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Review Article

Docosahexaenoic acid supplementation: a need or a commercial hype?

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ABSTRACT

Docosahexaenoic acid (DHA) is an important component of the brain and is essential critical for optimal brain health and function. With revealing of its beneficial effects on cognitive function, neurological, cardiovascular system and anti-inflammatory benefits, DHA has recently gained huge attention. As a result, the market is stocked with products supplemented with DHA claiming various health benefits. This review attempts to elucidate the current findings of DHA supplementation as a pharmacological agent with both preventive and therapeutic value.

Keywords: Docosahexaenoic acid, δ-linolenic acid, Eicosapentaenoic acid

INTRODUCTION

Fat is an essential component of our diet. Humans can synthesize saturated and monounsaturated fatty acids, but not n-3 and n-6 families of long chain polyunsaturated fatty acids (LCPUFA) and thus these are termed as "essential" fatty acids. There are three major dietary n-3 fatty acids: δ-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA, a 22-carbon LCPUFA of omega-3 family, is a key component of cell membranes and has gained much attention over the past decade with evidences of its essentiality for fetal growth and development especially brain and eye.[1] This has increased the inquisitiveness of researchers to explore the role of DHA in health and pathophysiology of various diseases in adults. Recently, the positive roles of DHA in cancer, cardiovascular diseases and various mental ill-nesses including depression, attention-deficit hyperactivity disorder and dementia have been suggested. DHA is also being claimed to have pleiotropic effects against inflammation, platelet aggregation, hypertension and hyperlipidemia. Exploiting the current situation, food and dietary supplement market is being flooded with costly DHA enriched food not only for infants but also for adults claiming various health benefits. This review tries to explore whether DHA actually provides the said benefits or it is just a commercial hype created by industries for their commercial benefit.

SOURCES OF DHA AND NEWER DHA ENRICHED PRODUCTS

The best natural source of DHA for newborns is mother's milk. DHA is also found in marine foods, both of animal or vegetal origin, especially in fatty fish such as tuna, mackerel, menhaden, salmon and microalgae. In the body small amount of ALA can be converted to DHA. ALA rich products include

land-based plant foods, such as nuts, flax seeds, etc. Changes in eating habits have led to low consumption of ALA and DHA in the diet which has promoted the development of nutritional supplements rich in DHA. Formula feed with composition resembling mother's milk that contain the required amount of DHA are available. DHA additions to various foods such as dairy products, juices, beverages, bakery products, etc. are being tried and are available in some countries. The most recent advance is the generation of transgenic animals. Fat-1 gene has been identified in the conversion of n-6 fatty acid to n-3 fatty acid.[2] Expression of this gene in animals has resulted in high DHA contents in the animals' products, including milk, fat, and meat.

DHA AND HEALTH BENEFITS

DHA in pregnancy

DHA supplementation during pregnancy has been associated with longer gestation and increased concentrations of EPA and DHA in fetal tissues.[3] One mechanism by which DHA may decrease the incidence of preterm birth is by decreasing prostaglandin (PG) E2 and F2α production.[4] Ramakrishnan et al. found that women who had DHA supplementation from gestation week 24 until full-term delivery carried their infants significantly longer than did the women in the placebo group. DHA ingestion during pregnancy leads to optimal pregnancy length and decreases pre-term births.[5]

Fetal, infant growth and development

Brain development in humans takes place primarily in the last trimester in utero and in the first few years of post-natal life. During pregnancy, the placenta transfers nutrients, including DHA, from the mother to the fetus. The amount of DHA in the fetus is correlated with the amount ingested by the mother.[5]

Several studies confirm the benefits of DHA supplementation during pregnancy in terms of proper cell membrane function and development of the fetal brain and retina. Judge et al. found that children whose mothers had taken DHA supplementation during pregnancy had significantly better problem-solving skills at 9 months than those whose mothers had not taken DHA supplementation during pregnancy, but these results were not seen on recognition memory tasks.[6] Another study in children of 2.5 years of age whose mothers had EPA + DHA supplementation during pregnancy (20 weeks of gestation until delivery) compared with children in a placebo group. Children in of mothers supplemented with EPA + DHA group attained significantly higher scores for eye and hand coordination than those in the placebo group.[7]

Infants are born with a poorly developed visual system, but during the first year of life vision develops rapidly. DHA accounts for approximately 50-60% of the total fatty acid content within rod outer segments of photoreceptors.[8] It is thought to play an important role in providing an adequate environment for conformational rhodopsin changes and in modifying the activity of retinal enzymes. Bush et al. demonstrated that DHA plays an important role in the regeneration of rhodospin.[8]

