New Breakthroughs in OMEGA-3 Research

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Omega-3 fatty acids, in particular the long-chain fats eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found abundantly in oily fish, continue to shine as nutrients that promote health and wellbeing. In addition to well-known benefits to the heart and vascular system, researchers investigating omega-3s are uncovering new arenas for their broad spectrum of health effects, including some not previously explored.

The importance of omega-3s supplementation stems from several factors; firstly, modern diets are woefully inadequate in terms of their omega-3 content, whereas traditional diets were much higher in omega-3s. Additionally, anti-inflammatory omega-3s counteract the effects of the more ubiquitous omega-6 fats (from various vegetable oils), which are pro-inflammatory by nature and are overabundant in modern diets. Restoring this imbalance and shifting the omega-3:omega-6 intake ratio to include more omega-3s should be a goal for anyone who is looking to stay healthy.

Studies show that adults in the United States are falling short of even modest intake goals for omega-3 fats. American Heart Association recommendations include an emphasis on the intake of two 3.5-oz servings per week of oily fish in order to increase EPA and DHA intake, while the 2010 Dietary Guidelines for Americans recommended the consumption of two 4-oz servings of seafood per week to provide an average amount of 250 mg/day of long-chain omega-3 fatty acids. A study using observational data from the National Health and Nutrition Examination Survey (NHANES) from 2003–2008 revealed that average daily intakes of EPA and DHA were only 23 mg/day and 63 mg/day, respectively.\(^1\) It is clear that a greater emphasis on diet and supplementary measures is needed to enhance individual intakes of these critical health-promoting fats.

Emerging data has opened the door to research into significant benefits of omega-3s for unique indications. Recent studies have explored the effects of omega-3s in aging adults and in several chronic illnesses. Also, further investigations have been conducted to explore the association between fish oil omega-3 intake and prostate cancer in light of a 2013 study that speculated that increased intake of certain omega-3 fatty acids adversely raises the risk for prostate cancer. Ahead, we review current studies in these diverse and fascinating areas of interest.

**Aging Adults: Muscle Mass, Healthy Bones, Brain Structure, and Cognitive Function**

Sarcopenia is a condition affecting the elderly that is characterized by a loss of muscle mass. Gordon Smith and colleagues from the Washington University School of Medicine in St. Louis conducted a study assessing the ability of omega-3 fats from fish oil to slow the loss of muscle mass and function in the elderly.\(^2\)
In the study, 60 healthy men and women aged 60–85 received a daily omega-3 supplement (four 1-g pills of ethyl ester fish oil providing 1.86 g EPA and 1.50 g DHA per day) or placebo (corn oil) for six months.

Fish oil supplementation was shown to reduce the normal decline in muscle mass and function in older adults by increasing thigh muscle volume, hand grip strength, and one-repetition maximum upper and lower body strength. As such, omega-3s offer a therapeutic approach for preventing sarcopenia in older adults.

Earlier studies have shown fish oil to benefit bone mineral density through various mechanisms, including the modulation of the inflammatory response in bone tissue as well as through a regulatory effect on the function of osteoblasts and osteoclasts, the cells responsible for bone remodeling.

Tamara Harris and colleagues from the National Institute on Aging in Bethesda, MD, aimed to look at the association between fish oil consumption and the risk of osteoporotic fracture in later life. The authors analyzed data from medical records over 5–9 years of follow-up in 1,438 men and women aged 66–96. Fish oil consumption was assessed using a validated questionnaire, and individuals were classified into using fish oil “never,” “less than daily,” or “daily.” Plasma measures of phospholipid fatty acid content were also taken by gas chromatography.

The analysis showed that, in men, the group in the highest third of fish oil consumption and also with higher EPA intake had a decreased risk of fractures. In women, overall intake of omega-3 fatty acids also trended towards a protective effect against fractures, although this did not reach the level of statistical significance. The authors further found that daily consumption of fish oil in late life was associated with lower fracture risk in men, whereas daily consumption of fish oil in mid-life was most associated with lower fracture risk in women. Thus, regular consumption of omega-3 fatty acids from fish may be an important addition to an overall nutritional strategy for enhancing and maintaining bone health.

Looking into a groundbreaking new area of research, Veronica Witte and colleagues from the Department of Neurology at Charité–Universitätsmedizin Berlin investigated the impact of high intake of omega-3 fatty acids from fish on the aging brain. The prospective interventional study included 65 healthy men and women between the ages of 50 and 75 and aimed to assess whether supplementation with fish-based omega-3 fats could improve cognition and brain structure. The participants consumed fish oil containing 2,200 mg total omega-3 fats (1,320 mg EPA and 880 mg DHA), or a sunflower oil placebo, daily for 26 weeks. The results showed that the fish oil intervention improved cognitive executive functioning by 26% from baseline, whereas the placebo group showed no improvement.

