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Fish Oils in Health and Disease

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A B S T R A C T

Fish oils derived from oily fish are an excellent source of omega -3 fatty acids. Omega 3 fatty acids are poly unsaturated fatty acids (PUFA) and are essential fatty acids (EFA), as humans cannot synthesise them de novo and must depend on dietary sources. Data suggests a role of omega-3 EFA in the prevention and treatment of gastrointestinal, rheumatologic, bone and respiratory illness. The National Institute of Nutrition recommends including 100-200g of fish twice a week as a preventive dietary approach for heart disease (Krishnaswamy). Epidemiological studies have linked low maternal DHA to increased risk of poor child neural development. Intervention studies have shown improving maternal DHA nutrition decreases the risk of poor infant and child visual and neural development. In children with attention problems or hyperactivity, several studies have shown depletions of omega-3 EFA in erythrocyte membranes and/or plasma compared with controls, with more severe symptoms associated with the lowest levels of DHA. Consumption of oily fish is also associated with a reduced risk of asthma in childhood. Older adults it has potential in treating age-related memory disorders and maintaining cognitive function, muscle performance and immune function during ageing.

Introduction

Fish oil is oil derived from the tissues of oily fish. Fish oil can be obtained from eating fish or by taking supplements. Fish that are especially rich in the beneficial oils known as omega-3 fatty acids include mackerel, herring, tuna, salmon, cod liver, whale blubber, and seal blubber. Omega -3 fatty acids are poly unsaturated fatty acids (PUFA) and are essential fatty acids (EFA), as humans cannot synthesise them de novo and must depend on dietary sources. Fish and sea foods are the richest dietary sources of the long-chained omega-3 EFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA is selectively concentrated in synaptic neuronal membranes and contributes to unique biophysical properties and mediate receptor activity and signal transduction. Early intervention might also prove useful in potentially treating age-related memory

disorders and maintaining cognitive function, muscle performance and immune function during ageing

General health benefits are associated with omega-3 EFA, such as cardiovascular benefits. Data suggests a role of omega-3 EFA in the prevention and treatment of gastrointestinal, rheumatologic, bone and respiratory illness. Omega-3 EFA consumption may decrease the risk of breast, prostrate and lung cancer. In utero exposure to high to higher levels of omega-3 EFA and supplementation in infant formula are associated with improved cognitive and visual performance in children. Epidemiological studies in Greenland Eskimos led to the hypothesis that marine oils rich in n-3 fatty acids (also referred to as omega -3 fatty acids) are hypolipidemic and ultimately antiatherogenic.

The National Institute of Nutrition recommends including 100-200g of fish twice a week as a preventive dietary approach for heart disease (Krishnaswamy). According to American Heart Association (AHA) Guidelines, the cardiovascular benefits of omega-3 EFA include decreased risk of arrhythmias and thrombosis, decreased triglycerides and atherosclerotic plaque growth, improved endothelial function, possible improvement in hypertension, and reduced inflammatory response.

The AHA recommends that adults eat fish atleast twice weekly, that patients with coronary heart disease should consume 1g total of EPA plus DHA per day, and that a supplement may be useful in patients with hypertriglyceridemia (2-4 g/day). The AHA suggests that consumption of more than 3g/day should be monitored by a physician, due to the potential complication of excessive bleeding with high doses. (Kris-Etherton P *et al.,* 2003)

Fish oil for the treatment of cardiovascular disease

Mechanism of Action (Daniel Weitz *et al.*, 2010)

Inflammation modulation

Fish oil's most potent effect on atherosclerosis may be related to its potential to alter plaque inflammation, thereby stabilizing vulnerable plaques. In recent years there has been a growing body of evidence that is shifting the paradigm of how inflammation is contained and dissipated. In this new model, inflammation resolution is an active process mediated by lipid-derived compounds. Newly discovered families of chemical mediators, resolvins, and protectinsare directly involved in blocking neutrophil migration, infiltration, and recruitment, as well as in blocking T-cell migration and promoting T-cell apoptosis. In addition, protectins can reduce tumor necrosis factor and interferon secretion. Interestingly, both protectins and resolvins are strictly derived from omega-3 FA. EPA is the substrate of the resolvins family and DHA can be converted to both resolvins and protectins. It may be that the effects of fish oil on inflammatory mediators underlie the positive findings demonstrated in several trials assessing fish oil and plaque stability.

Triglyceride reduction

Omega-3 FA most likely reduces serum triglyceride levels by modulating very-low-density lipoprotein (VLDL) and chylomicron metabolism. There is a consistent finding in the literature that the end effect of fish oil is decreased hepatic secretion of VLDL17—the major endogenous source of triglycerides. This effect occurs most likely through multiple mechanisms, including: (1) decreased synthesis of triglycerides because

these omega-3 FA may not be the preferred substrates of the enzyme diacylglycerol O-acyltransferase, or they may interact with nuclear transcription factors that control lipogenesis19; cellular metabolism consequently shifts toward a decrease in triglyceride synthesis and an increase in FA oxidation; and (2) the promotion of apolipoprotein B degradation in the liver through the stimulation of an autophagic process. This means that fewer VLDL particles can be assembled and secreted. Fish oil may also accelerate VLDL and chylomicron clearance by inducing lipoprotein lipase activity.

