Clinical Applications of Fish Oil Supplements

OPA ANNUAL CONFERENCE
CHRISTOPHER OSWALD, DC, CNS
4/15/2016
EPA, DHA: Quintessential Functional Nutrients

Quintessential: being the most typical representative

Body  Organ Systems  Organs  Tissues  Cellular elements (membranes)
Pleiotropic Effects of EPA/DHA

Omega-3’s

- Regulation of inflammatory Response
- Optimize cell membrane complexes
- Endocannabinoid System
- Eicosanoid modulation
- Expression of regulatory genes that dampen inflammatory response
- Lipid-protein complexes
- Food intake, satiety
- Cardiovascular effects
Many clinical uses

• “Swiss army knife” of supplements

• Due to the complex biochemistry associated
  • Eicosanoid modulation
  • Endocannabinoid system
• Quick biochemistry review
  • Eicosanoid Modulation
  • Endocannabinoid System

• Identification of need

• Clinical interventions

• Contraindications and drug interactions

• Questions and discussion
Eicosanoid Modulation

Omega-3 family
- α-linolenic acid 18:3 ω-3
- stearidonic acid 18:4 ω-3
- eicosatetraenoic acid 20:4 ω-3
  - Slin's Stunt
  - Eicosapentaenoic acid EPA 20:5 ω-3
  - Docosapentaenoic acid DPA 22:5 ω-3
  - Docosahexaenoic acid DHA 22:6 ω-3

Eicosanoids
- pg = prostaglandin
- pgi = prostacyclin
- tx = thromboxane
- l = leukotriene

- Δ6 desaturase
- Elongase
- Δ5 desaturase
- Δ4 desaturase

Omega-6 family
- Linoleic acid 18:2 ω-6
- γ-linolenic acid GLA 18:3 ω-6
- Dihomo γ-linolenic acid DGLA 20:3 ω-6
- Arachidonic acid AA 20:4 ω-6
- Docosatetraenoic acid 22:4 ω-6
- Docosapentaenoic acid 22:5 ω-6
- Docosahexaenoic acid 22:6 ω-6

A/J-Ring Neuroprostane
17S Resolvins
blocks prostanoids
Eicosanoids modulate many important cell processes

Platelets
Endothelial cells
Mucosal endothelial cells
Neutrophils, Lymphocytes (T-cells, B-cells), Monocytes / Macrophages, Eosinophils, Basophils, Mast cells

Smooth muscle (contraction, relaxation)
  • Brain, Kidney, Spleen, Heart, Lungs
Prostaglandin

Functions

- Constriction of dilation of vascular smooth muscle
- Platelet aggregation/disaggregation
- Spinal neuron sensitivity to pain
- Labor induction
- Decreased intraocular pressure
- Regulation of inflammation
- Regulation of calcium movement
- Hormone regulation
- Cell growth control
- Action on hypothalamus to produce a fever
- GFR increase via action on the mesangial cells in the kidneys
- Inhibit stomach acid via action on parietal cells
Thromboxane

Functions

Vasoconstrictor (hypertensive agent)

Facilitation of platelet aggregation (clot production)

Their function is believed to have a role in Prinzmetal's angina
Prostacyclin

Functions

- Inhibits platelet activation
- Prevents formation of platelet plug, thus inhibiting clog formation
- Increases Apoptosis
- Vasodilator
- Decreased pro-inflammatory cytokines
- Increased anti-inflammatory cytokines.
- The actions contrast that of thromboxane A₂
Leukotriene

Functions

In leukocytes and other immune cells

Regulation of immune responses

Overproduction is a major cause of asthma and allergic rhinitis
  ◦ Airflow obstruction
  ◦ Increased mucus
  ◦ Bronchoconstriction
  ◦ Airway wall is infiltrated with inflammatory cells
A “Fork” in the Road

- **Arachidonic acid**
  - COX: 2-series PGs (High pro-inflammatory potential)
  - 5-LOX: 4-series LTs

- **EPA**
  - COX: 3-series PGs
  - 5-LOX: 5-series LTs
  - COX & LOX: E-series resolvins

- **DHA**
  - COX & LOX: D-series resolvins & protectins

**Summary:**
- **Arachidonic acid** leads to high pro-inflammatory potential.
- **EPA** leads to low pro-inflammatory potential and anti-inflammatory & inflammation resolving effects.
- **DHA** leads to D-series resolvins & protectins.
Specialized Pro-Resolving Mediators (SPM)

