic Acid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal skin, growth, reproduction</td>
<td>Reduced learning</td>
<td>Growth retardation</td>
</tr>
<tr>
<td>Reduced learning</td>
<td>Abnormal electroretinogram</td>
<td>Skin lesions</td>
</tr>
<tr>
<td>Abnormal electroretinogram</td>
<td>Impaired vision</td>
<td>Reproductive failure</td>
</tr>
<tr>
<td>Impaired vision</td>
<td>Polydipsia</td>
<td>Fatty liver</td>
</tr>
<tr>
<td>Polydipsia</td>
<td></td>
<td>Polydipsia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biochemical markers</th>
<th>Omega-3 (α-Linolenic Acid)</th>
<th>Omega-6 (Linoleic Acid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased 18:3 ω-3 and 22:6 ω -3</td>
<td>Increased 22:4 ω-6 and 22:5 ω 7</td>
<td></td>
</tr>
<tr>
<td>Increased 20:3 ω-9 (only if ω -6 also low)</td>
<td>Decreased 18:2 ω-6 and 20:4 ω-6</td>
<td></td>
</tr>
<tr>
<td>Increased 20:3 ω-9 (only if ω -3 also low)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Who are at risk for deficiency?

- Long-term TPN patients without adequate lipid
- Cystic Fibrosis
- Low Birth Weight Infants
- Premature infants
- Severely malnourished patients
- Patients on Long-term MCT as fat source
- Patients with fat malabsorption
- Acrodermatitis Enteropathica
- Hepatorenal Syndrome
- Sjogren-Larsson Syndrome
- Multisystem neuronal degradation
- Crohn’s disease
- Cirrhosis and alcoholism
- Reye’s Syndrome
- Short bowel syndrome
Reports of $\omega$-3 Deficiency

- Holman and colleagues reported a case of peripheral neuropathy and blurred vision in a child receiving total parenteral nutrition devoid of omega-3 fatty acids for 5 months.

  - Holman et al. AM J Clin Nutr 35:617, 1982

- Bjerve and his coworkers reported linolenic acid deficiency in nine patients fed by gastric tube for 2.5 to 12 years, who had received only 0.025% to 0.09% of their total kilocalories as omega-3 fatty acids.

### Sources of Dietary Lipids

<table>
<thead>
<tr>
<th>Dietary fat</th>
<th>Cholesterol (mg/tbsp)</th>
<th>Breakdown of fatty-acid content (normalized to 100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canola oil</td>
<td>0</td>
<td>6% 22% 10% 62%</td>
</tr>
<tr>
<td>Safflower oil</td>
<td>0</td>
<td>10% 77% Trace 13%</td>
</tr>
<tr>
<td>Sunflower oil</td>
<td>0</td>
<td>11% 69% 20%</td>
</tr>
<tr>
<td>Corn oil</td>
<td>0</td>
<td>13% 61% 25%</td>
</tr>
<tr>
<td>Olive oil</td>
<td>0</td>
<td>14% 8% 77%</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>0</td>
<td>15% 54% 7% 24%</td>
</tr>
<tr>
<td>Margarine</td>
<td>0</td>
<td>17% 32% -2% 49%</td>
</tr>
<tr>
<td>Peanut oil</td>
<td>0</td>
<td>18% 33% 49%</td>
</tr>
<tr>
<td>Vegetable shortening</td>
<td>0</td>
<td>28% 26% -2% 44%</td>
</tr>
<tr>
<td>Palm oil</td>
<td>0</td>
<td>45% 12% -1% 37%</td>
</tr>
<tr>
<td>Palm kernel oil</td>
<td>0</td>
<td>52% 10% -1% 11%</td>
</tr>
<tr>
<td>Coconut oil</td>
<td>0</td>
<td>92% 2% 6%</td>
</tr>
<tr>
<td>Lard</td>
<td>12</td>
<td>41% 11% -1% 47%</td>
</tr>
<tr>
<td>Beef fat</td>
<td>14</td>
<td>52% 3% -1% 44%</td>
</tr>
<tr>
<td>Butter fat</td>
<td>33</td>
<td>66% 2% -2% 30%</td>
</tr>
</tbody>
</table>

