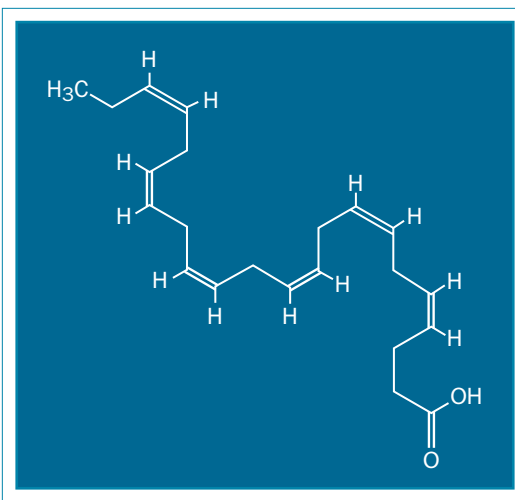


Docosahexaenoic Acid (DHA)

Introduction

Docosahexaenoic acid (DHA) is an omega-3 fatty acid that falls into the larger category of polyunsaturated fatty acids (PUFAs). Although many chronic conditions are associated with excessive intake of dietary saturated and trans fatty acids (including obesity, insulin resistance, coronary heart disease, and some forms of cancer), research shows omega-3 fatty acids, including DHA, are essential in the prevention and treatment of numerous diseases. DHA has been shown to be particularly important for fetal brain development, optimal development of motor skills and visual acuity in infants, lipid metabolism in children and adults, and cognitive support in the elderly. *In vitro* and animal studies also suggest a beneficial role for DHA in certain types of cancer.



Biochemistry

DHA is a 22-carbon carboxylic acid with six cis double bonds, the first being on the third carbon from the omega end, hence the fatty acid nomenclature 22:6, n-3. Other names for DHA include cervonic acid¹ and all-cis-docosa-4,7,10,13,19-hexaenoic acid. Although fish oils are rich sources of DHA, most commercially available fish oils contain higher amounts of eicosapentaenoic acid (EPA) than DHA, as well as lesser amounts of other fatty acids. Most DHA found in extracted fish oil preparations is derived from microalgae consumed by the fish. Pure DHA from fish oil is not readily available on the commercial market due to difficulties in the extraction and purification processes. Currently, the best commercial source of pure DHA is derived from a controlled fermentation process using two microalgae, *Cryptocodinium cohnii* and another species of the *Schizochytrium* genus. DHA produced from this fermentation process is of high purity, vegetarian, and is the only type of DHA currently accepted for use in infant formulas in the United States.²