- Lipoxin
- Resolvin D series
- Resolvin E series
- Protectins (Neuroprotectins)
- Maresins

Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature 2014; 510:92-101
functions discovered in microbial defense, pain, organ protection, tissue regeneration, wound healing, cancer, reproduction, and neurobiology – cognition.
Lipoxin

Potent anti-inflammatory lipid metabolite
End result of the LOX pathway
Part of the resolution of inflammation
Derived from AA
Blocks the action of LTB$_4$, PGE$_2$, and TXA$_2$
Also helps to block the expression of IL-8, TNF-$\alpha$
There is also regulation of histamine, which can lead to a reduction in swelling due to edema
Shown to regulate cholesterol metabolism

we definitively show that the AA metabolome plays a physiological role in whole body cholesterol homeostasis and HDL function in mammals
Resolvins and Protectins

Anti-inflammatory actions that lead to resolution of the inflammatory cycle

Resolvin D and Protectin
- Anti-apoptotic, anti-inflammatory signaling and is neuroprotective
- Neuroprotective action during ischemia-reperfusion injury

Resolvin E1 and E2
- Action on monocytes, dendritic cells and neutrophils

Protectin D1

Derived from DHA

Human ALOX15 (15-LOX1) is key enzyme for the eventual formation of PD1
  - Predominantly expressed in the epithelial cells of leukocytes in lungs

Inhibits the nuclear export of viral RNA

Could be a new innate suppressor of influenza virus replication
Maresins

Derived from DHA

Inhibits LTA₄H

Believed to be involved in
- Tissue homeostasis
- Inflammation resolution
- Would healing
- Host defense

Macrophage mediator

Comes on very late in the resolution phase of inflammation

Endocannabinoid System

CB1 – Most abundant G-coupled protein receptor in the brain
  ◦ Substantia nigra
  ◦ Globus pallidus
  ◦ Hippocampus
  ◦ Cerebral cortex
  ◦ Putamen
  ◦ Caudate
  ◦ Cerebellum
  ◦ Amygdala
  ◦ Also found in MSK tissues, adipocytes, and hepatocytes

CB2
  ◦ Primarily associated with cells governing immune function

Role is summarized by “Relax, eat, sleep, forget, and protect”

Modulates
  ◦ Embryological development
  ◦ Neural plasticity
  ◦ Neuroprotection
  ◦ Immunity and inflammation
  ◦ Apoptosis and carcinogenesis
  ◦ Pain
  ◦ Emotional memory
  ◦ Hunger
  ◦ Feeding
  ◦ Metabolism

ENDOCANNABINOIDS
(ANANDAMINE and/or 2-AG)
(Local effect of CB1 and/or CB2 activation)

- Cardiac contractility
- Platelet activation
- VSMC proliferation and migration
- Endothelial cell activation
- Release of inflammatory cytokines

- Adhesion of inflammatory cells
- Lymphocyte and neutrophils activation
- Monocyte recruitment/transmigration
- Macrophages inflammation
- T-Cell recruitment/activation

Protection Against Ischemic Injuries
(Mainly CB2)

Reduction of Blood Pressure
(Mainly CB1)

Antiarrhythmic Effect
(Mainly CB1)

Reduction of Shock episodes
(CB1 and CB2)

Anti-atherogenic Activity
(Mainly CB2)
Endocannabinoid Production

Released on demand from cell membrane

Produced from AA
- AEA and 2-AG
- Too much is a bad thing

Omega-3 FA both balance AEA and 2-AG levels, but also compete for the enzymes involved in biosynthesis of ECBs

