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## Omega-3 fatty acids: An update emphasizing clinical use

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### Introduction

The health benefits of omega-3 fatty acids (n-3) are well-known to scientific, clinical, and industry experts, with research examining effects on almost every body system and for numerous health conditions. Some of the interest in n-3 can be traced back to observations that Greenland Inuit, with a diet high in fish oils, have lower serum cholesterol, triglycerides and low-density lipoprotein (LDL) than might otherwise be expected (1). Since then, evidence is accumulating for positive effects on other disease processes and risk factors. A vote of confidence about the strength of scientific evidence for n-3 occurred in 2004, when the United States Food and Drug Administration announced one of its most stringent labeling allowances, the Qualified Health Claim, permitting n-3 products to state a reduced risk of coronary heart disease with the intake of n-3. Along with the increase in scientific research results and clinical guidelines has been an exploding market for n-3. For example, in the United States, the n-3 market makes up the strongest sector of the functional foods market, and grew from about \$100m in 2002 to more than \$2 billion in 2006, expecting to have reached \$7 billion in sales by 2011, though there are varying figures about whether or not that milestone has been met (2).

With all of the recent developments, it is a challenge for patients, consumers, clinicians, and industry experts to stay up to date about current n-3 recommendations and research results. Some debate exists regarding the preference of n-3 in food versus supplements, n-3 sources and their sustainability, and whether n-3 intake can prevent or treat particular medical conditions. This article will review some of the more current data and offer crucial distinctions in n-3 understanding, providing important references and clinical nuances.

### Physiology

N-3 are one group of fatty acids that make up polyunsaturated fats (or PUFA), and are either plant-based (stearidonic acid (SDA), or alpha-linolenic acid, ALA), or derived from oily fish, algae or krill oil (eicosapentaenoic acid, or EPA, and docosahexaenoic acid, or DHA). An enzymatic desaturation step (of variable efficiency, some sources mention 1–5%) is required to convert dietary ALA to EPA and DHA. SDA has been demonstrated to have an increased conversion to EPA than ALA, potentially making SDA a good sustainable source of EPA (3,4). EPA and DHA serve as precursors to eicosanoids; which have a variety of physiological effects as noted below (5).

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The n-3 fatty acids EPA and DHA compete with dietary or n-6-derived arachidonic acid as substrates for metabolism by cyclo-oxygenase and lipoxygenase enzymes (6); arachidonic acid leads to the formation of series 2 prostaglandins (PGs), series 4 leukotrienes (LTs), and thromboxane A<sub>2</sub>, all of which are more inflammatory in the human body, while n-3 fatty acids lead to the formation of series 3 PGs, series 5 LTs, and thromboxane A<sub>3</sub>, which are less inflammatory (3,6). The decreased inflammatory effects noted with the series 3 PGs, series 5LTs and thromboxane A<sub>3</sub>s may be responsible for the touted beneficial clinical effects of n-3 fatty acids.

The lipid effects of n-3 have other mechanisms of action. N-3 fatty acids inhibit hepatic triglyceride (TG) synthesis resulting in a decreased rate of very low-density lipoprotein (VLDL)-TG secretion from the liver (7,8,9) as well as decreased content of TG in VLDL particles (10,11). N-3 fatty acids also change the resulting low-density lipoprotein (LDL) subfractions to the less-atherogenic, larger, lighter LDL particles (10). The exact lipid effects can be complex, and may be linked to underlying differences in LDL composition, LDL metabolic behavior, or baseline TG levels, for instance.

## Clinical research

Research about the health benefits of omega-3 fatty acids has covered almost every body system and numerous health conditions. Below is an overview of some of the important findings, realizing that it is beyond the scope of this article to describe in-depth the results of hundreds of research articles. The reader is encouraged to further examine these topics through the references provided.