Dietary omega 3 fatty acids and the developing brain (Sheila M. Innis. 2008)

The ω-3 fatty acids are essential dietary nutrients and one of their important roles is providing the fatty acid with 22 carbons and 6 double bonds known as docosahexaenoic acid (DHA) for nervous tissue growth and function. Inadequate intakes of ω-3 fatty acids decrease DHA and increase ω-6 fatty acids in the brain. Decreased DHA in the developing brain leads to deficits in neurogenesis, neurotransmitter metabolism, and altered learning and visual function in animals. Western diets are low in ω-3 fatty acids, including the 18 carbon ω-3 fatty acid alpha linolenic acid found mainly in plant oils, and DHA, which is found mainly in fish. The DHA status of the newborn and breast-fed infant depends on the maternal intake of DHA and varies widely. Epidemiological studies have linked low maternal DHA to increased risk of poor child neural development. Intervention studies have shown improving maternal DHA nutrition decreases the risk of poor infant and child visual and neural development. Thus, sufficient evidence is available to conclude that maternal fatty acid nutrition is important to DHA transfer to the infant before and after birth, with short and long-term implications for neural function. However, genetic variation in genes encoding fatty acid desaturases also influence essential fatty acid metabolism, and may increase requirements in some individuals. Consideration of ω-3 fatty acid to include brain development, optimizing ω-3 and ω-6 fatty acids in gestation and lactation, and in fatty acid nutrition support for intravenous and formula-fed neonates is important.

Dietary omega 3 fatty acids and mental health

To date, positive results have been reported in 3 double-blind, placebo-controlled studies utilizing either 98% pure ethyl ester EPA without DHA or a combination of EPA and DHA as an adjunctive treatment for antidepressant-refractory *major depressive disorder*. In a placebo-controlled trial of EPA as an add-on therapy for major depressive disorder, Peet and Horrobin found that patients who received 1g/day of EPA were significantly more likely than controls to display a 50% reduction in Hamilton Rating Scale for Depression (HAM-D) scores. Higher doses (2-4g/day) were not more effective than placebo. Nemets *et al.,* found significant antidepressant effects using ethyl ester EPA (2g/day) in a placebo-controlled adjunctive study for refractory depression. Su *et al.,* reported a significantly greater reduction in HAM-D scores with the combination of EPA plus DHA (9.6g/day) compared to placebo.

Marangell *et al.,* conducted a 6 week double-blind, placebo-controlled study of 2 g/day of DHA monotherapy for 36 subjects with major depressive disorder. The response rates of 27.8% in the DHA group and 23.5% in the placebo group during the 6 weeks of the study were not significantly different. Positive studies either included doses of ethyl ester EPA of 1-2 g/day or used a higher dose in

combination with DHA, which might indicate that a combination of EPA and DHA maybe needed when doses greater than 2g/day are used

Attention-deficit/hyperactivity disorder and learning disabilities

In children with attentional problems or hyperactivity, several studies have shown depletions of omega-3 EFA in erythrocyte membranes and/or plasma compared with controls, with more severe symptoms associated with the lowest levels of DHA. There are currently two published placebo-controlled trials of adjunctive DHA treatment in ADHD demonstrating lack of benefit. However, combined omega-3 and omega-6 supplements (fish oil and evening primrose oil) in children with behaviour and learning difficulties have shown therapeutic benefit in 3 other studies. Richardson and Puri randomly assigned 41 children with learning difficulties and DHD-type symptoms to 12 weeks of monotherapy treatment with either a fatty acid supplement with 480 mg DHA, 186 mg EPA, 864 mg cis-linoliec acid, 96 mg γ-linolenic acid (GLA), 42 mg AA, and 60-IU vitamin E daily or placebo. ADHD symptoms were significantly reduced in children who received active treatment compared to placebo. Stevens *et al.,* randomly assigned 50 children with DAHD-type symptoms into 2-treatment groups stratified for medication and gender. Compared to placebo, fatty acid treatment for 4 months was associated with improvements in teacher-rated attention and parent-rated conduct, as well as reduction in proportion of children whose behaviour fulfilled clinical criteria for oppositional defiant disorder. Richardson and Montgomery reported on 117 children aged 5 to 12 years with developmental coordination disorder and associated behaviour and/or learning difficulties who were treated for 12 weeks with an omega-3/omega-6 supplement or olive oil placebo in a randomized, double-blind trial. Highly significant benefits for active treatment over placebo were found for both reading and spelling progress and teacher-rated ADHD symptoms, while motor skills improved significantly but similarly in both treatment groups.no adverse side-effects of fatty acid treatment were reported in these studies.

No significant protective effects were reported in other mental disorders such as Bipolar disorder, Schizophrenia, Dementia and Alzheimer's disease.