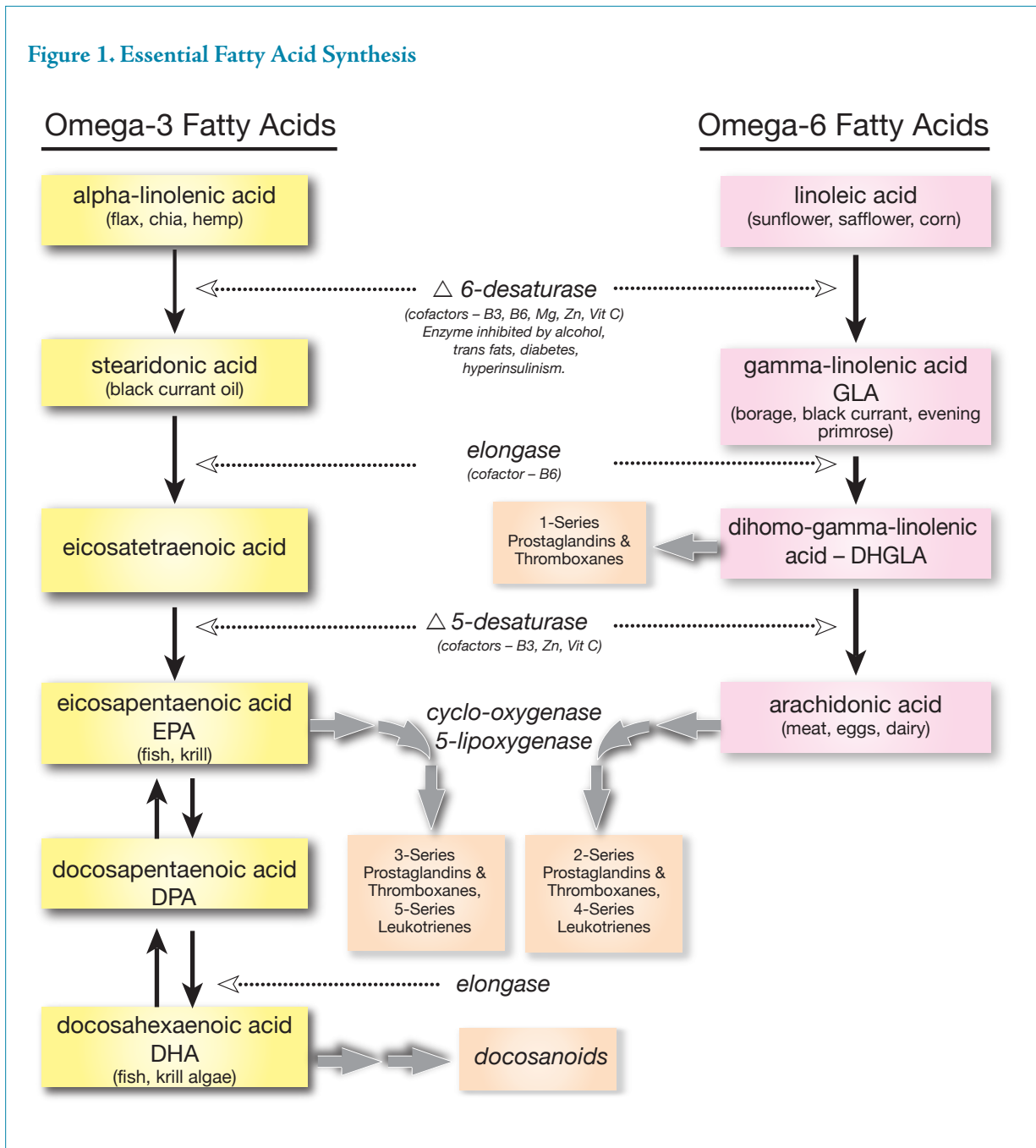
In humans, DHA not consumed in the diet is biosynthesized via conversion of EPA to docosapentaenoic acid (DPA), which is then converted to DHA (Figure 1). DHA comprises 40 percent of the PUFAs in the brain and 60 percent in the retina. DHA – present in three membrane phospholipids: phosphatidylserine (PS), phosphatidylethanolamine, and ethanolamine plasmalogen – regulates many cell transport and synaptic functions.^{3,4}

Mechanisms of Action

Central Nervous System

As a predominant component of neural membranes in the brain and retina, DHA has a positive effect on membrane fluidity and permeability, receptor structure and quantity, carrier-mediated transport of nutrients in and out of the cell, enzymatic activities, cell-to-cell communication, and the microenvironment of retinal photoreceptor

Figure 1. Essential Fatty Acid Synthesis



outersegments.⁵ Animal studies show DHA inhibits amyloid plaque and tau protein formation in models of Alzheimer's disease.^{6,7} Clinical trials are in progress to determine whether DHA's effects are attributable to the same mechanism in humans with Alzheimer's disease.⁸ These effects on the central nervous system, particularly

on brain and retinal development and function, are likely responsible for the observed benefits of DHA in fetal maturation, infant development, and visual acuity.

Anti-inflammatory

In vitro studies demonstrate DHA is superior to EPA in inhibiting the expression of inflammatory markers such as pro-inflammatory cytokines, monocyte adhesion to endothelial cells, and cell-adhesion molecules, particularly vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and E-selectin.⁹ Fish oil has been shown to improve pregnancy duration and birth weight in populations with high fish consumption.¹⁰ Although not clearly understood, DHA's role is thought to be attributed to its inhibition of prostaglandins F_2 and E_2 , with subsequent delays in cervical ripening. Delaying birth onset often results in higher neonatal birth weights. DHA may also relax the myometrium via increased production of prostacyclins PGI_2 and PGI_3 .¹¹

Cardiovascular

It is well documented that fish oil administration has numerous beneficial effects on cardiovascular health. Until recently it was unclear whether EPA or DHA was primarily responsible for these effects, as few studies were available that separated the two fatty acids for comparison. Data now demonstrates DHA has important hemodynamic and anti-atherogenic properties. In terms of cholesterol and lipid metabolism, DHA, but not EPA, increased HDL cholesterol and increased LDL particle size, possibly preventing atherogenesis.¹² Both DHA and EPA reduced triglyceride levels, possibly via increased hepatic glucose output.¹³ DHA, but not EPA, can also significantly decrease heart rate, blood pressure,¹⁴ and platelet aggregation.¹⁵

