The Importance of Maintaining a Low Omega-6/Omega-3 Ratio for Reducing the Risk of Autoimmune Diseases, Asthma, and Allergies

by James J. DiNicolantonio, PharmD & James O'Keefe, MD

Considering that most of the population is deficient in long-chain omega-3s, there is an increased need for educating the public on the importance of increasing marine omega-3 intake. At the same time, background intake of omega-6 polyunsaturated fatty acids also needs to be reduced.

James J. DiNicolantonio, PharmD, (left), and **James H. O'Keefe, MD**, (right), are at Saint Luke's Mid America Heart Institute, Kansas City, Missouri.

Abstract

Up until about 100 years ago, the omega-6/3 ratio has been around 4:1 or less. However, the typical Western diet now provides an omega-6/3 ratio of approximately 20:1 in favor of omega-6. This predisposes to supraphysiologic inflammatory responses and perpetuates chronic low-grade inflammation. The overconsumption of linoleic acid, mainly from industrial omega-6 seed oils, and the lack of long-chain omega-3s in the diet creates a pro-inflammatory, pro-allergic, pro-thrombotic state. Reducing the omega-6/3 ratio, particularly through reductions in the intake of refined omega-6 seed oil, and increasing the intake of marine omega-3s, either through dietary means or supplementation, may be an effective strategy for reducing inflammation, allergies, and autoimmune reactions.

Introduction

Marine omega-3s have been consumed by our ancestors for millions of years. Estimates indicate that during the Paleolithic era, the intake of the marine omega-3s eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) was approximately 660-14,250 mg/day,[1, 2] compared to just 100-200 mg/day today.[3, 4] Furthermore, the omega-6/3 ratio has increased from around 4:1 during Paleolithic times to 20:1 today.[1, 5]

Over the last 100 years, the intake of the omega-6 fat linoleic acid in the United States has more than doubled.[6] This is primarily due to the increased consumption of omega-6 rich seed oils, such as soybean, corn, and safflower oil, the latter two having an omega-6/3 ratio of approximately 60:1 and 77:1, respectively. Additionally, since the 1950s, there has been an approximate 2.5-fold increase in linoleic acid stored in adipose tissue in the United States.[7] The increase in the omega-6/3 ratio has paralleled the rise in numerous autoimmune, inflammatory, and allergic diseases. Omega-3s are utilized by the body to resolve and lower inflammation, whereas omega-6 polyunsaturated fatty acids are primarily used for increasing inflammation. Thus, the rise in the omega-6/3 ratio over the past 100 years may be driving chronic low-grade inflammatory conditions including autoimmune diseases, allergies and asthma. Table 1 and Table 2 list dietary sources of marine omega-3s and omega-6 fats in the diet.

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory autoimmune condition, whereby the immune system attacks the lining of joints causing joint inflammation and pain. Clinical studies have suggested that omega-3s may play a role in improving rheumatoid arthritis. Indeed, a meta-analysis of 17 randomized controlled trials in humans concluded that omega-3 polyunsaturated fatty acids (PUFAs) are effective in improving symptoms in patients with rheumatoid arthritis, inflammatory bowel disease, and dysmenorrhea.[11] A diet low in arachidonic acid (less than 90 mg/day) has also been found to lower clinical signs of inflammation in patients with rheumatoid arthritis and these effects were enhanced with the addition of a fish oil supplement.[12] At least 11 randomized double-blind placebo-controlled trials have found benefits of fish oil in rheumatoid arthritis including reductions in the need for pain relievers.[13] This may be due to the fact that the EPA/DHA content of immune cells is important for preventing the conversion of the immune system to an inflammatory phenotype and also for reverting chronic inflammatory immune cells back to their native state.

DHA, but not EPA, has been found to reduce the expression of vascular cell adhesion molecule-1 (VCAM-1) and monocyte adhesion to human endothelial cells after inflammatory cytokine stimulation.[14, 15] In young men, when six grams of DHA replaced six grams of linoleic acid (15 grams of DHA-rich alga oil replacing 15 grams of safflower oil) for 90 days the authors reported, "DHA consumption does not inhibit many of the lymphocyte functions which have been reported to be inhibited by fish oil consumption."[16] In other words, DHA does not appear to inhibit immune system function. DHA also lowered prostaglandin E2 (PGE2) and leukotriene B4 production in response to lipopolysaccharide by 60-75% and interleukin-1beta and TNF-alpha release from peripheral blood mononuclear cells by 40-45%.[17] This suggests that DHA calms an overactive immune system, which is at the root of chronic inflammatory disease states and autoimmune conditions. It can take up to 18 weeks to reach maximal DHA content in cells, whereas EPA takes only about six weeks.[18] Furthermore, EPA concentrates largely in circulation whereas DHA concentrates in the cell membranes of brain and heart tissue. Thus, the full benefits of increasing the intake of omega-3s PUFAs may not be realized for months.