Mice deficient in Omega-3 showed impairment in the CB1 signaling pathway

Omega-3 seems to act as a homeostatic regulator of the system

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Table 1

<table>
<thead>
<tr>
<th>Supplemented PUFA</th>
<th>assay / result compared to unsupplemented controls(^1)</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA+AA</td>
<td>in vivo piglets, whole brain homogenates; ↑AEA, ≈2-AG</td>
<td>[137]</td>
</tr>
<tr>
<td>AA</td>
<td>in vivo mice, whole brain homogenates; ↑AEA</td>
<td>[137]</td>
</tr>
<tr>
<td>DHA</td>
<td>in vivo mice, whole brain homogenates; 12-AG</td>
<td>[325]</td>
</tr>
<tr>
<td>AA</td>
<td>in vivo mice, whole brain homogenates; ↑2-AG</td>
<td>[325]</td>
</tr>
<tr>
<td>DHA</td>
<td>in vitro mouse 3T3-F442A adipocytes; 12-AG, ↓AEA</td>
<td>[326]</td>
</tr>
<tr>
<td>AA</td>
<td>in vitro mouse 3T3-F442A adipocytes; ↑2-AG</td>
<td>[326]</td>
</tr>
<tr>
<td>DHA+EPA</td>
<td>in vivo rats, whole brain homogenates; ≈AEA, ≈2-AG</td>
<td>[327]</td>
</tr>
<tr>
<td>or AA</td>
<td>in vivo rats, jejunum homogenates; ↑AEA, ↑2-AG</td>
<td></td>
</tr>
<tr>
<td>DHA+EPA</td>
<td>in vivo Zucker rats, viscera, adipose tissue;↑12-AG, ↓AEA</td>
<td>[142]</td>
</tr>
<tr>
<td>DHA+EPA</td>
<td>in vivo Zucker rats, whole brain homogenates; 12-AG, ≈AEA</td>
<td>[143]</td>
</tr>
<tr>
<td>DHA+EPA</td>
<td>in vivo rats, serum; ↑11AEA, 12-AG, brain; ↑1AEA, ≈2-AG</td>
<td>[133]</td>
</tr>
<tr>
<td>DHA+EPA</td>
<td>in vivo obese humans; serum; 12-AG, ≈AEA</td>
<td>[144]</td>
</tr>
<tr>
<td>DHA+EPA</td>
<td>in vivo mice, liver; ↓1AEA, ≈2-AG, brain; ↓1AEA</td>
<td>[131]</td>
</tr>
</tbody>
</table>

\(^1\)↑: increase; ↓: decrease; ≈: no change;

Omega-6s aren’t all bad

The western diet is just full of the stuff

Getting omega-6 from the proper sources can have some fairly impactful outcomes on inflammation driven disorders

Serves similar structural role as Omega-3
Chronic dietary n-6 PUFA deprivation leads to conservation of arachidonic acid and more rapid loss of DHA in rat brain phospholipids.

Lin LE¹, Chen CT¹, Hildebrand KD¹, Liu Z¹, Hopperton KE¹, Bazinet RP¹.

Abstract
To determine how the level of dietary n-6 PUFA affects the rate of loss of arachidonic acid (ARA) and DHA in brain phospholipids, male rats were fed either a deprived or adequate n-6 PUFA diet for 15 weeks postweaning, and then subjected to an intracerebroventricular infusion of (3)H-ARA or (3)H-DHA. Brains were collected at fixed times over 128 days to determine half-lives and the rates of loss from brain phospholipids (Jout). Compared with the adequate n-6 PUFA rats, the deprived n-6-PUFA rats had a 15% lower concentration of ARA and an 18% higher concentration of DHA in their brain total phospholipids. Loss half-lives of ARA in brain total phospholipids and fractions (except phosphatidylinerine) were longer in the deprived n-6 PUFA rats, whereas the Jout was decreased. In the deprived versus adequate n-6 PUFA rats, the Jout of DHA was higher. In conclusion, chronic n-6 PUFA deprivation decreases the rate of loss of ARA and increases the rate of loss of DHA in brain phospholipids. Thus, a low n-6 PUFA diet can be used to target brain ARA and DHA metabolism.

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ALAs, EPA and DHA

Alpha linolenic acid – seed oils, green leaves
- Chia, flax, hemp, walnuts
- Most seeds are more rich in Linoleic acid (Omega-6)
- Very small amount is converted to EPA and even less to DHA

Eicosapentaenoic acid
- Oily fish, cod liver, cold water fish
  - Fish get it from the algae they consume

Docosahexaenoic acid
- Cold water ocean fish, algae

All are essential because humans don’t possess the 12- and 15-desaturase enzymes
- This would synthesize PUFA from saturated fats
Nearly Everyone Needs More Omega-3

Percentage of Various Fatty Acids in the Typical American

- 36.77% N-3 Polyunsaturated Fatty Acids
- 30.03% N-6 Polyunsaturated Fatty Acids
- 20.98% Monounsaturated Fatty Acids
- 10.00% Saturated Fatty Acids
- 2.23% Other

National Center for Environmental Health
Division of Laboratory Sciences
Recognizing deficiency

Assume we all are!