*Polyunsaturated fat:*

- Saturated fatty acid
- Linoleic acid
- Alpha-linolenic acid
- Monounsaturated fatty acid
Essential Fatty Acid Families

ω-6 family

C18:2 ω-6
Corn Oil
Safflower Oil
Sunflower Oil

C20:4 ω-6
Meat, Eggs, Brains

Eicosanoids
Thrombotic
Inflammatory

ω-3 family

C18:3 ω-3
α-Linolenic
Flaxseed Oil
Canola Oil
Soybean Oil

C20:5 ω-3
Eicosapentaenoic
EPA

C22:6 ω-3
Docosahexaenoic
DHA
Oily Fish
Fish Oil Capsules

Eicosanoids
Less thrombotic
Less inflammatory
**α-Linolenic Acid Conversion to EPA and DHA**

- In adults, the conversion rate is less than 1% for ALA to EPA, and <0.01% to DHA
- No known need for ALA independent of its conversion to EPA/DHA
- Adequate EPA/DHA may eliminate the need for dietary ALA
- With low consumption of EPA/DHA, higher n-6 FA intake will inhibit conversion of ALA to EPA/DHA
Faulty Assumptions Regarding the n6/n3 Ratio

That ALA is physiologically equivalent to EPA and DHA

That LA is physiologically equivalent to AA

That amounts of consumed FA is irrelevant; only the ratio is important

That lowering tissue AA content can be achieved by lowering LA intake
### Alpha-linolenic acid: Sources

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving</th>
<th>Alpha-linolenic acid (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flaxseed oil</td>
<td>1 tablespoon</td>
<td>8.5</td>
</tr>
<tr>
<td>Walnuts, English</td>
<td>1 ounce</td>
<td>2.6</td>
</tr>
<tr>
<td>Flaxseeds</td>
<td>1 tablespoon</td>
<td>2.2</td>
</tr>
<tr>
<td>Walnut Oil</td>
<td>1 tablespoon</td>
<td>1.4</td>
</tr>
<tr>
<td>Canola Oil</td>
<td>1 tablespoon</td>
<td>1.2</td>
</tr>
<tr>
<td>Mustard Oil</td>
<td>1 tablespoon</td>
<td>0.8</td>
</tr>
<tr>
<td>Soybean Oil</td>
<td>1 tablespoon</td>
<td>0.9</td>
</tr>
<tr>
<td>Walnuts, Black</td>
<td>1 ounce</td>
<td>0.6</td>
</tr>
<tr>
<td>Olive Oil</td>
<td>1 tablespoon</td>
<td>0.1</td>
</tr>
<tr>
<td>Broccoli, raw</td>
<td>1 cup, chopped</td>
<td>0.1</td>
</tr>
</tbody>
</table>
## EPA and DHA: Sources

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving</th>
<th>EPA (g)</th>
<th>DHA (g)</th>
<th>Amt providing 1 g of EPA + DHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herring, Pacific, cooked</td>
<td>3 ounces</td>
<td>1.06</td>
<td>.75</td>
<td>1.5 ounces</td>
</tr>
<tr>
<td>Salmon, chinook, cooked</td>
<td>3 ounces</td>
<td>.86</td>
<td>.62</td>
<td>2 ounces</td>
</tr>
<tr>
<td>Salmon, Atlantic, cooked</td>
<td>3 ounces</td>
<td>.28</td>
<td>.95</td>
<td>2.5 ounces</td>
</tr>
<tr>
<td>Oysters, Pacific, cooked</td>
<td>3 ounces</td>
<td>.75</td>
<td>.43</td>
<td>2.5 ounces</td>
</tr>
<tr>
<td>Salmon, sockeye, cooked</td>
<td>3 ounces</td>
<td>.45</td>
<td>.60</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Trout, rainbow, cooked</td>
<td>3 ounces</td>
<td>.40</td>
<td>.44</td>
<td>3.5 ounces</td>
</tr>
<tr>
<td>Tuna, white, packed in water</td>
<td>3 ounces</td>
<td>.20</td>
<td>.54</td>
<td>4 ounces</td>
</tr>
<tr>
<td>Crab, dungeness, cooked</td>
<td>3 ounces</td>
<td>.24</td>
<td>.10</td>
<td>9 ounces</td>
</tr>
<tr>
<td>Shrimp, cooked</td>
<td>3 ounces</td>
<td>.15</td>
<td>.12</td>
<td>11 ounces</td>
</tr>
<tr>
<td>Cod, Pacific, cooked</td>
<td>3 ounces</td>
<td>.09</td>
<td>.15</td>
<td>12.5 ounces</td>
</tr>
<tr>
<td>Fish oil, menhaden</td>
<td>1 gram</td>
<td>.13</td>
<td>.09</td>
<td>5 grams</td>
</tr>
<tr>
<td>Fish oil, salmon</td>
<td>1 gram</td>
<td>.13</td>
<td>.18</td>
<td>3 grams</td>
</tr>
</tbody>
</table>
Recommendations: Infants & Children