Consumption of oily fish and childhood asthma risk (Linda Hodge *et al.,* 1996)

Reduced risk of current asthma was associated with the consumption of oily fish, but not with non-oily fish. Fish oil contains the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have anti-inflammatory effects. Theoretically, EPA could either prevent the development of asthma or reduce its severity by altering two of the cardinal features of asthma, namely airway inflammation and AHR. Supplementation with EPA reduces production of leukotriene B4, a chemical mediator responsible for the recruitment of inflammatory cells, such as neutrophils, into the airways. It also reduces production of the cytokine tumour necrosis factor (TNF), which increases airway responsiveness.

Fish oil supplements given over 6-10 weeks cause a substantial uptake of EPA in neutrophil membrane phospholipids. In asthmatics, this may reduce the allergen-induced late asthmatic response, but does not change severity of asthma. However, a recent study suggests that a longer period of supplementation may be required to reduce asthma severity. Data of recent fish consumption (during the last 12 months) were

used in the present study, but may also reflect lifetime dietary habits.

In conclusion, it was shown that consumption of oily fish is associated with a reduced risk of asthma in childhood. Although further studies are required to confirm these benefits, public health interventions to increase the consumption of oily fish may reduce the morbidity and prevalence of asthma in children.

The role for dietary omega-3 fatty acids supplementation in older adults

A review by AllesioMorfino *et al.,* (2014) gathered all the most relevant recent clinical trials on omega-3 PUFAs supplementation in older adults. In particular, the effects of omega-3 FAs on different clinical outcomes, namely cognitive decline, cardiovascular system, bone health, muscle performance and immune function were examined. The literature review suggests that the omega-3 FAs may have substantial benefits in reducing the risk of cognitive decline in older people. The available data encourage higher intakes of omega-3 PUFAs in the diet or specific supplements, but more studies are needed to clarify the conflicting results in the literature on the effectiveness of omega-3 FAs in maintaining bone health and preventing the loss of muscle mass and function associated with physiological ageing. Immune function declines with age and older adults are more susceptible to infections. These ageing deficiencies can be a consequence of derangements in food intake, nutrient absorption and metabolism of nutrients, but also to alterations associated with normal ageing.

Omega-3 FAs may affect the immune response in older adults under dietary supplementation, but the available studies have not evaluated the long-term effects and the modification of immunological biomarkers after supplementation is stopped. Longer-term studies are needed to identify greater changes in study participants due to the effects of omega-3 PUFAs supplementation and to establish definitive influences on quality of life. No significant side effects were reported after omega-3 PUFAs administration, confirming the safety of using these nutritional supplements. Finally, earlier intervention might prove useful in potentially treating age-related memory disorders and maintaining cognitive function, muscle performance and immune function during ageing.

Maximum intake

The Food and Drug Administration (FDA) recommends that consumers do not exceed more than three grams per day of EPA and DHA combined, with no more than 2 grams from a dietary supplement. This is not the same as 3000 mg of fish oil. A 1000 mg pill typically has only 300 mg of omega-3; 10 such pills would equal 3000 mg of omega-3. According to the European Food Safety Authority's (EFSA) Panel on Dietetic Products, Nutrition and Allergies, supplementation of 5 grams of EPA and DHA combined does not pose a safety concern for adults. Dyerberg studied healthy Greenland Inuit and found an average intake of 5.7 grams of omega-3 EPA per day; among other effects these people had prolonged bleeding times, i.e., slower blood clotting.

Vitamins

The liver and liver products (such as cod liver oil) of fish and many animals (such as seals and whales) contain omega-3, but also the active form of vitamin A. At high levels, this form of the vitamin can be dangerous (Hypervitaminosis A).

Toxic pollutants

Consumers of oily fish should be aware of the potential presence of heavy metals and fat-soluble pollutants like PCBs and dioxins, which are known to accumulate up the food chain. After extensive review, researchers from Harvard's School of Public Health in the *Journal of the American Medical Association* (2006) reported that the benefits of fish intake generally far outweigh the potential risks. A report by the Harvard Medical School studied five popular brands of fish oil, including Nordic Ultimate, Kirkland and CVS. They found that the brands had "negligible amounts of mercury, suggesting either that mercury is removed during the manufacturing of purified fish oil or that the fish sources used in these commercial preparations are relatively mercury-free".

Microalgae oil is a vegetarian alternative to fish oil. Supplements produced from microalgae oil provide a balance of omega-3 fatty acids similar to fish oil, with a lower risk of pollutant exposure.

It can be concluded that, in order to get maximum benefits from fish consumption, it is recommended to consume 100-200g of oily fish at least twice a week. It is essential for the cognitive development of growing foetus and infants, for the mental well being of children and adults, children with ADHD are especially benefitted. Consumption of oily fish is also associated with a reduced risk of asthma in childhood. Older adults it has potential in treating age-related memory disorders and maintaining cognitive function, muscle performance and immune function during ageing.

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