Signs/Symptoms
- Dry skin, eyes
- Small bumps on back of arm – Keratosis Pilaris
- Eczema
- Dandruff
- Concentration issues
- Mood problems
- Joint pain

Lab analysis
- FA analysis from RBC’s
- Whole blood
- Blood spot
Chronic Inflammation is a component within many medical conditions

- Type I & II Diabetes mellitus
- Juvenile Rheumatoid Arthritis
- Juvenile Ankylosing Spondylitis
- Juvenile Dermatomyositis
- Rheumatic Fever
- Scleroderma
- Hemolytic anemia
- Idiopathic Thrombocytopenic Purpura
- Inflammatory Bowel Disease (IBD)
- Necrotizing Enterocolitis
- Vasculitis
- Kawasaki Disease
- Fibromyalgia
- Disseminated Intravascular Coagulation
- Immunodeficiency disorders
- Injuries
- Infections
- Irritants
- Autoimmune Disease
  - Rheumatoid arthritis; Osteoarthritis
  - Systemic Lupus Erythematosus (SLE)
  - Inflammatory Bowel Disease (IBD)
- Cardio-Cerebrovascular Disease
  - Stroke
  - Heart Disease
- Depression / Mental illness
- Spinal & Neurodegenerative Disease
  - Alzheimer’s
  - Multiple Sclerosis
  - Neuropathy – from autoimmune, metabolic disorders
  - Herniated Disc; Compression injuries
  - Spinal Stenosis and Degenerative Disease
- Acute and Chronic MSK pain
- Sarcopenia
- Allergy / Atopy
- Cancer
2010 TOP CAUSES OF MORTALITY

- Heart disease: 596577
- Cancer: 576691
- Chronic lower respiratory diseases: 142943
- Stroke (cerebrovascular diseases): 128932
- Accidents (unintentional injuries): 126438
- Alzheimer's disease: 84974
- Diabetes: 73831
- Influenza and Pneumonia: 53826
- Nephritis (Kidney related disorders): 45591
- Intentional self-harm (suicide): 39518
Annual Deaths from All Causes in the US Due to Dietary Factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Annual Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>High sodium</td>
<td>102,000</td>
</tr>
<tr>
<td>Low EPA and DHA omega-3s</td>
<td>84,000</td>
</tr>
<tr>
<td>High trans fatty acids</td>
<td>82,000</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>64,000</td>
</tr>
<tr>
<td>Low intake of fruits and vegetables</td>
<td>58,000</td>
</tr>
<tr>
<td>High saturated fatty acids, low PUFAs</td>
<td>15,000</td>
</tr>
</tbody>
</table>

Heart Disease – Omega-3, Triglycerides and Lipids

4:1 EPA/DHA ratio “had a significant effect on plasma triglyceride concentrations”

Omega-3 supplementation may provide clinical benefit to those with healthy blood lipid levels

This study was performed using 2640 mg fo per day for 28 days

Henderson S, Lampel J, Hollenbeck C. J of Am Dietetic Assoc 2008 Sept; 108;9:A104*
Heart Disease: Omega-3 and Lipid Profiles in Athletes

Increase in HDL, 27% decrease in LDL, 17% decrease in vLDL, 8% decrease in triglycerides

Increase blood levels of DHA and EPA

Study was done with professional football players

2200mg was provided daily for 60 days

Yates A, Norvig J, et. al. Sports Health 2009 Jan;1:1 21-30*
Heart Disease: Omega-3 and CRP

C-reactive protein is a marker of inflammation and strong predictor of future cardiovascular events

Patients with an elevated baseline CRP were selected for the study and were randomized into a PUFA group and a placebo group

PUFA group had 40.3% decrease while placebo group only had a 16.4% decrease

1575mg was used daily for 8 weeks in a 4:1 EPA:DHA ratio

Heart Disease: Red Yeast Rice and Omega-3

Red Yeast Rice exhibited significant lowering effects of serum total cholesterol, triglycerides, and LDL-C with no serious side effects reported

“Lifestyle changes combined with red yeast rice and fish oil reduced LDL-C in proportions similar to standard therapy with simvastatin.”
- 42.4% reduction in LDL-C (39.6% for simvastatin)
- 29% decrease in triglycerides

Clinical recommendation
- 1200mg RYR
- 1000mg Omega-3

Heart Disease: Omega-3 and Implantable devices

No contraindications in literature

Combined use is safe

Studies are equivocal on anti-arrhythmic effects, but have shown a 20% decrease in pacing or shock.

