



DHA AS A HEALTH SUPPLEMENT: A REVIEW

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ABSTRACT

Docosahexaenoic acid (DHA), an omega-3 fatty acid essential for the growth and functional development of the brain in all the ages of human being which includes infants, children as well as adults. DHA is the major component of the sea food mainly fish. Fish gets DHA directly from the consumption of marine organisms like algae or plankton. Tuna, Salmon, herring are the good sources of omega-3 fatty acids. According to WHO, recommended daily intake of omega-3 polyunsaturated fatty acids (EPA and DHA) is 0.3-0.5g/day. Deficiency of DHA in infants is associated with learning impairment, cardiovascular diseases, depression and cystic fibrosis. Various studies have shown a strong correlation between deficiency of DHA and increase in sudden cardiac death. Many independent studies shows that the children with higher levels of DHA in breastfed have affected better in mental and visual abilities as compared to the children not containing DHA in their diets. This review focuses on the role of DHA in prenatal, lactating women, infants or growing children and other vital diseases. It also discusses the therapeutic uses, metabolic pathway, adverse effect of DHA and its interactions with other drugs.

KEYWORDS: Docosahexaenoic acid DHA, Eicosapentaenoic acid EPA, LCPUFAs, Prenatal, cardiovascular diseases.

INTRODUCTION:

DHA, an essential long chain polyunsaturated omega-3 fatty acid (LCPUFAs) that humans are unable to synthesize *de novo*. In 1923, the notion of essential fatty acids were evolved after it was discovered that rats deprived of polyunsaturated fatty acids developed illness and named as Vitamin F. The clinical use of LCPUFAs was confirmed in the nineties when epidemiological data supported the hypothesis and clinical trials preferred DHA for population with risk of heart disease¹². Anthropological data reported that modern man has shifted away with the enclosure of marine foods in the diet and seems toward a diet high in saturated fats which led to the predominance of more intakes of omega-6 fatty acids. Green vegetables especially salad; vegetable oils such as soyabean oil, flaxseed oil and sea food like fatty fish mainly salmon, tuna contain the alpha-linolenic acid (Precursor of DHA) which metabolically converts into EPA (20:5 n-3) and DHA (22:6 n-3) in the body. But, unfortunately quantity taken in the food is not enough for the proper maintenance of the body in maximum population and in addition, some individuals don't want to consume sea food in their diet.

The beneficial effects of DHA have been reported in various clinical trials³. Role of DHA in every age group plays a key role itself especially in children. It is the structural and functional component of the proper vision and number of other body functions such as development of cell membranes in the brain and manages blood clotting. During fetal development, DHA is preferentially transported across the placenta into fetal circulation⁴. In 2010, U.S. Department of Health and Human Services dietary guidelines recommend that women who are pregnant or breastfeeding should consume 8 to 12 ounces of seafood per week from a variety of seafood types⁵. Average daily intake of DHA in pregnant and lactating women should be 200 mg/day⁶. At the early ages of life (upto 5 years) brain mass increases approximately 3.5 times, so as a result at this age, neurological development is highly dependent on proper intake of omega-3. DHA supplementation is associated with higher scores on listening comprehension and active attentive mind in school going children when compared to DHA deficit children⁷. The American Dietetic Association recommends 500 mg/day intake of DHA in infants and children⁸⁹. Other uses of DHA involve prevention of cardiovascular disease, depression, autoimmune disease, inflammation¹⁰. Recent preclinical studies demonstrate the use of DHA against dementia or Alzheimer disease¹¹.

In the present time, many therapeutic uses of DHA have increased the demand of DHA. In past, major source of DHA was fish and other sea foods and due to this reason it was not available to maximum population. In recent past as commercial level DHA has synthesized from fermentation technology using microalgae, resulting in high purity of DHA in addition with good availability and reduced cost leading to increased use of DHA day by day. Soft gelatin capsules of DHA in combination with EPA (SEACOD[®]) are commercially available.