Table 1. Dietary Sources of Marine Omega-3[8,9]

Food Source	Grams of EPA/DHA per 3 oz. serving
Salmon roe	2.70
Halibut	2.21
Herring	1.7–1.8
Salmon (wild)	1.0–3.0
Sardines	1.0–1.74
Trout	1.0
Oysters	0.45–1.15
Mackerel	0.35–1.80
Tuna (fresh)	0.25–1.30

Table 2. Dietary Sources of Omega-6[10]

Food Source	Total omega-6 grams per 1-ounce serving
Walnuts	10.8
Pine nuts	9.5
Sunflower seeds	6.5
Sesame seeds	6.0
Brazil nuts	5.8
Pumpkin seeds	5.8
Pecans	5.8
Pistachios	3.7
Almonds	3.4

Ulcerative Colitis and Crohn's Disease

Ulcerative colitis and Crohn's disease are both chronic inflammatory diseases. The main pathological finding is infiltration of neutrophils and mononuclear cells into the affected parts of the intestine.[19] Interluekin-8 (IL-8) is a chemokine and a potent signaling molecule that recruits neutrophils into inflammatory tissues. Compared to normal control subjects, patients with active inflammatory bowel disease have mucosa that contains more IL-8. In one

study, there was a nine-fold increase in IL-8 secretion when smooth muscle cells isolated from the strictures of Crohn's patients were exposed to linoleic acid, which did not occur with oleic acid.[20] Furthermore, linoleic acid activates the arachidonic acid pathways and increases the pro-inflammatory arachidonic metabolites from both lipoxygenase (LOX) (such as leukotriene-B4) and cyclooxygenase (COX) (such as prostaglandin-E2 and thromboxane-B2). Thus, the omega-6 polyunsaturated fatty acid linoleic acid may have proinflammatory effects, particularly in those with inflammatory bowel disease.

In normal cells, oxidized linoleic acid activates Nuclear Factor-Kappa Beta (NF-kB), which is a transcription factor that promotes inflammation.[19] Thus, oxidized linoleic acid may stimulate inflammation in normal healthy intestinal smooth muscle cells. The mononuclear cells and macrophages of Crohn's patients have an increased expression of tumor necrosis factor-alpha (TNF-alpha) and interleukin-1beta (IL-1B) and the inflamed mucosa in these patients produces increased amounts of TNF-alpha, interleukin-6 (IL-6) and IL-1B), which likely drives further activation of NF-kB.[19] The suppression of the chronic inflammatory pathway may be why supplementing with fish oil seems to improve these inflammatory/auto-immune conditions.

In Crohn's patients there is increased COX-2 expression in colonic epithelium.[19] The inflamed colon produces large amounts of prostaglandins, thromboxane and leukotrienes. Oxidative stress is also significantly increased in Crohn's cells exposed to oxidized linoleic acid. A combination of oxidative stress and linoleic acid stimulated IL-8 production in both normal and Crohn's cells, whereas linoleic acid alone stimulated IL-8 production in Crohn's cells.[19] Inhibitors of either COX or LOX suppressed the ability of oxidative stress plus linoleic acid to increase IL-8, suggesting that an increase in arachidonic acid metabolites mediate inflammatory responses to linoleic acid. The authors of the study concluded, "These data suggest that dietary restriction of linoleic acid, antioxidant supplementation, and treatment with arachidonic acid pathway inhibitors may be beneficial for treating Crohn's patients."[19]

In summary, the Western diet is now much higher in omega-6 than omega-3 compared to just 100 years ago. This may predispose to chronic inflammatory conditions including autoimmune diseases. Supplementing these patients with marine omega-3s such as EPA and DHA may provide improvements in their condition.

Allergies

The increase in the omega-6/3 ratio occurred in parallel with the rise in the prevalence "hyperallergic" atopic conditions as well as other allergic diseases including rhino-conjunctivitis, allergic asthma, and atopic eczema.[21] The parent omega-3 fatty acid alpha-linolenic acid (ALA) and the parent omega-6 fatty acid linoleic acid compete for the same enzymes. Thus, a high dietary intake of linoleic acid reduces the elongation of ALA into EPA and DHA. Moreover, the bioactive metabolites formed from omega-6 are more inflammatory compared to the omega-3 pathway. Indeed, many of the leukotrienes formed from the omega-6 pathway are implicated in allergic asthma and other atopic diseases. The current imbalance in the omega-6/3 ratio may lead to a "hyperallergic" state through an increase in reactive leukotrienes formed from the omega-6 pathway compared the omega-3 pathway.