Those with the highest n-3PUFA increase had a lower incidence of arrhythmic events

Heart Disease: Clinical Considerations, Contraindications

Common medications seen in patients with CVD include:

- ACE inhibitors (Lisinopril)
- Aldosterone inhibitors (Spironolactone)
- Diuretics (Lasix, Hydrochlorothiazide)
- ARBs (Losartan)
- Beta-Blockers (Atenolol)
- Calcium channel blockers (Amlodipine)
- Statins (Atorvastatin)
- Digoxin
- Vasodilators (Clonidine)
- Warfarin (Coumadin)

Omega-3 and -6 fatty acids have been shown to be safe with most of the common medications prescribed in cardiovascular disease management.

Warfarin (Coumadin) and Omega-3 fats might increase the chances of bruising or bleeding, but the risk is small under proper management, with older research has shown no risk at all, and more recent research unable to show increased risk.

Omega-3 fats used in the presence of statin medication improves outcomes

- Recommended dose is 2640mg 4:1 EPA:DHA ratio

Omega-3 and Warfarin

No evidence to support increased bleeding risk

2-6g fish oil daily shown to not affect INR status

The lack of risk is likely due to the fact that omega-3 fats improve the signaling mechanisms associated with coagulation.

- Fish oils don’t act as an anti-coagulant

## Sudden Cardiac Death Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Reduction From Lowest to Highest Quartiles of Risk Factors</th>
<th>P-Values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3 Index</td>
<td>90%</td>
<td>0.0001</td>
</tr>
<tr>
<td>C-Reactive Protein</td>
<td>65%</td>
<td>0.0001</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>37%</td>
<td>0.1700</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>33%</td>
<td>0.5600</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>31%</td>
<td>0.3700</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>6%</td>
<td>0.9800</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2%</td>
<td>0.8700</td>
</tr>
</tbody>
</table>

*P-values below 0.05 denote statistical significance.*

Increased Omega-3/Omega-6 ratio is inversely associated with breast cancer risk and has been shown to be causally linked to tumor prevention (in animal models)

The Vitamins and Lifestyle study looked at 70,495 people and found that higher levels of EPA/DHA intake decreased cancer mortality

- 23% decrease in all types of cancer
- 18% decrease from all causes of death
- 49% decrease in colorectal cancer (3+ years of 4+ days a week of supplement use) This was primarily in men

Improved CRP, CRP/albumin status, and potentially prevents weight loss during chemotherapy treatment

EPA’s chemo protective potential in squamous cell carcinoma through amplification of the EGFR/ERK/p90RSK pathway – even in low doses

Cancer: Adjunct Care

Improved body weight and cachexia

***Improving the Omega-3/Omega-6 ratio delays prostate cancer progression***

Combination of gemcitabine and IV Omega-3 emulsion reduced levels of pro-inflammatory cytokines and growth factors in patients with advanced pancreatic cancer
- Up to 100g IV a week for 3 weeks immediately following chemo infusion (5:4:1 MCT:Soya:omega-3 FA triglycerides)

Prophylaxis against peripheral neuropathy associated with paclitaxel
- 2x at many developed PN in control vs those taking Omega-3 fatty acids (60% vs. 30%)
- 640mg EPA/DHA t.i.d. during chemo and for 1 month following

Improvement of inflammatory markers and antioxidant status in patients with advanced lung cancer
- Increase in body weight, decreased CRP and IL-6 levels
- 4 capsules with 850mg of EPA/DHA for 66 days

EPA may support the retention of lean body mass during chemotherapy
- Results point to earlier intervention having the best outcomes

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“Our current understanding of breast cancer points to the importance of lipid synthesis and lipid related signaling alterations in the cells that cause this disease.”
“It’s important to note, however, that these results do not address the question of whether omega-3s play a detrimental role in prostate cancer prognosis,” – T. Brasky (press release following publishing of study)
Chronic Lower Respiratory Disease
COPD, Emphysema, Chronic bronchitis

Airway inflammation is a very large component

What does the research say?