What was even more fascinating about the study were the beneficial effects attributed to fish oil in supporting the microstructural integrity of white matter, as well as supporting gray matter volume in the frontal, temporal, parietal, and limbic areas of the left hemisphere of the brain.
These findings are important in that brain atrophy is a characteristic of dementia and other brain diseases, and the improvement in structural integrity with fish oil supplementation indicates its benefit in supporting cognitive function and brain structure with increasing age.

Several studies also indicate that essential omega-3 fatty acids can help support various aspects of memory function in adults. In a recently published meta-analysis, Karin Yurko-Mauro and colleagues conducted a review of clinical trials and observational studies assessing the role of omega-3 fatty acids on memory function in healthy adults. Sixteen intervention trials and 13 observational studies were included in the review and comprised participants—who were free of neurologic disease at the time of inclusion—either with or without mild memory complaints at baseline.

The final analysis revealed that supplementation of 1 g or more per day of DHA and/or EPA improved episodic memory function in adults with mild memory complaints, while changes in semantic and working memory were also significant with DHA supplementation compared to baseline measures.

**Chronic Conditions: Fatty Liver, Epilepsy, Rheumatoid Arthritis**

Non-alcoholic fatty liver disease (NAFLD) is a condition associated with the onset of metabolic syndrome and dysregulation characterized by excess fat accumulating within liver cells. NAFLD increases the risk of chronic liver conditions, liver cancer, diabetes, and heart disease. Apart from lifestyle changes, there are few other proven interventions for effectively addressing this condition.

In a recent study, Eleonora Scorletti and colleagues from the University of Southampton in the UK sought to assess the effects of supplementation with DHA and EPA on liver fat content in individuals with NAFLD. This double-blind, placebo-controlled study included 103 participants with histological confirmation of NAFLD, imaging evidence of liver fat accumulation, or presenting with features of metabolic syndrome. Individuals were randomized into two groups: the first supplemented with 4 g/day of the ethyl ester form of fish oil (providing 460 mg of EPA and 380 mg of DHA per gram) or 4 g/day of an olive oil placebo for a period of 15–18 months. Liver fat was measured by magnetic resonance spectroscopy, and red blood cells EPA and DHA levels were also assessed.

While in the overall group of participants no significant changes were noted in liver fat percentage, in those participants in which red blood cell enrichment was achieved via supplementation with DHA and EPA, levels of red blood cell DHA were linearly associated with decreased liver fat percentage. In other words, the results indicate that in those with increased uptake of DHA into red blood cells, substantial reductions in liver fat accumulation can be achieved.
Drug-resistant epilepsy is a condition defined as the failure of an individual with epilepsy to respond to two or more antiepileptic drugs. Also accompanying this serious condition is an increased risk of death from myocardial infarction. Previous animal studies have shown that the administration of omega-3 fats reduces seizures; however, two human clinical trials using relatively high doses of fish oil showed inconclusive results.

Christopher DeGiorgio and colleagues from the UCLA School of Medicine conducted a placebo-controlled crossover study of fish oil in drug-resistant epilepsy to test the efficacy of high-dose versus low-dose supplementation. Twenty-four individuals with an average age of 33 and a history of drug-resistant epilepsy were included in this triple-crossover trial in which the three groups alternated between low-dose fish oil (total omega-3 intake 1,080 mg/day), high-dose fish oil (2,160 mg omega-3/day), or a corn oil placebo for 10 weeks each, with two six-week washout periods between treatments.

The researchers found that low-dose fish oil was effective at reducing the incidence of seizures compared to placebo on a similar magnitude as that seen in antiepileptic drug trials. In addition, the low-dose fish oil moderately reduced blood pressure levels, reducing overall heart risk.

The high-dose fish oil, on the other hand, showed no difference versus placebo in reducing seizures or in improving cardiac risk factors. The authors speculate that the reason for the ineffectiveness of the high dose of fish oil may have to do with differences in lipid processing, such as causing excessive reductions of arachidonic acid and other non-esterified fatty acids in individuals with drug-resistant epilepsy compared to healthy individuals. This has been shown previously in animal models. The efficacy of fish oil in this condition likely derives from the ability of omega-3 fats to cross the blood–brain barrier, incorporate themselves into neuron membranes, modify calcium and sodium channels, and reduce membrane excitability of both neurons and heart cells.