In 2010 U.S. Department of Health and Human Services dietary guidelines recommend that pregnant or breastfeeding women should "consume 8-12 ounces of seafood per week from a variety of seafood types". Ingesting 8-12 oz of seafood per week, depending on the type of fish, is equivalent to w 300-900 mg EPA + DHA per day.[9]

Role of DHA in adults

DHA and CNS

DHA & neurotransmitters: DHA promotes optimal neuron functioning. A number of studies have shown that a DHA-supplemented diet can restore neurotransmitter release in the hippocampus and reverse age-related impairment of memory acquisition.[10] This may be due to the fact that DHA increases the fluidity of cell membranes, which improves their ability to release neurotransmitters and cell signaling.[11,12] Another important effect of DHA is an increase in the density of nerve outgrowths called dendrites responsible for improved learning in rats as well as humans.[13]

DHA has rather complex effects on a number of neurotransmitters, including serotonin, norepinephrine, acetylcholine, glutamate, and dopamine.[14] Deficiencies in DHA have been shown to lower level of dopamine and the dopamine receptor D2 in the frontal lobe, which can result in problems with attention and learning.[15]

DHA & neurodegenerative diseases: With an increase in life expectancy, there has been a considerable increase in the prevalence of diseases associated to age related diseases, especially neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.[16]

DHA is present in high concentrations, especially in the phospholipids of neuronal and glial membranes. However it reduces significantly as ageing progress. Besides this, DHA also mediates neuroprotective effects by a metabolic derivative neuroprotectin D-1 which protect neurons against oxidative stress, inflammation, disruption of the cytoskeleton and from the activation of apoptotic signaling pathways. In neurodegenerative diseases, there is a significant reduction in the DHA content of the brain leading to reduction in the fluidity of neuronal membranes and an alteration of the neuronal homeostasis.[17]

The greatest evidence about the neuroprotective effect of DHA has been observed in Alzheimer's disease. DHA has been proposed to suppress the cytotoxic effects of the accumulation of the β-amyloid peptide.[18] Results from a

randomized double-blind placebo controlled study showed that patients with very mild Alzheimer's disease, n-3 fatty acid supplementation was associated with a significantly higher mean Mini Mental State Examination scores (i.e. less severe Alzheimer's disease symptoms) at 6 months compared to placebo-treated group. Effects of treatment were not significantly different in patients with severe cases of Alzheimer's disease.[19] These results indicate that supplementation with n-3 fatty acids may be more effective in the treatment of early stage Alzheimer's disease. Patients with cognitive impairment given 240 mg/day DHA for 90 days displayed improved short-term memory; however, visuo-spatial/construction and language scores did not improve. Boston et al. have reported no improvement in Alzheimer's symptoms in patients with Alzheimer's disease receiving 1 g/day EPA for 12 weeks. These studies continue to support the notion of varying efficacy depending on Alzheimer's severity.[20] An additional factor to consider when interpreting data on Alzheimer's disease is the allele, apolipoprotein E epsilon 4 which influences development of Alzheimer's disease, regardless of diet.[21]

DHA, depression & suicidal risk are emerging problems. Furthermore, rates of anxiety disorders, anger dys-control, insomnia, violent suicides are increasing. Scientists have proposed a common link between these disorders and chronic brain inflammation with a high level of inflammatory mediators, such as cytokines and inflammatory PGs.[22] DHA has anti-inflammatory action and affects serotonergic and dopaminergic neurotransmission[14,15,23] and is expected to positively influence neuro-psychiatric disorders such as schizophrenia, borderline psychotic personality, suicide, hostility/aggression, bipolar disorder, and major depression.

Suicide risk has also been linked to low omega-3 levels in the blood and cell membranes.[24] In a study at the Department of Neuroscience at the New York State Psychiatric Institute 33 medication-free, depressed patients were followed for two years. Seven of the subjects attempted suicide. Low plasma DHA percentage in serum phospholipids and a high ratio of omega-6 fats to omega-3 fats accurately predicted the suicide attempts.[25]

The evidence for the effect of omega-3 oils on another neurotransmitter, glutamate is still being debated. There is compelling evidence that a number of neuropsychiatric disorders, including schizophrenia, bipolar disorder, major depression, are related to abnormalities in glutamate neurotransmission.[26] DHA may play a significant role in these diseases by reducing excitotoxicity.[27] Kamphuis et al. have reported that every 50 mg/day increase in n-3 fatty acid intake was correlated with a 7% risk reduction of depressive symptoms in elderly men.[28] Furthermore, Su et al. found that following 4 weeks of intervention, subjects treated with EPA/DHA displayed significantly lower depression scores as compared to controls.[29] On the other hand, beneficial effects of n-3 fatty acids on prevention or improvement of perinatal depression were not observed in recent clinical trials.[30]