- "Fish oil supplementation should be considered as an alternative treatment for exercise-induced bronchoconstriction"*
  - Significant inhibition of hyperpnea-induced bronchoconstriction
  - PUFA “intake was significantly inversely associated with incidence of asthma”
  - 1100mg to 2200mg EPA+DHA daily
  - PUFA have vasodilatory properties
  - The Ω-3:Ω-6 ratio seems to be the important factor in positive outcomes

Stroke

In-vivo studies showed a 51% decrease in infarct volume when 0.1-0.375 g of DHA/kg was administered immediately after event (within 2 hours)

- In 150 pound human this would be 6.9 to 25.875 g

High EPA/AA ratio was associated with good outcome in ischemic stroke

DHA signaling has a potential in the development of treatments for those suffering the consequences of stroke

Stroke

EPA levels prior seem to be more beneficial in positive outcomes
- **1-2g EPA+DHA daily** – 4:1 ratio would be appropriate depending on risk factors

DHA seems to be more beneficial in treatment of acute stroke consequences and those that remain after the event
- **1400mg+** DHA focused formula
Pain

Everyday people have physical trauma occur to their bodies. This trauma, many times, results in pain.

Compared to ibuprofen, Omega-3 EFAs demonstrate an equivalent effect in reducing arthritic pain*.

Omega-3 fatty acids support musculoskeletal health through better signaling.

Maroon J, and Bost J. Surgical Neurology 2006 65:326-331
Arthritis/Pain

Alternative to ibuprofen*
- 4:1 EPA:DHA formula at a dose of 1050mg to 2100mg daily for 75 days

Musculoskeletal health through improved signaling
- 1000mg to 2000mg daily for 75 days

EPA has more anti-inflammatory effect than DHA, so higher doses of EPA generally work well with acute MSK injuries
**Rheumatoid Arthritis**

RCT trial shows patients with RA less than 12 months responded very well to high dose fish oil in conjunction with current medications.

- Triple DMARD therapy: methotrexate, sulphasalazine, and hydroxychloroquine
- 76% decrease in failure of triple DMARD therapy with FO group
- Remission was significantly greater in the FO group with patients 2.09 times more likely to experience remission

Long term intake of FO is associated with a 52% decreased risk of RA (>0.21g/day)

EPA and DHA exert anti-inflammatory and pro-resolving properties via resolvins and are log-orders more potent than their precursors

The combination of GLA, EPA and DHA is useful in correcting dyslipidemia in patient with RA

- 8.4 mb/dL total cholesterol decrease
- 9.4 mg/dL LDL decrease
- 5.0 mg/dL HDL increase
- 24.4 mg/dL triglyceride decrease

Over the course of 12 months GLA treatment resulting in clinically significant reductions in RA signs and symptoms

Moderate evidence exists to support the use of GLA to RA symptom reduction

- 33% decrease in pain
- 15.75% decrease in disability

One of the main benefits is affect on the biochemical pathways associated with inflammation

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**References**


Rheumatoid Arthritis

EPA + DHA at a level of 5.5 g per day taken with DMARDs

Added GLA does show promise

◦ 4:1 EPA:DHA formula with GLA: up to 2.8g daily

The primary clinical benefits are seen in CVD risk reduction and symptomatic improvements, likely due to biochemical interaction with inflammatory molecules.
A combination of Omega-3 fatty acids and alpha lipoic acid over the course of 12 months showed less decline in MMSI and IADL vs. control and Omega-3 fatty acids alone*

Depleted levels of DHA in CSF are seen in those with Alzheimer’s

Increased risk of Alzheimer’s disease when in the lower quartile of Ω-3 fatty acids intake or blood levels

1550mg Omega 3 plus 600mg Alpha Lipoic Acid Daily

Diabetes

Fish oil has a potential benefit on glucose uptake and cell livability (in-vivo study)*
  ◦ The major concern in the total uptake concentration of omega-3 by the muscle cells

Daily omega-3 consumption decreases the risk of LADA
  ◦ .3 g daily of omega-3 PUFA resulted in a decrease of 40%
  ◦ .3 g daily of omega-3 fish oil resulted in a decrease of 53%

Higher serum omega-3 concentration is associated with decrease risk of type 2 diabetes

Promising early results in the prevention and treatment of obesity
  ◦ Affect the endocannabinoid and mesocorticolimbic pathways
  ◦ Hypothesized that EPA/DHA can reduce reward associated with food, thus reducing appetite and food intake

DHA can attenuate inflammation and improve insulin sensitivity (in vitro)

Fish oils may help to decrease obesity-induced insulin resistance

Eye Health

Increased DHA and reduced LA consumption beneficially effects age-related macular degeneration (AMD)
- Via reduction of MCP-1 expression via PPARγ and NF-κB

Red blood cell membrane EPA and DHA + EPA are highly associated with AMD
- Highest EPA levels had 75% decrease in risk
- Highest EPA + DHA levels had 48% decrease in risk