The primary contributor to the rise in intake of omega-6 linoleic acid is from the consumption of industrial seed or vegetable oils such as safflower, sunflower, cottonseed, soybean, and corn oil. These omega-6 seed oils provide very high amounts of concentrated linoleic acid. Linoleic acid competes with ALA for elongation but it also is in competition between eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and arachidonic acid (AA) in membrane phospholipids. A low intake of EPA/DHA will lead to an increase in AA and an overproduction of the inflammatory and pro-allergic metabolites such as 2-series eicosanoids and 4-series leukotrienes, respectively, the latter of which can lead to the recruitment and accumulation of mast cells.[22] Moreover, EPA and DHA inhibit cyclooxygenase (COX) and lipoxygenase (LOX); thus, reducing the breakdown of AA and linoleic acid into pro-allergic metabolites while simultaneously boosting anti-inflammatory and anti-allergic metabolites. Importantly, allergic diseases are characterized by a chronic inflammatory state and the anti-inflammatory mediators formed from EPA/DHA such as resolvins and protectins may help to resolve and reduce the

Table 3. Studies of Omega-3s in pregnancy for reducing allergic disease in offspring

Population	Omega-3 Dose	Outcome
98 atopic pregnant women[23]	3,700 mg of long-chain omega-3 PUFAs (56% DHA, 27.7% EPA)/day given at 20 weeks gestation until delivery	Reduced sensitization to eggs at 12 months by 66% and severity of eczema by 91%.
154 pregnant women affected by allergies or having a husband or previous child with allergies[24]	2.7 grams of EPA/DHA/day given at 25 weeks gestation until 3-4 months of breastfeeding	Reduced the risk of food allergy by over 7-fold and lead to a 3-fold reduction in IgE-associated eczema.
533 women with normal pregnancies (30 weeks gestation)[25]	2.7 grams of omega-3 PUFAs from fish oil/day given at 30 weeks gestation	Significant reductions in asthma (-63%) and allergic asthma (-87%) in offspring.
706 pregnant women with a fetus at high risk of developing allergic diseases	900 mg of omega-3 PUFAs from fish oil given at 21 weeks gestation	Reduced atopic eczema and egg sensitization.

inflammatory and allergic state, respectively. Resolvins and protectins are specialized pro-resolving mediators derived from omega-3 fatty acids that have anti-inflammatory effects helping inflammatory conditions return back to normal homeostasis.

Omega-3s in Pregnancy Reduce Allergic Disease in Offspring: Clinical Studies

Randomized controlled trials have found significant reductions in allergic diseases in offspring when long-chain omega-3 PUFAs are provided during pregnancy. One randomized controlled trial in 98 atopic pregnant women showed that compared to olive oil capsules, 3,700 mg of long-chain omega-3 PUFAs (56% DHA, 27.7% EPA) given at 20 weeks gestation until delivery reduced sensitization to eggs at 12 months by 66% and severity of eczema by 91%.[23] Another randomized placebo-controlled trial, this time in 154 pregnant women affected by allergy themselves or having a husband or previous child with allergies, found that 2.7 grams of EPA/DHA given at 25 weeks' gestation until three to four months of breastfeeding reduced the risk of food allergy by over seven-fold and lead to a three-fold reduction in IgE-associated eczema.[24] Another randomized controlled trial in 533 women with normal pregnancies found significant reductions in asthma (-63%) and allergic asthma (-87%) in offspring when 2.7 grams of omega-3 PUFAs from fish oil were given at 30 weeks gestation compared to olive oil.[25] Lastly, a randomized controlled trial in 706 pregnant women with a fetus at high risk of developing allergic diseases found that 900 mg of omega-3 PUFAs from fish oil given at 21 weeks gestation reduced atopic eczema and egg sensitization compared to placebo vegetable oil capsules.[26]