• The American Academy of Pediatrics recommends that infant milk formula should provide at least 2.7% of total kilocalories in the form of linoleic acid.

• Of note, human milk provides 3.5% to as high as 12% of total kilocalories in the form of linoleic acid depending on the fat composition of the maternal diet.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>AI for Infants and Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mos</td>
<td>0.5 g/day of n-3 PUFA</td>
</tr>
<tr>
<td>7-12 mos</td>
<td>0.5 g/day of n-3 PUFA</td>
</tr>
<tr>
<td>1-3 yrs</td>
<td>0.7 g/day of α-linolenic acid</td>
</tr>
<tr>
<td>4-8 yrs</td>
<td>0.9 g/day of α-linolenic acid</td>
</tr>
</tbody>
</table>

**Boys**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>AI for Infants and Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-13 yrs</td>
<td>1.2 g/day of α-linolenic acid</td>
</tr>
<tr>
<td>14-18 yrs</td>
<td>1.6 g/day of α-linolenic acid</td>
</tr>
</tbody>
</table>

**Girls**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>AI for Infants and Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-13 yrs</td>
<td>1.0 g/day of α-linolenic acid</td>
</tr>
<tr>
<td>14-18 yrs</td>
<td>1.1 g/day of α-linolenic acid</td>
</tr>
</tbody>
</table>

Food and Nutrition Board, Institute of Medicine (FNBIOM, 2001)
Recommendations: Adults

- Requirements for EFAs are 1 to 2% of dietary calories for adults.

- Recommended 0.2% to 1% of total calories should be provided by omega-3 fatty acids.

<table>
<thead>
<tr>
<th>AI for Adults</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>19- &gt;70 yrs</td>
<td></td>
</tr>
<tr>
<td>1.6 g/day of α-linolenic acid</td>
<td></td>
</tr>
<tr>
<td>17 g/day of linoleic acid</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>19- &gt;70 yrs</td>
<td></td>
</tr>
<tr>
<td>1.1 g/day of α-linolenic acid</td>
<td></td>
</tr>
<tr>
<td>12 g/day of linoleic acid</td>
<td></td>
</tr>
</tbody>
</table>

Food and Nutrition Board, Institute of Medicine (FNBIOM,2001)
All of the pills contained roughly as much EPA and DHA as their labels promised. None showed evidence of spoilage, and none contained significant amounts of mercury, the worrisome PCBs, or dioxin.
First Question:

Will increased omega-3 FA intakes reduce risk for heart disease?

Next Question:

What blood level of omega-3 fatty acids is associated with the lowest risk for death from CHD?
n3 and Plasma Lipids

• Consistent reduction in plasma triglycerides, 23 to 30%, have been noted with supplementation of EPA and DHA (2 to 4 g/day)

• Benefits of fish oil on LDL and/or high-density lipoprotein cholesterol metabolism appear inconsistent
Other Vascular n3 Effects

- Decrease in some inflammatory markers, e.g. TNFα, C-reactive protein
- Decreased platelet-monocyte aggregates by 35%
- Reports on antihypertensive effects are inconsistent
- Anti-arrhythmic properties have been reported

Fish Consumption
And Coronary Heart Disease

• One study followed 1,822 men for 30 years and found that mortality from CHD was 38% lower in men who consumed an average of at least 35 g (1.2 ounces) of fish daily than in men who did not eat fish, while mortality from myocardial infarction (MI) was 67% lower
Fish Consumption
And Sudden Cardiac Death

• Several studies have found inverse relationships between fish consumption and sudden cardiac death.