DHA & attention deficit hyperkinetic disorder (ADHD): DHA seems to play an important role in the treatment of ADHD. ADHD is associated with low red blood cell DHA and high n-6 fatty acid levels. Stevens et al. found that EPA levels of red blood cells were positively associated with reduced disruptive behavior in children with ADHD receiving 480 mg/day DHA and 80 mg/day EPA for 4 months.[31] Conversely, in some studies no improvement in ADHD symptoms in children receiving DHA was seen.[32,33]

DHA and cardiovascular diseases

Cardiovascular diseases are one of the leading causes of morbidity and mortality in the world. DHA exerts cardiovascular benefits through beneficial modifications in the lipoprotein profile. Studies suggest supplementation with DHA alone or in combination with EPA in subjects with hypertriglyceridemia results in reductions in plasma triglyceride levels.[34,35] Contrary to this some clinical trials did not report significant triglyceride-lowering effects.[36,37]

Benefits of fish oil on LDL and/or high-density lipoprotein cholesterol metabolism appear inconsistent.[38,39] Inflammation is now recognized to be a major contributor to the underlying mechanism of atherosclerosis.[40] DHA is thought to have anti-inflammatory,[23] anti-oxidative effects[41] and improve cellular function through changes in gene expression.[42] Circulating markers of inflammation, such as C-reactive protein (CRP), TNF a, and some interleukins (ILs) (IL-6, IL-1), correlate with an increased probability of experiencing a cardiovascular event.[43] Treatment with n-3 fatty acids was associated with reductions in plasma levels of tumor necrosis factor and interleukin-1in healthy subjects.[44] Conversely, Mori et al. showed that neither purified EPA nor DHA given at 4 g/day for 6 weeks to subjects with type 2 diabetes significantly decreased IL-6 or CRP levels.[45]

There have been conflicting results about omega-fatty acids use with regard to major coronary events and myocardial infarction. EPA + DHA has been associated with a reduced risk of recurrent coronary artery events and sudden cardiac death after an acute myocardial infarction and a reduction in heart failure events.[46] However in another study, no significant difference in sudden cardiac death or total mortality was found between an EPA + DHA supplementation group and a control group in those patients treated after myocardial infarction.[47]

Omega-3 fatty acids have been shown to increase platelet responsiveness to subtherapeutic anticoagulation therapies. In a study, patients receiving standard dual antiplatelet therapy (aspirin 75 mg/d and clopidogrel 600-mg loading dose followed by 75 mg/d) were assigned to either EPA + DHA supplementation or placebo. After 1 month of treatment, the P2Y12 receptor reactivity index (an indicator of clopidogrel resistance) was significantly lower in patients taking EPA + DHA.[48]

DHA may also play a role in regulation of blood pressure. This effect may be mediated through an alteration in the balance between vasoconstrictive PGs and increasing production of vasodilatory prostacyclin. A study by Mori et al. reported a significant reduction in systolic and diastolic blood pressure in subjects with overweight by feeding 4g/day purified DHA.[49] Anti-arrhythmic properties of n-3 fatty acids are another area of interest associated with CVD. The membrane enrichment with EPA/DHA may result in increasing membrane fluidity in cardiac cells, thereby preventing atrial fibrillation.[50] Consuming 3 g/day encapsulated fish oil for 6 weeks reduced inducible ventricular tachycardia and risk of sudden cardiac death among patients with coronary artery disease.[51]

DHA and cancer

Arachidonic acid (AA), a precursor of PGs and lipoxygenase products stimulates proliferation of several types of tumor cells. Human breast cancer cells grown in athymic nude mice, on fish oil diet exert suppressive effects on growth and metastasis. The effects of fish oil are due to the EPA and DHA in the fish oil and the mechanism likely involves inhibition of eicosanoid synthesis from AA.[52] Arachdonic acid also suppresses apoptosis of W256 carcinosarcoma cells in culture. No suppression was observed with DHA.[53]

DHA and vision

Many studies demonstrated that DHA has a protective role in the retina. Connor et al. in a mouse model of oxygen-induced retinopathy showed that increasing omega-3 PUFA tissue levels by dietary or genetic means decreased the avascular area of the retina by increasing vessel regrowth after injury, thereby reducing the hypoxic stimulus for neovascularization.[54]

DHA, immune system and inflammation

DHA is shown to have a positive effect on the immune system of the individual. Mechanisms to explain the anti-inflammatory actions of omega-3 PUFAs include: Prevention of conversion of AA into proinflammatory eicosanoids, such as PGs and leukotrienes (LTs) via substrate competition, provide alternative substrate to produce less potent LTs, PGs, thromboxanes and convert EPA and DHA into bioactive metabolites, such as resolvins with anti-inflammatory and pro-resolving properties both *in vitro* and *in vivo*.[23] Resolvins block neutrophils transendothelial migration, enhance phagocytosis, ROS generation, pathogen killing and inhibit pro- inflammatory cytokine production, adhesion molecule mRNA expression.[55]