## Cardiovascular

Perhaps the most well-known human effects of n-3 are on the cardiovascular (CV) system. Dietary fish consumption and fish oil supplementation have been studied on morbidity and mortality related to cardiovascular conditions such as coronary artery disease (CAD), arrhythmias, heart failure, and hypertension. There are a multitude of reviews in the medical literature on these topics to which the reader is referred (3,12, 13, 14, 15). Probably the largest amount of n-3 CV evidence relates to primary and secondary CV prevention. While most experts recommend two servings of fish weekly (approximately equal to 400–500 milligrams daily) for primary CV prevention, and 1000 milligrams of EPA + DHA supplementation daily for secondary CV prevention (5), recent research has attempted to refine these recommendations. The challenge of determining concrete clinical recommendations is interpreting research results in the context of n-3 dose and form, study methodology including length and placebo arms, and subject demographic. That said, the effect of n-3 on hypertriglyceridemia (approximately 2–4 grams of EPA + DHA daily) is well established (5,12,16), and may lead to smaller low-density and high-density lipoprotein particle size, possibly correlated with improved CV outcomes (12). The data is mixed for the effect of n-3 intake on fatal and non-fatal CV events, with many nuances of the published research accounting for discrepancies and details that need to be further elucidated (12,13,14). Nonetheless, the fact that n-3 are generally well tolerated tips the scales in the favor of treatment for primary and secondary prevention until further research results surface.

With respect to heart failure, some initial studies have shown benefit (13,17), and the data on arrhythmias includes anti-arrhythmic effects in animal studies, and human clinical trials investigating n-3 supplementation on atrial fibrillation and ventricular tachycardia or fibrillation (13,15). Overall, the results for arrhythmias have been mixed, and depend on the patient demographic and type of arrhythmia, though some experts point to slightly more convincing evidence for the benefit of DHA rather than EPA on atrial fibrillation (12,15,18).

## Ophthalmological

The dietary intake of n-3 may benefit age-related macular degeneration (AMD) and dry eye syndrome. In one meta-analysis of nine studies involving a total of 88,974 people including 3203 AMD cases, people that ate fish two or more times per week had a decreased risk of AMD (19). Other studies have corroborated this relationship, finding that increased n-3 may decrease the risk for AMD (20,21,22,23). Dry eye syndrome (DES) is the result of changes in the amount or profile of tear production and DES has been shown to be linked to a decreased dietary intake of n-3 and/or a high ratio of dietary n-6 to n-3 (24,25). In one study of 36 patients with symptoms of dry eyes, 450 milligrams of EPA, 300 milligrams of DHA, and 1,000 milligrams of flax seed oil daily led to decreased symptoms after 90 days compared to the placebo (wheat germ oil) group (26). Other studies have found a subjective improvement in dry eye syndrome with n-3 supplementing even if objective measures don't change (27).

## Neurological and Psychological

Research has begun to document the connection between n-3 intake or status and several neurological and psychological conditions (28,29). This relationship is grounded in known aspects of brain and neuron physiology; there is a high phospholipid content (primarily DHA and arachidonic acid) in the central nervous system (28). With respect to clinical trials, many have followed up the basic science research. For example, maternal n-3 supplementation (during pregnancy and lactation) can lead to improved childhood neurological development (30). Another result showed that increasing maternal DHA intake by 100 milligrams daily could lead to an improvement in a child's IQ of 0.13 (31). In addition, low serum DHA levels in children may be associated with any number of neuropsychiatric disorders (32). Furthermore, adequate n-3 intake seems to help prevent cognitive decline in people's middle and later years. A recent study found a correlation between the n-3 content of red blood cells and both brain volume and cognitive tests that are related to increased risk of Alzheimer's disease (33). Omega-3 content of red blood cells represents n-3 intake over the past 120 days, and low red blood cell levels were associated with lower brain volume (the equivalent of 2 years more aging) and poorer performance in cognitive and memory testing.

Omega-3 fatty acids have also been studied in the context of attention deficit and hyperactivity disorder (ADHD), autism and depression (28). One review of n-3 and ADHD pointed out the heterogeneity of research methodology has made it difficult to compare studies and come to definitive clinical conclusions (34). Nonetheless, some children do seem to respond to n-3 supplementation, often in the realm of 300–600 milligrams of total n-3 daily. Another review found that n-3 supplementation correlated with a slight, but statistically-significant, improvement in ADHD symptoms (35). The effect size (SMD) was 0.31, less than pharmaceutical ADHD treatments, and seemed to correlate most with the EPA content of the supplements.

## Dermatological

Several skin conditions may benefit from either dietary or supplemental n-3. For example, by competing with arachidonic acid and lessening the concentration of the pro-inflammatory product, leukotriene B<sub>4</sub>, n-3 may help improve the clinical symptoms of psoriasis (36). Of note, the doses used to help improve psoriasis are higher than what is used in other medical conditions: benefits have been seen with EPA doses between 3.6–14 grams daily, whereas clinical trials using lower EPA amounts, with or without combination with DHA, have shown less impressive improvements in various parameters measuring the extent and severity of psoriasis (36). Another interesting area of research is the connection between



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