A systematic review and meta-analysis encompassing 10 prospective cohort studies and 5 randomized controlled trials concluded that if pregnant women ingest appropriate amounts of EPA/DHA they may be able to reduce their risk of allergic diseases in their children.[21] Indeed, the authors of the study concluded, "Our systematic review and meta-analysis was suggestive of benefits of increased omega-3 long-chain-PUFAs in the maternal diet and outcomes of childhood allergic disease... increasing omega-3 long-chain-PUFA intake during pregnancy may offer the best opportunity for a primary prevention strategy, decreasing the burden of allergic disease for future generations."[21] Moreover, about 70% of the observational and randomized publications found a reduced incidence of allergic disease symptoms in offspring with increased omega-3 long-chain PUFA or fish intake in pregnancy. Additionally, there were highly significant reductions in "atopic eczema" (-47%), "any positive skin-prick test" (-32%), "sensitization to egg" (-45%), and "sensitization to any food" (-41%) in the first 12 months of life ($p=0.004$, $p=0.006$, $p=0.0004$, and $p<0.0001$, respectively) with increased omega-3 PUFA intake in pregnancy.[21] Thus, ensuring an optimal long-chain omega-6/3 ratio in pregnancy, before the fetal immune system is programed to an allergic phenotype, may be an important strategy to prevent allergic diseases in the offspring.[21] Table 3 summarizes the clinical studies of omega-3s in pregnancy for reducing allergic disease in offspring.

Table 4. Observational data of higher omega-3 intake and lower risk of asthma, eczema and atopic wheeze

Omega-3 Intake	Outcome
Not eating fish at all vs. consistent high fish intake during pregnancy[27]	30% increased risk of asthma in the offspring, 46% increased risk of ever being hospitalized for asthma, and 37% increased risk for ever being prescribed a medication for asthma
Higher dietary omega-6/3 ratio in pregnancy[28]	37% increased risk of allergic rhinitis in the offspring by 5 years of age
A low intake of ALA and total omega-3 PUFAs[29]	67% and 66% increased risk of asthma in the offspring, respectively
7.2 oz. or more of fish per week in pregnancy[30]	43% reduction in the risk of eczema in offspring
Maternal fish intake greater than 2-3 times per week[31,32]	Reduces the incidence of persistent wheeze by 66%, eczema by 37% (in offspring at 1 year), positive skin-prick test to house dust mites by 35% (at 6 years) and atopic wheeze by 45% in offspring at 1 year
Fish intake 1 time per week or more in pregnancy[33]	43% reduction in doctor-confirmed eczema and a 72% in doctor-confirmed hay fever at 5 years

Asthma

Asthma has increased in prevalence over the past several decades, which may be due to a reduction in dietary omega-3 intake. For example, compared with consistently high fish intake in pregnancy, not eating fish at all is associated with a 30% increased risk of asthma in the offspring as well as a 46% increased risk of ever being hospitalized for asthma, and a 37% increased risk for ever being prescribed a medication for asthma.[27] A higher dietary omega-6/3 ratio in pregnancy is associated with a 37% higher risk of allergic rhinitis in the offspring by five years of age.[28] A low intake of ALA and total omega-3 PUFAs in pregnancy is associated with a 67% and 66% increased risk of asthma in the offspring, respectively.[29] An intake of 7.2 oz. or more of fish per week in pregnancy is associated with a 43% reduction in the risk of eczema in offspring.[30] Maternal fish intake greater than two to three times per week has been found to reduce the incidence of persistent wheeze by 66%,[31] eczema by 37% (in offspring at one year) and positive skin-prick test to house dust mites by 35% (at six years).[32] Fish intake was also associated with a reduced risk atopic wheeze by 45% in offspring at one year.[32] And fish intake one time per week or more in pregnancy versus never is also associated with a 43% reduction in doctor-confirmed eczema and a 72% in doctor-confirmed hay fever at five years.[33] Table 4 summarizes the observational data of higher omega-3 intake and lower risk of asthma, eczema and atopic wheeze.