• In a prospective study, omega-3 fatty acid intakes equivalent to two fatty fish meals per week were associated with a 50% decrease in the risk of primary cardiac arrest.

• Plasma levels of EPA and DHA were found to be inversely related to the risk of sudden death, supporting the idea that omega-3 fatty acids are at least partially responsible for the beneficial effect of fish consumption and sudden cardiac death.
Fish Consumption
And Stroke

- A stroke is a result of impaired blood flow to a region of the brain, which may be due to obstruction of a blood vessel by a blood clot (thrombotic or ischemic stroke) or the rupture of a blood vessel (hemorrhagic stroke).

- Even though the effects of increased omega-3 fatty acid intake and the incidence of stroke have not been studied as thoroughly as the relationship with CHD, what is available suggests that increased fish intake may decrease the risk of thrombotic or ischemic stroke but not hemorrhagic.
A measure of the amount of EPA+DHA in Red Blood Cell membranes expressed as the percent of total fatty acids.

There are 64 fatty acids in this model membrane, 3 of which are EPA or DHA.

\[
\frac{3}{64} = 4.6\%
\]

The Omega-3 Index = 4.6%
Risk of Primary Cardiac Arrest and the RBC EPA+DHA

Odds Ratio

<table>
<thead>
<tr>
<th>3%</th>
<th>4.4%</th>
<th>5.1%</th>
<th>8.2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>90% reduction in risk</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Midrange RBC EPA+DHA by Quartile

Risk after adjustment for age, smoking, family history of MI/SCD, fat intake, HTN, DM, PA, Ht, Wt, Edu.

* p<0.05 vs Q1

Adapted from Siscovick, *JAMA*, 1995
**Omega-3 Index**

*Harris and von Schacky, Preventive Medicine 2004*

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**Greatest Protection**

- Stavanger\(^1\): > 9.5%: No Added Protection?
- GISSI-P\(^2\): \(\approx 9-10\%\)
- CHS\(^3\): 8.8%
- DART\(^4\): \(\approx 8-9\%\)
- SCIMO\(^5\): 8.3% 8.1%
- 5 epi. studies: \(\approx 8\%\)
- PHS\(^6\): 7.3%
- Seattle\(^7\): 6.5%

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**Least Protection**

- PHS\(^6\): 3.9%
- SCIMO\(^5\): 3.4%
- Seattle\(^7\): 3.3%

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Omega-3 Index Risk Zones

Relative Risk for Death from CHD

- Undesirable: 0%
- Intermediate: 4%
- Desirable: 8%, 10%

Percent of EPA+DHA in RBC

Harris and von Schacky, Preventive Medicine 2004
AHA Recommendations

- For patients with documented CHD, about 1g of EPA+DHA per day
  - Fish
    - About 3 oz. Sardines, Salmon
    - About 4 oz. White Tuna (Albacore)
    - About 12 oz. Light Chunk Tuna, Clams, Shrimp
    - Fast food fish sandwiches or breaded/fried fish are not recommended
AHA Recommendations

• For patients with documented CHD, about 1g of EPA+DHA per day
  – Capsules
    Low Potency - 300 mg EPA+DHA/g (Typical drug store capsules)
    High Potency - 500-700 mg EPA+DHA/g (CardioTabs, Triomega, OmegaRx)
    Pharmaceutical – 850 mg EPA+DHA/g (Omacor®, Reliant Pharmaceuticals)
  – Cod Liver Oil
    • 1 tsp (RDA for Vit. D; 2x RDA Vit. A)
AHA Recommendations

For patients *without* CHD “at least two (preferably oily) fish meals per week” (or about 500 mg of EPA+DHA per day)

– Fish
  • 8-9 oz sardines, salmon and/or albacore tuna per week

– Capsules
  • 2, “low potency” or 1 “high potency”

– Cod Liver Oil
  • 1 tbsp per week
Disease Prevention:
Impaired Visual and Neural Development

- Because the last trimester of pregnancy is a critical period for the accumulation of DHA in the brain and retina, preterm infants are particularly vulnerable to adverse effects of insufficient DHA on visual and neural development.