Anti-carcinogenic

More than other omega-3 PUFAs, DHA has been shown to inhibit growth of human colon carcinoma cell lines. DHA's cytotoxic effect was attributed to its inhibition of cell growth regulators and its apoptotic properties.^{16,17}

Deficiency States

Without adequate intake of dietary or supplemental DHA, deficiency states can develop and have been associated with cognitive decline in adults.¹⁸ DHA is a significant component of neural cell membrane phospholipids and as such supports cell integrity, and may play a role in preventing neuronal apoptosis.¹⁹

Deficiencies of DHA may result in increased neuronal cell apoptosis observed in Alzheimer's disease and cognitive decline. Pregnant and nursing women in the United States consume an average of 60-80 mg DHA daily, only about 25 percent of the recommended daily intake of 300 mg.² Research in non-pregnant adults also reveals a lower-than-recommended intake of DHA.²⁰

Because of the tendency for the average diet to be low in DHA, supplementation may be indicated. Studies show DHA from algae is a good vegetarian source of omega-3 fatty acids, bioequivalent to DHA derived from fish and safe for supplementation to all age groups, including preterm infants.²¹⁻²³ Supplementation of DHA from algal oil or fish oil are both effective methods of increasing plasma and red blood cell DHA levels in adults.^{24,25} Research shows DHA, in combination with arachidonic acid (AA), the most abundant omega-6 fatty acid in the brain, improves mental and visual development in infants.

Clinical Indications

Pregnancy, Fetal Brain Development, and Infancy

DHA is currently recognized as an important dietary fatty acid during pregnancy because of its effects on fetal brain and visual development. Breast-fed infants receive at least 60 mg DHA daily in breast milk and will accumulate at least 10 mg/day, increasing whole-brain DHA concentrations by 39 percent (905 mg) through the first six months of life. Whole-body DHA in breast-fed full-term infants is approximately 3,800 mg. Conversely, infants consuming formulas without added DHA accumulate approximately half that amount. Whole-body DHA stores in non-supplemented formula-fed infants decrease over the first six months at a rate of 5.1 mg daily, for a total loss of nearly 1,000 mg DHA in the first six months of life.²⁶ The central nervous system undergoes rapid growth in the first 12 months of life, and DHA content in the forebrain increases five-fold during this time.²⁷

Infant Cognitive Development

DHA appears to be essential for optimal infant cognitive development. Research investigating DHA's effects from breast milk and supplemental forms of DHA is ongoing. In a small study of 20 full-term,

normal-size, nine-day-old infants, Hart et al measured maternal breast milk DHA content and assessed the infants' behavioral development using the Brazelton Neonatal Behavioral Assessment Scale (NBAS). NBAS assessment yields scores for orientation, motor skills, range of state (variations in state of arousal), regulation of state (ability to quickly change state of arousal), and autonomic stability. Infants whose mothers had higher breast milk DHA concentration scored significantly better than those with lower levels of DHA, particularly on the range of state assessment, indicating DHA appears to have an effect on arousal.²⁸

Drover et al investigated whether feeding infants formula supplemented with long-chain polyunsaturated fatty acids (LCPUFAs), including DHA, improves cognitive function of nine-month-old infants.²⁹ Participating infants (n=229) were single-birth infants born at 37-40 weeks gestation and originally enrolled in three different clinical trials investigating the effects of LCPUFAs on visual acuity.

In one feeding trial, infants received DHA/AA-supplemented formula (Enfamil with 0.36 percent DHA and 0.72 percent AA) or a control formula (same formula without LCPUFAs) beginning at 1-5 days of age and continued for 12 months.³⁰ The other two trials were weaning studies, in which infants were breast fed initially and then weaned at either six weeks³¹ or 4-6 months³² and switched to the assigned formula (supplemented or non-supplemented). All children were assessed at nine months with a two-step problem solving task, which involved retrieving an out-of-reach toy and then recovering the same toy from under a cloth.