Omega-3s and Asthma: Clinical Studies

One randomized, double-blind, controlled study in 39 asthmatic children (8-12 years-old) of six months compared fish oil capsules plus canola oil and margarine (omega-3 group) versus safflower oil capsules (0.45 grams plus 0.1 grams of olive oil) plus sunflower oil and margarine (omega-6 group).[34] The majority of patients in the study were already on inhaled corticosteroids and beta-agonists. The omega-6 group was asked not to eat fish which translated to the omega-3 group eating more fresh fish vs. the omega-6 group (340 g/month vs. 109 g/month, p=0.0045). The average number of consumed capsules was three out of four in both groups, which equated to 900 mg of EPA/DHA per day (0.18 g EPA and 0.12 g DHA per capsule) in the omega-3 group. The omega-6 group received around 1.35 grams of safflower oil in the capsules on average per day. The changes in plasma phospholipid omega-3 and omega-6 were +3.18% vs. -0.21% at three months and +2.19% vs. 0.05% at six months, respectively. The changes for plasma EPA was +1.98% and -0.11% at three months and +1.2% vs. +0.19% at six months, respectively. Tumor necrosis factor (TNF)-alpha fell significantly vs. baseline in the omega-3 group (-416 $pg \cdot mL^{-1}$) with a slight increase in the omega-6 group (+ 44 $pg \cdot ml^{-1}$) and a trend for a significant difference between the groups (p=0.075). Eosinophil numbers also fell in the omega-3 group from $0.91x10^{9} \cdot L^{-1}$ cells at baseline to $0.74x10^{9}$ $cells \cdot L^{-1}$ at three months

Table 5. Clinical studies testing omega-3s in asthma

Population	Omega-3 Dose	Outcome
39 asthmatic children[34]	More fresh fish vs. the omega-6 group (340 g/month vs. 109 g/month, p=0.0045) plus ~ 900 mg of EPA/DHA per day	The median asthma severity score was lower in the omega-3 group but not significantly less compared to the omega-6 group.
98 patients with obesity and uncontrolled asthma[35]	4 grams/day of omega-3 PUFAs	Significantly reduced asthma-related phone contacts by 66%.

and 0.65 x10^9 cells·L^{-1} at six months, whereas the eosinophil count rose in the omega-6 group from 0.62x10^9 cells·L^{-1} at baseline to 0.70x10^9 cells·L^{-1} at three months and 0.81x10^9 cells·L^{-1} at six months (p=0.11). The continued reduction in TNF-alpha and eosinophil with the intake of omega-3s suggested a reduction in airway inflammation. Additionally, the median asthma severity score was lower in the omega-3 group but not significantly less compared to the omega-6 group.[34] Larger trials of longer duration are needed to conclude if long-chain omega-3s can provide clinical benefits to patients with asthma. The dose of omega-3s used in this study (900 mg of EPA/DHA per day) may not have been optimal for maximal anti-inflammatory effects that higher doses, such as three to four grams of EPA/DHA per day, may have provided.[34]

A recent randomized study in 98 patients with obesity and uncontrolled asthma found that four grams/day of omega-3 PUFAs significantly reduced asthma-related phone contacts by 66%.[35] Despite this benefit the others concluded that omega-3 PUFAs did not improve most asthma-related outcomes (such as leukotriene-E4, forced expiratory volume in one second, and asthma exacerbations at six months). Thus, further studies are required to ascertain the benefits of marine omega-3s in asthma patients. Table 5 summarizes the clinical studies of omega-3s in asthma.

Conclusion

Reducing the omega-6/3 ratio in pregnancy may help to reduce allergic conditions in offspring and may help patients with asthma. Larger clinical studies are required to confirm these benefits particularly in the setting of asthma. It is our contention, that the increase in the omega-6/3 ratio may have contributed to a rise of allergic and autoimmune diseases over the last several decades. Additionally, a high dietary omega-6/3 ratio creates supraphysiologic inflammatory responses and perpetuates chronic low-grade inflammation. The overconsumption of linoleic acid, mainly from industrial omega-6 seed oils, and the lack of long-chain omega-3s in the diet puts the population in a pro-inflammatory, pro-allergic, pro-thrombotic and autoimmune-prone state. This pro-inflammatory state may also predispose to cytokine storms during viral infections.

Considering that most of the population is deficient in long-chain omega-3s, there is an increased need for educating the public on the importance of increasing marine omega-3 intake. Supplementation or fortification of foods with marine omega-3s is one way to increase population-wide omega-3 intake. Additionally, increasing the consumption of seafood, such as fatty fish, crustaceans, and shellfish, is another way to increase marine omega-3 intake. At the same time, background intake of omega-6 PUFA also needs to be reduced. In particular, omega-6 seed oils such as soybean, cottonseed, corn, and safflower oil are some of the largest contributors to the omega-6 intake in the Western world. These sources of omega-6 are highly refined and are more susceptible to oxidation compared to whole foods that contain omega-6 PUFAs such as nuts, seeds, vegetables, and eggs. A reduction in the intake of industrial omega-6 seed oils will help reduce the high dietary omega-6/3 ratio and the pro-inflammatory state that ensues.

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Disclosure

JJD is Director of Scientific Affairs at Advanced Ingredients for Dietary Products. JOK is an owner of a nutraceutical company that sells omega-3 supplements. **MM**