Lutein and Zeaxanthin both have favorable evidence supporting clinical use for AMD
- Have been shown to increase macular pigment optical density
- Lutein enhances retinal sensitivity

Influenza and Pneumonia

Protectin D1 (PD1) is derived from Omega-3 fatty acids
- PD1 suppresses influenza virus replication

Fish oil may support immune function through enhancement of B cell function (in vivo)

Fish oil protects against post exercise immune decrease
- Helps to reduce increased PBMC IL-2 production and NK cell cytotoxic activity post exercise

Potential for support of innate immunity development in infants, especially those who are not breast fed
- Asthma, Crohn’s disease, rheumatoid arthritis
- Early intervention is necessary

Prentice AM, vander Merwe L. Matern Child Nutr 2011 Apr;7 Suppl 2:89-98
Depression and Mood Disorders

Combination therapy of high dose EPA and citalopram demonstrated a “significantly greater improvement in Hamilton Depression rating scores”*

Omega-3 PUFAs in clinical trial to be used as first line therapy in young people with MDD – 1.4g/day

The use of Omega-3 PUFAs in MDD and in those not diagnosed as MDD has significant clinical efficacy

High levels of AA were associated with suicide risk and major depressive episodes among pregnant Brazilian women

These findings have important implications for human health and the prevention of cognitive disease, particularly for populations eating a plant-based diet.
Traumatic Brain Injury

DHA can mitigate mild TBI

DHA provides “nutritional armor” for common brain injuries

It may be a “prophylactic” against cerebral concussion

EPA and DHA increase serum levels and reduce the number of APP-positive axons at 30 days post-injury to levels similar to those in uninjured animals

Elevated DHA content in brain helps to normalize levels of BDNF (Study using ProDHA) and helped return to membrane homeostasis after trauma, potentially translating into preserved cognitive capacity*

Curcumin helps to enhance the effect of ProDHA in TBI*

Wu A, Ying Z, Gomez-Pinilla F. Neurorehabil Neural Repair 2014 Jan;28(1):75-84*
Common Prescription Meds and Fish oils
Drug Interactions

Omega-3 and -6 fatty acids have been shown to be safe with most of the common medications prescribed in cardiovascular disease management.

Warfarin (Coumadin) and Omega-3 fats can increase the chances of bruising or bleeding, but the risk is small under proper management – older research has shown no risk at all.

Omega-3 fats used in the presence of statin medication improves outcomes:
- Combo therapies have better results at attaining goal lipid level

Potential interaction when used in conjunction with glibizide, Metformin, or insulin due to action on insulin sensitivity.

## Ulcerative colitis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drugs</th>
<th>Product Recommendation</th>
<th>Supports, replaces, or contraindicated</th>
<th>Interactions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerative colitis</td>
<td>budesonide</td>
<td>ProOmega, 2-4 soft gels daily</td>
<td>Support</td>
<td>no</td>
</tr>
</tbody>
</table>

An estimated 30% of cases could be due to high levels of AA. Improve the Omega-3 : Omega-6 ratio.

Hart AR. Linoleic Acid, a Dietary N-6 Polyunsaturated Fatty Acid, and the Aetiology of Ulcerative Colitis - A European Prospective Cohort Study. Gut. 2009.
## Pain

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drugs</th>
<th>Product Recommendation</th>
<th>Supports, replaces, or contraindicated</th>
<th>Interactions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>• Acetaminophen/hydrocodone</td>
<td>• ProOmega</td>
<td>• Support or replace</td>
<td>• no</td>
</tr>
<tr>
<td>• Fibromyalgia</td>
<td>• NSAIDS</td>
<td>• 2-4 soft gels daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Opioid effectiveness very similar to NSAIDs which happen to work about as well as EPA. PUFAs play a vital role in pain regulation in regards to chronic pain syndromes such as fibromyalgia.

*Maroon J, and Bost J. Surgical Neurology 2006 65:326-331*

## Lower Respiratory Disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drugs</th>
<th>Product Recommendation</th>
<th>Supports, replaces, or contraindicated</th>
<th>Interactions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Asthma</td>
<td>• Albuterol</td>
<td>• ProOmega</td>
<td>• Support or replace</td>
<td>• no</td>
</tr>
<tr>
<td>• Chronic bronchitis</td>
<td>• ProAir HFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• COPD</td>
<td>• Ventolin HFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Emphysema</td>
<td>• Advair Diskus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Spiriva</td>
<td>• Symbicort</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Omega-3 FAs are a viable treatment modality and/or adjunct therapy in airway constriction/inflammation
- Increased ratio of omega-3 : omega-6 PUFA can help in reducing chronic inflammatory diseases
- PUFAs support pro-resolving mediators