Due to the anti-inflammatory effects of omega-3 fats, researchers have often explored their benefits for joint health. Susanna Proudman and colleagues from the University of Adelaide in Australia recently conducted a trial using fish oil in patients with recent-onset rheumatoid arthritis (RA). As omega-3 fatty acids are well-known for their suppressive effect on the synthesis of omega-6–derived pro-inflammatory eicosanoids, including prostaglandin E2 and leukotriene B4, the researchers chose to examine the benefits of a high-dose fish oil (5.5 g/day of the omega-3s DHA and EPA) versus a low-dose fish oil (designated as the control group and administered 0.4 g/day of DHA plus EPA) in individuals with early-onset RA also taking a combination of anti-rheumatic drugs. The triple anti-rheumatic drug protocol included methotrexate, sulfasalazine, and hydroxychloroquine, and doses were modified throughout the trial period based on symptom presentation. A total of 139 individuals with diagnosed RA of less than 12 months in duration were included in the year-long study (86 in the fish oil group and 53 in the control group).
The primary outcome defined by the investigators was failure of the triple-drug protocol. Failure was indicated by a change to leflunomide therapy (an immunosuppressive agent used in those with moderate-to-severe disease). After one year, only 10.5% of the subjects in the fish oil group progressed to failure of the drug therapy, while 32.1% of those in the control group progressed to failure, indicating significant benefits for the high-dose fish oil in patients with early-onset RA. Individuals in the fish oil group also experienced a higher rate of remission of disease activity compared to the control.

**Prostate Cancer Risk**

There has been increased media coverage recently related to earlier data showing a potential association between the intake of omega-3 fats and prostate cancer in men. In order to explore this connection further, Francesca Crowe from the Cancer Epidemiology Unit of the University of Oxford and co-researchers from around the world contributed to a collaborative meta-analysis to investigate the role circulating fatty acids play in prostate cancer risk. The analysis included 5,891 individuals who had developed prostate cancer and 6,649 control cases from seven studies with an average follow-up of 5.1 years. Studies were eligible for inclusion if blood levels of circulating fatty acids had been analyzed prior to a diagnosis of prostate cancer.

The results of the analysis revealed significant differences between studies in terms of the association between levels of circulating fatty acids and prostate cancer risk. The collaboration of researchers ultimately concluded that it is unclear if the modest associations of the fatty acids EPA and docosapentaenoic acid (DPA)—another omega-3 fatty acid—with cancer seen in some studies are causal factors. Overall, the researchers concluded that there is no strong evidence that circulating fatty acids are important predictors of prostate cancer risk.

Interestingly, this conclusion contrasts with the conclusions of a 2013 SELECT trial coauthored by Theodore Brasky and Alan Kristal, among others, who are also coauthors of the meta-analysis led by Francesca Crowe. The strongly worded conclusion of the initial Brasky et al. analysis of the SELECT trial stated that “this study confirms previous reports of increased prostate cancer risk among men with high blood concentrations of long-chain omega-3 polyunsaturated fatty acids. The consistency of these findings suggests that these fatty acids are involved in prostate tumorigenesis.” Apparently, after a more comprehensive review of published data in the current meta-analysis led by Francesca Crowe, the coauthors of the 2013 paper felt less strongly about the link between circulating omega-3 levels and the risk of prostate cancer.

A further meta-analysis led by Dominik Alexander of the EPidStat Institute in Ann Arbor, MI, and supported by omega-3 industry association GOED (Global Organization for EPA and DHA Omega-3s) also downplays any association between omega-3 levels and prostate cancer. In their comprehensive and systematic review, the authors included prospective studies that reported omega-3 levels quantitatively either through supplemental or dietary intake or via biomarker status. The primary outcome analyzed was incidence of prostate cancer. A total of 21 prospective cohort studies comprising 461,050 participants were included in the analysis.
Based on their findings, the researchers concluded that the meta-analysis failed to support an association between the intake of omega-3 fatty acids and the risk of prostate cancer. Taking the findings from this meta-analysis together with the one conducted by Francesca Crowe, it is clear that the association between omega-3 intake and prostate cancer is tenuous at best.

The Field Is Wide Open
Research keeps reinforcing the broad benefits of the fatty acids DHA and EPA for a variety of conditions. Despite recent negative reports in the mainstream media concerning the intake of these healthy fats, it is clear that their health benefits extend to multiple areas. In view of the fact that most adults in the United States have inadequate intakes of these nutrients, it is important that public health policymakers continue to pursue efforts to increase omega-3 consumption through diet and also emphasize supplementation as a means to bridge the gap.

References
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