In both the 12-month feeding study and the six-week weaning study, infants fed LCPUFA-supplemented formula had higher average scores than those fed the unsupplemented control formula. In infants weaned at six weeks, 35 percent of the group had perfect intention scores (indicating a more mature state of intentional control) on the two-step task compared to only seven percent in the control formula group. There were no differences between formula groups for infants in the 4-6 month weaning group, suggesting that the supplementation period was too short (3-5 months prior to testing) or that there may be a critical cutoff point after which DHA supplementation is no longer able to influence this aspect of brain development.³²

DHA supplementation during pregnancy has also been shown to confer cognitive benefit to children as old as four years. In a randomized, double-blind, placebo-controlled trial (RCT), dietary information was submitted for 76 infants (cod liver oil [source of DHA] group=41, corn oil group=35) confirming the mothers took either cod liver or corn oil from week 18 of pregnancy to three months postpartum (during lactation). Children were assessed at age four years using the Kaufman Assessment Battery for Children (K-ABC), which is administered as a measure of intelligence. On the Mental Processing Composite portion of the K-ABC, children in the cod liver oil group scored significantly higher (106.4) compared to children in the corn oil group (102.3) (p=0.049). On the Sequential Processing Scale, Simultaneous Processing Scale, and Non-verbal Scale, children born to mothers consuming cod liver oil tended to score better than those in the control group, although the differences did not reach statistical significance. Mental processing scores correlated strongly with DHA content of breast milk and maternal and infant plasma measured at four weeks postpartum, indicating maternal supplementation with DHA during pregnancy and lactation improves the intelligence of offspring at age four years.³³

Infant Visual Acuity

DHA comprises 20 percent of total fatty acid content of the infant retina. In the outer segments of rod photoreceptors DHA comprises 35 percent of total fatty acids, making adequate DHA intake in infancy important for optimal visual development.³⁴

A systematic review³⁵ and meta-analysis³⁶ of clinical trials conducted between 1965 and 1999 on LCPUFA intake during infancy examined the combined estimate of DHA's effect on infant visual acuity. Using a combined estimate statistical analysis provides a weighted mean of the results and allows for variations in study size and results among studies.³⁷ Twelve trials fitting the criteria were identified in which infants (both full and pre-term) were given DHA-supplemented formula or formula with no DHA for at least three months.

The five randomized trials³⁸⁻⁴² included in the analysis showed significant improvements in visual acuity scores at two and four months for infants taking DHA-supplemented formula compared to non-supplemented formulas; the effect was more pronounced

at two months. For non-randomized studies comparing visual acuity in breast-fed infants to those given DHA-free formulas,⁴³⁻⁴⁸ the combined visual acuity difference between the two groups was also more pronounced at two months than four months. Combined estimates for all study types revealed infants fed DHA (in breast milk or formula) had visual acuity at two (0.47 ± 0.14 octaves difference) and four (0.28 ± 0.08 octaves difference) months superior to infants who received DHA-free formula.³⁶ More recent research has demonstrated both breast feeding and DHA-supplemented formulas can contribute to improving visual acuity in preterm⁴⁹ and full-term infants,³² supporting the earlier research.

Gestation Duration and Fetal Growth

Women living in communities with high fish intake, such as the Faroe Islands in the North Atlantic, tend to have longer gestational periods coupled with higher-birth-weight-and-length babies compared to other populations. While the studies did not independently examine the role of DHA versus EPA in the observed effects, DHA is likely to be at least in part responsible due to its inhibition of prostaglandins F_2 and E_2 , which may delay ripening of the cervix. DHA also appears to relax uterine smooth muscle via increased production of prostacyclins PGI_2 and PGI_3 , thereby slowing contractions in the last weeks of pregnancy.^{10,50}

In an RCT, 350 pregnant women (291 completers) at 24-28 weeks gestation were randomized to consume DHA-enriched eggs (133 mg DHA daily) or non-enriched eggs (33 mg DHA daily) until delivery. Subjects in the DHA-enriched egg group had longer gestational periods by 6.0 ± 2.3 days ($p=0.009$) than subjects receiving non-enriched eggs. Birth weight, length, and head circumference also were increased in the treatment group, but results were not statistically significant ($p=0.06-0.18$).⁵¹

Postpartum Depression

Because a mother actively transfers DHA to her fetus and nursing infant, a deficiency may result if dietary intake is inadequate. Observational studies suggest an association between postpartum depression and low maternal plasma DHA levels. Otto et al investigated DHA status and possible depression in 112 women at delivery and 32 weeks postpartum. The Edinburgh Depression Scale was used to define “possibly

depressed” with a score of ≥ 10 and no depression with scores < 10 . Results demonstrated that women who had a delayed postpartum return to normal of DHA/DPA ratios (DHA status) had a 10-percent higher risk of postpartum depression. No significant correlation between postpartum plasma DHA levels and Edinburgh scores could be established.⁵²

Cognitive Decline and Alzheimer’s Disease

DHA deficiency has been linked to cognitive decline and Alzheimer’s disease.^{53,54} Animal studies demonstrated DHA administration reduced β -amyloid toxicity and plaque burden in a mouse model of Alzheimer’s disease⁶ and increased antioxidant defenses while improving reference and working memory in a rat model of Alzheimer’s disease.⁷ Clinical trials examining the effect of DHA on cognitive decline and Alzheimer’s support these results.