Anti-inflammatory actions and positive modulation of immunity has led to potential role of DHA in asthma, ocular angiogenesis, inflammatory bowel disease and peritonitis.[56] There is also evidence that mothers who use DHA supplementation during pregnancy and breastfeeding may protect their children against allergies. This may be due to decreased levels of body cells associated with inflammation and immune response.[57]

Rheumatoid arthritis is one of the most common inflammatory illnesses that have shown improvement by n-3 fatty acid supplementation. In a meta-analysis conducted by Goldberg and Katz, it was found that n-3 fatty acid supplementation may improve pain intensity, morning stiffness, number of affected joints, and amount of medication needed to alleviate symptoms of this disorder.[58]

DHA and other benefits

There are some evidences in favor of effectiveness of DHA in improving functions of other systems, including immune system, reproductive system, skin, and others. Supplementation with n-3 fatty acid during infancy with cod liver oil may also prevent type 1 diabetes, another autoimmune condition.[59] The role of n-3 fatty acids in the reproductive system appears to benefit both sexes; decreased DHA in spermatozoa may be associated with infertility.[60] Kim et al. have shown that topical agents containing n-3 fatty acids may possess anti-aging effects by increasing gene expression of collagen and elastic fibers in both young and aged human skin.[61] Finally, the pleiotropic effects of n-3 fatty acids may be the reasons behind their effectiveness in reducing post-transplant complications and improving the graft function observed in human cases.[62]

HARMFUL EFFECTS

Despite beneficial effects of LCPUFA supplementation, their use is not fully devoid of harmful effects. The anti-thrombotic action of LCPUFAs could be of concern in high risk people.[63] The inhibition of platelet aggregation which is responsible for some efficacious effects of LCPUFA in cardiovascular disease[64] can contribute to stroke or bleeding in high risk populations such as women with complicated pregnancies. However, there are no current reports of LCPUFAs and adverse birth outcomes. Second potentially harmful effect can be immune depression. The anti-inflammatory benefits of DHA could further decrease immune responses in an already immune-compromised person, However, detrimental effects to immune compromised persons have not been reported thus far. Third effect of LCPUFA supplementation is gastrointestinal intolerance. Rice et al. demonstrated no positive effect of supplementation on ventilator-free days and observed an increase in gastrointestinal morbidity.[65] However, this trial didn't single out DHA as a supplement but was combined with other antioxidant and micronutrient ingredients which may have caused the observed morbidities. Finally, the most significant potential effect could be related to the chemical oxidation products formed from LCPUFAs. Although these oxidation products have not yet been identified *in vivo*, their actions *in vitro* indicate that they produce mutagenic and carcinogenic responses.[66,67] Oxidation products are of greatest concern in foods that

have been artificially enhanced with LCPUFAs because they lack naturally occurring antioxidants that are available in foods which have endogenous LCPUFA, such as fish.[68] Correct storage and cooking of supplemented foods are a source of concern for exposure to oxidation products such as unsaturated aldehydes which have defined mutagenic properties. Furthermore, these products vary in their omega-3 fatty acid contents, making it difficult to regulate the net daily omega-3 fatty acid intake. Above all, higher cost of these products than their non-enriched counterparts is a major area of concern. Although products from transgenic animals seems promising, but time will identify whether or not they will be able to appear and survive in the market place with potential sensory and safety issues yet to be addressed.

CONCLUSION

DHA plays an important role in normal functioning of the body and is a dietary necessity. There is no doubt in DHA essentiality for proper fetal and infant development. The consensus document recommends an average DHA intake of at least 200 mg/day during both pregnancy and lactation.[9] There are evidences of improved cardiovascular function in terms of anti-inflammatory properties, reduced major coronary events, and improved anti-platelet effects with DHA supplementation. Another area that has recently gained attention is positive effects of DHA supplementation on cognition, in depression and neurodegenerative disorders.

The so claimed preventive role of DHA in various diseases along with safety issues can only be established through long term studies. Nevertheless, the available results of the studies about pleotropic effects of DHA make it a safe link to a healthier life. The commercial sector particularly the food market and dietary supplements is making huge benefits out of the situation and the market is being bombarded with such products. Though seems to be a valid and beneficial approach for all but an area of concern with DHS supplementation or consumption are the potential harmful effects that are speculated though not confirmed yet.

Further research will determine the biological effects, cost-effectiveness, and consumer acceptability of such enriched products. Furthermore, additional controlled clinical trials are needed to assess long-term consumption or supplementation clinical outcomes including quality of life and safety aspects.

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