- Although preterm infants can synthesize DHA from ALA, they can’t synthesize enough to prevent declines in plasma and cellular DHA levels without additional dietary intake.

- Preterm infants fed formulas with DHA added had significantly improved measures of visual function compared to preterm infants fed DHA-free formulas in 5 out of 5 randomized controlled trials.
Type II Diabetes

- **Cardiovascular diseases** are the leading causes of death in individuals with diabetes

- Hypertriglyceridemia (fasting serum TG of 200 mg/dl or higher) is a common lipid abnormality in individuals with Type 2 diabetes

- A number of randomized controlled trials have found that fish oil supplementation significantly lowers serum triglyceride levels in diabetic individuals
Type II Diabetes

- But, few control trials have examined the effect of fish oil supplementation on cardiovascular disease outcomes in diabetics

- One prospective study, following 5103 women diagnosed with type 2 DM but free of cardiovascular disease at the start of the study, found decreased risks.

- Those with higher fish intakes were associated with significantly decreased risks of CHD over the 16 years that the study lasted, suggesting that increasing EPA and DHA levels may be beneficial to diabetic individuals, especially those with elevated serum triglycerides.
Studies have noted that diets rich in monounsaturated fats, n-3 fatty acid (e.g., fish oil and flaxseed oil), were inversely correlated with the development of colorectal cancer and breast cancer. However, well-designed, large-scale clinical trials are required to verify the potential anticancer effects of dietary n-3 fatty acid.
n3 and Mental Health

- Low plasma DHA status in individuals with schizophrenia, attention-deficit hyperactivity disorder (ADHD), dyslexia, personality disorder, depression, and bipolar disorder have been reported. Clinical trials are warranted.

- Some studies have reported improvements in depression scores and Alzheimer's disease after n3 supplementation, however studies are inconsistent.
ω 3 and Inflammatory Diseases

Rheumatoid arthritis

- Rheumatoid arthritis is the most common systemic inflammatory rheumatic (joint) disease
- Studies have been conducted to determine the effects of omega-3 fatty acids on rheumatoid arthritis
- Clinical benefits were observed at a minimum dose of 3 g/day of EPA + DHA, and were not apparent until at least 12 weeks of supplementation
Some investigators report that patients taking omega-3 fatty acid supplementation were able to lower their doses of nonsteroidal anti-inflammatory drugs (NSAIDS), but not all findings on this issue were consistent.
ω-3 and Inflammatory Bowel Disease
Ulcerative colitis and Crohn’s Disease

• Clinical trial results were less consistent with inflammatory bowel diseases than in patients with rheumatoid arthritis

• A significantly higher proportion of Crohn’s disease patients supplemented with 2.7 g/day of EPA + DHA remained in remission over a one-year period than those given placebo
ω-3 and Inflammatory Bowel Disease
Ulcerative colitis and Crohn’s Disease

- In 3 randomized controlled trials of EPA + DHA supplementation in Ulcerative colitis patients, significant improvements were reported in at least one outcome measure, including decreased corticosteroid use, decreased production of inflammatory mediators, and improvements in disease activity scores, histology scores, and weight gain.
Summary – For Healthy Individuals

- **Increase intake of n3 fatty acids by**
  - Consumption of fish (2 servings/week) or
  - Supplement with fish oil capsules (500 mg EPA-DHA/day)
- **Decrease intake of n6 fatty acids, e.g. corn oil, sunflower oil, safflower oil, soybean oil**
- **Replace n6 rich oils with olive and canola oils**

See Previous Recommendation for Populations with Health Risks