According to WHO, recommended daily intake of omega-3 polyunsaturated fatty acids (EPA and DHA) is 0.3-0.5g/day. Deficiency of DHA in infants is associated with learning impairment, cardiovascular diseases, depression and cystic fibrosis. Various studies have shown a strong correlation between deficiency of DHA and increase in sudden cardiac death. Many independent studies shows that the children with higher levels of DHA in breastfed have affected better in mental and visual abilities as compared to the children not containing DHA in their diets.

DHA in Prenatal and Childhood:

- 1. DHA in prenatal:** Both neural integrity and function can be permanently disturbed by deficits of omega-6 and omega-3 essential fatty acids during foetal and neonatal development^{12,13}. DHA plays an important role in the maintenance of normal functions. During foetal development, DHA is preferentially transported across the placenta into fetal circulation¹⁴. The 2010 U.S. Department of Health and Human Services dietary guidelines recommend that women who are pregnant or breastfeeding should consume 8 to 12 ounces of seafood per week from a variety of seafood types⁵. Ingesting 8–12 oz of seafood per week, depending on the type of fish, is equivalent to 300–900 mg EPA+DHA per day. Unfortunately, this amount is not being met by most mothers in the United States and Canada, which means that infants many not be receiving adequate amounts of these vital nutrients in the womb¹⁵.
- 2. DHA in childhood:** DHA is important for the proper functional growth throughout life, but it plays a significant role in the development mainly of neural tissues and brain in early life stages i.e. first 2 years of life. Human brain rapidly increases (approx. 3.5 times) in mass during early stages of life. The important role of optimal DHA and ARA nutrition in cognitive development has also been established through numerous studies during infancy and through preschool. DHA supplementation keeps heart healthy.

DHA in Cardiovascular Diseases:

Consumption of saturated fats has increased the number of patients with coronary heart disease. The American Heart Association estimates that 57 million Americans have heart problems, causing 9,54,00 deaths per year. Various pharmaceutical drugs are mainly statins such as lovastatin, cholestyramine are given to decrease the serum triglycerides and LDL-cholesterol. But these drugs have significant side effects, for e.g. Statins disturb the GI tract and may elevate the liver enzymes etc. However, reduction in lipid level can be better achieved with omega-3 fatty acids specially DHA with no side effects. Fish oil not only reduces triglycerides in the blood, it also prevents cardiac arrhythmias.

DHA in Depression:

Antidepressants drugs have their adverse effects such as behavioral changes and suicidal attempts in adults as well as children. Recently, FDA has restricted all drug manufacturer to add 'black box' warnings to antidepressant drug. The study of nearly 22,000 patients revealed that those who regularly took cod liver oil, which is rich in omega-3 fatty acids, were about 30% less likely to have symptoms of depression than those who did not⁴.

Omega-3 fatty acids deficiency changes the fatty acid composition of key organs mainly brain which affects the membrane viscosity. Any change in the membrane viscosity affects the steps in the metabolism of the neurotransmitter serotonin, which plays an important role in the pathophysiology of depression. One of scientist reported a relation between human milk DHA content and the chances of depression. He concluded that women are less likely to PPD as their DHA status improves, apparently by intake of omega-3 fatty acids¹⁶.

EXPERT RECOMMENDATIONS:

A number of expert groups have considered the safety of, and the physiological need for, the addition of preformed LCPs to infant formulas. As early as 1991 the

European Society for Pediatric Gastroenterology and Nutrition (ESPGAN) recommended addition of DHA and ARA to formulas intended for preterm infants¹⁷. This was followed in 1992 by a similar recommendation from the British Nutrition Foundation¹⁸.

In 1993 an expert committee was assembled under the auspices of the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations and tasked with drafting a report on the role of fats and oils in human nutrition; as part of their considerations they surveyed the role of lipids in early development. As a result, this committee recommended the addition of preformed ARA and DHA to both term and preterm infant formulas¹⁹. In addition, the Bureau of Nutritional Science of the Canadian Health Protection Branch assembled an expert committee to address the nutritional needs of the preterm infant; this expert group also recommended that preformed ARA and DHA be added to preterm infant formulas, so long as the safety of the LCP source used had been demonstrated. An expert panel assembled by the International Society for the Study of Fatty Acids and Lipids (ISSFAL) has also recommended the addition of DHA and ARA to infant formulas²⁰.