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335257
### Hypothyroidism

<table>
<thead>
<tr>
<th>Condition</th>
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<th>Product Recommendation</th>
<th>Supports, replaces, or contraindicated</th>
<th>Interactions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypothyroidism</td>
<td>• Levothyroxine • Synthroid</td>
<td>• ProOmega • 2-4 soft gels daily</td>
<td>• Support</td>
<td>• no</td>
</tr>
</tbody>
</table>

Omega-3 FAs can have a neuro-protective effect against hypothyroid induced cognitive impairment

# GERD

<table>
<thead>
<tr>
<th>Condition</th>
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<th>Product Recommendation</th>
<th>Supports, replaces, or contraindicated</th>
<th>Interactions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD</td>
<td>Nexium, esomeprazole</td>
<td>ProOmega, 2-4 soft gels daily</td>
<td>Support</td>
<td>no</td>
</tr>
</tbody>
</table>

People with higher omega-3 intakes had a 54% decrease in Barrett's esophagus

[http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2765669/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2765669/)
## Diabetes

### Condition
- Type 1 Diabetes
- Type 2 Diabetes

### Drugs
- Lantus
- Levemir
- NovoLog
- HumaLog
- Januvia

### Product Recommendation
- ProOmega
  - 2-4 soft gels daily

### Supports, replaces, or contraindicated
- Support

### Interactions?
- no

- Healthy omega-3 : omega-6 levels have been associated with decreased incidence
- There is potential the fish oils also improve glucose uptake
- EPA and DHA may improve kidney health in relation to diabetes
- Cod liver oil early

--

**References**

- [http://www.ajcn.org/content/78/6/1128.long](http://www.ajcn.org/content/78/6/1128.long)
<table>
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<tr>
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<th>Supports, replaces, or contraindicated</th>
<th>Interactions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>SSRI</td>
<td>ProEPA</td>
<td>Support or replace</td>
<td>no</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Cymbalta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar</td>
<td>Abilify</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic pain</td>
<td></td>
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</tr>
</tbody>
</table>

Combination therapies have significantly better outcomes and can be used as first line therapy in youth.

### CVD

<table>
<thead>
<tr>
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<th>Product Recommendation</th>
<th>Supports, replaces, or contraindicated</th>
<th>Interactions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High cholesterol</td>
<td>• Statins</td>
<td>• ProOmega</td>
<td>• Support</td>
<td>• no</td>
</tr>
<tr>
<td>• High blood pressure</td>
<td>• Crestor</td>
<td>• 2-4 soft gels daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Metoprolol</td>
<td>• ProOmega CoQ10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2-4 soft gels daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nordic CoQ10 Ubiquinol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 1-4 soft gels daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Combination therapies have better results at attaining goal lipid levels

Allergies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drugs</th>
<th>Product Recommendation</th>
<th>Supports, replaces, or contraindicated</th>
<th>Interactions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal allergy symptoms</td>
<td>Nasonex</td>
<td>ProOmega</td>
<td>Support</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-4 soft gels daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There is a lot of research on beneficial allergy outcomes when a pregnant women is exposed to PUFA or when the child is exposed early in childhood. There is early support for decreased airway inflammation after allergen exposures.

Safety first!

Purity – Heavy metals, Dioxins, PCBs
- Know your source and ask them to proof it

DHA has been studied in rats at a level of 3290 mg/kg a day for 90 days and found to be completely safe
- That would be over 224 g of DHA daily for a 150 pound human!

DHA studies have been done at doses of 1.5g – 7.5g a day in adults with no safety concerns

3-6 g of fish oil daily is safe with warfarin (Coumadin)

No excess bleeding due to fish oil given in addition to aspirin or warfarin (4g fish oil daily)

There is some evidence of a rise in ALT and AST (liver enzymes), so in patients with severe liver disease, these levels should continue to be closely monitored

One of the biggest challenges people may have is GI related and due to difficulty with digesting the oils

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Excellent clinical utility

Many conditions respond favorably to improved levels of EPA and/or DHA

Positive health outcomes are associated with appropriate membrane levels of EFA

Most of us are deficient or imbalanced, so test everyone!

Omega-3 use is relatively safe with appropriate monitoring
Questions
Thank you!

If you want to reach me with additional questions
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- droswald8@gmail.com