Mechanism of Action:

DHA is metabolically active and has been the focus of many studies in nutrition, neurodevelopment and immunology^{21,22,23}. Exact mechanism of DHA is not well known but it has effects on receptor-mediated signaling, changes in membrane fluidity and enhancement of the production of anti-inflammatory lipid mediators due to the availability of DHA as substrate.

DHA interacts with plasma membrane bound Toll-like receptors (TLRs), G-protein coupled receptor (GPR) 120 and nuclear receptor PPAR γ and functions as an agonist or antagonist in signaling responses. DHA deficient infants have decreased dopaminergic response²⁴. GPR120 is highly expressed on pro-inflammatory macrophages, interacts with DHA and amend anti-inflammatory pathways. TLRs play an important role in adaptive and innate immune responses²⁵.

Cellular membranes involve the mechanism of lipid-rafts formation, which are a collection of lipid membrane microdomains rich in glycolipids, cholesterol. Incorporation of DHA displaces saturated fatty acids within the membranes and thus disrupts lipid raft formation.

Other lipid-based anti-inflammatory mediators of cyclooxygenase collectively termed as resolving D series, oxygenated products of DHA possessing triple bonds are termed protectins and specialized form in the neural tissues termed as neuroprotectin D1 which prevents inflammation, and oxidative stress.

Metabolic Pathway:

A series of elongation enzymes add 2-carbon units to the fatty acid backbone. The conversion of ALA to EPA and DHA occurs in liver in the endoplasmic reticulum (Fig.1)

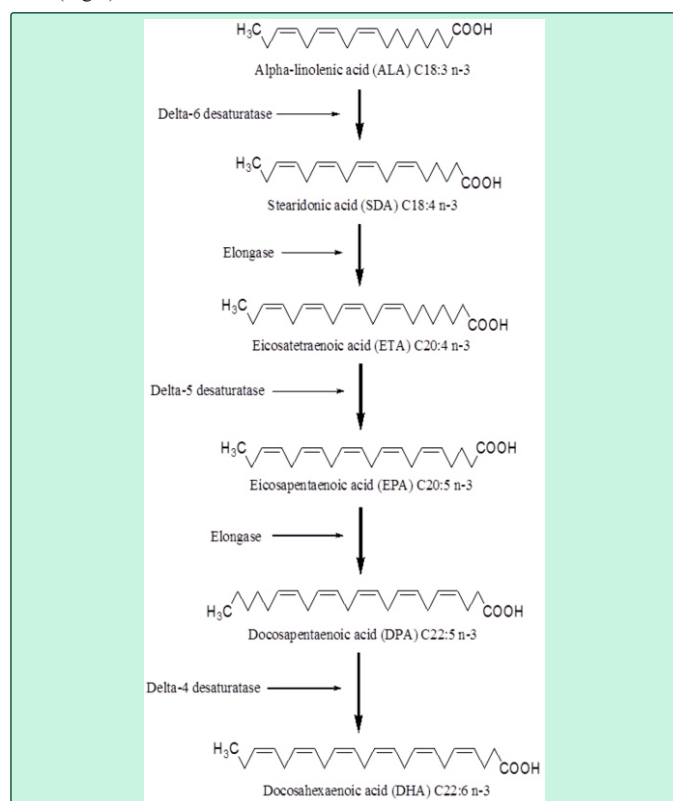


Fig.1: Biochemical pathway for the interconversion of ALA to DHA.

Therapeutic Uses:

DHA is an omega-3 fatty acid essential part of the cell membranes of the neurons as well as retinal cells plays an important role in the proper growth of the nervous systems and vision. High concentrations of DHA are found in the central nervous system. Researchers has shown that DHA plays a main role in the regeneration of rhodopsin, a visual pigment that functions to convert light to images received by the brain. When dietary omega-3 intake is low, the retina conserves and recycles DHA²⁶. In the last trimester of pregnancy, most of the DHA accumulates in the brain, due to this reason preterm infants may have improper development of vision and brain if they don't receive adequate amount of DHA through their diets.

DHA also have beneficial effects on cardiovascular diseases by enhance the HDL/LDL cholesterol ratio results in decrease risk of coronary heart disease. DHA has been employed in various diseases such as rheumatoid arthritis, depression, diabetes and cancer. Mice fed with omega-6 rich diet resulted in stimulation of growth and metastasis of human breast cancer cells (grown in mice) whereas diet containing DHA exhibited suppressive effects on the cancer cells²⁷.

Adverse Effects:

DHA is safe when used in appropriate amount. Higher amounts of DHA intake can cause side effects. According to FDA, consumption of more than 3g/day of DHA per person may increase bleeding time by thinning the blood, also have an effect on glycemic control in non-insulin dependent diabetics' patients or may increase low-density lipoproteins and cholesterol levels. Other side effects observed of DHA are gastric intolerance, bruising, nausea, nose bleeding etc.

Higher intake of omega-3 fatty acids mainly DHA, may decrease the capability of the immune system to demolish pathogens and also affect inflammatory responses in individuals with autoimmune and inflammatory disease²⁸. Some immunosuppressive effects from supplementation with EPA and DHA have been observed in studies comparing immune cell function *ex vivo* at doses as low as 0.6 grams DHA per day. It remains unclear whether the *ex vivo* evidence would translate to effect of impaired immune response *in vivo*²⁹. Therefore, caution should be considered while supplementation of DHA/EPA in already immune-compromised patient.

Other adverse effect of DHA is the most significant, related to the chemical oxidation products formed from long chain polyunsaturated fatty acids. Oxidative products are of greatest concern in foods that have omega-3 fatty acids and lacking naturally occurring antioxidants. Although, these oxidation products have not yet been identified *in vivo*, but their *in vitro* action indicates that they produce carcinogenic and mutagenic responses^{29,30,31}. So, proper storage and cooking of omega-3 are of concern to hinder the exposure to oxidative products such as α,β -unsaturated aldehydes which have mutagenic properties.

COMMERCIAL FORMULATIONS:

Table 1: Available marketed formulations of DHA of various dosage forms

Sr. No.	Brand Name	Dosage form	Company
1	Pure DHA	Soft gelatin capsules	Child Life
2	Baby's DHA	Liquid	Nordic Naturals
3	SEACOD®	Soft gelatin capsules	Sanofi consumers
4	Prenatal DHA	Soft gelatin capsules	Child Life
5	Nordic omega-3 Gummies™	Chewable gummies	Nordic Naturals
6	Nordic Omega-3 Fishes™	Fishes	Nordic Naturals
7	Toddler DHA	Toddler	Spectrum Essentials
8	Sara Lee® soft and smooth with DHA	Bread	Sara Lee
9	Vegan omega-3 DHA	Liquid	Deva
10	DHA	Soft gelatin capsules	Metabolics®

Interactions of DHA:

Table 2: Showing interactions of DHA with other drugs

Sr. No.	Drug	Interactions
1	Antihypertensive drugs such as captopril, enalapril, losartan, diltiazam, hydrochlorothiazide, furosemide	Consumption of DHA with high blood pressure medication may low the blood pressure too much
2	Anticoagulant/Antiplatelet drugs like heparin, warfarin, NSAIDs such as naproxen, ibuprofen, diclofenac	Intake of DHA with the drugs that slow blood clotting, might increase the chances of bleeding and bruising because of thinning of the blood
3	Aspirin	Aspirin sensitive patient may have breathing problems if intake DHA

CONCLUSION:

The demand of DHA in present population is increasing due to intake of high western diets, rich in omega-6 and beneficial effects of DHA on health especially in pediatrics and diseases like cardiovascular, depression. In past, as major source of DHA was only sea food whereas, in recent past, commercial level DHA is synthesizing with good availability and reduced cost, and therefore, use of DHA is increasing day by day.

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