In a prospective study, 899 men and women (median age 76 years) with no baseline dementia were followed for approximately nine years and assessed for incidence of Alzheimer’s disease, other forms of dementia, and DHA status via plasma levels and dietary intake questionnaire. Subjects in the upper quartile of baseline plasma DHA levels demonstrated a relative risk of 0.53 ($p=0.04$) of developing all-cause dementia and 0.61 relative risk of developing Alzheimer’s disease, compared to subjects in the other three quartiles. Mean DHA daily intake in the upper quartile group was 0.18 g daily and mean fish intake was three servings per week.⁵⁵

In an RCT, 174 people with mild-to-moderate Alzheimer’s disease (mean age 74 ± 9 years) were given 1.7 g DHA with 0.6 g EPA or placebo daily for six months. After six months, all subjects received the DHA/EPA combination for an additional six months. Subjects were assessed for cognitive decline with the Mini-Mental State Examination (MMSE) as well as the Alzheimer’s Disease Assessment Scale. Global function, safety and tolerability of the fatty acid supplement, and blood pressure were also assessed. Although at six months cognitive decline assessments were similar for the two groups, a small subgroup of subjects ($n=32$) in the treatment group with very mild cognitive dysfunction demonstrated a significant ($p<0.05$) reduction in the MMSE decline rate compared to placebo. The DHA/EPA treatment was safe and well-tolerated.⁵⁶



Monograph

Cardiovascular Disease

Dozens of studies have demonstrated the beneficial effects of omega-3 fatty acids on various aspects of cardiovascular disease, with most investigating the benefits of fish oil containing EPA and DHA. In the past decade several studies focused on the specific effects of DHA on cardiovascular disease.

Lipid Metabolism

A clinical overview of 16 published clinical trials examined the effect of algal DHA on serum triglycerides (TGs) in subjects with both normal and elevated triglyceride levels (those with elevated TGs were also taking statin medications). Doses of 1-2 g DHA daily for 4-15 weeks lowered TGs in a dose-dependent manner by 15-20 percent, an effect that was more pronounced in subjects with high TGs. When given with statin therapy, DHA lowered TGs by an additional 19-22 percent, demonstrating an additive effect. DHA supplementation also raised HDL cholesterol, lowered LDL cholesterol, and increased LDL particle size. Additional benefits observed from algal DHA administration were modest reductions in blood pressure and heart rate.⁵⁷

Hypertension

In an RCT, 56 overweight, mildly hyperlipidemic, otherwise healthy men received 4 g/day pure EPA, DHA, or olive oil (placebo) for six weeks; diet did not change. DHA, but not EPA or olive oil, reduced 24-hour and daytime ambulatory blood pressure (BP). A decrease of 5.8 mm Hg systolic and 3.3 mm Hg diastolic BP was demonstrated in 24-hour ambulatory blood pressure compared to the placebo group. DHA also resulted in a reduction in 24-hour heart rate of 3.5 ± 0.8 beats per minute.¹⁴

Research also suggests that giving LCPUFA-supplemented formula to infants results in lower blood pressure values in later childhood. In a follow-up of a multi-center RCT, 147 formula-fed children and 88 breast-fed children (controls) had blood pressure assessments at age six years. Of the 147 children given formula, 76 received the LCPUFA-supplemented formula (0.15-0.25 percent DHA). Children in the LCPUFA group had an average decrease in systolic BP of 3.0 mm Hg and in diastolic BP of 3.6 mm Hg, compared to children who received non-enriched formula.

Blood pressure in breast-fed infants was comparable to the LCPUFA-enriched group.⁵⁸

Cancer

In vitro and animal research has shown DHA from algae inhibited growth of human colorectal cancer cell line COLO 25 by 93 percent⁵⁹ and, in a dose-dependent manner, inhibited proliferation of Caco-2 colorectal cancer cells by as much as 55 percent.⁶⁰ The mechanism behind the observed effects was attributed to cell cycle arrest and subsequent apoptosis.

Side Effects and Toxicity

A review of the literature for DHA adverse effects on platelet function, lipid levels, oxidative potential, glycemic control, and immune function found DHA administration from breast milk, algal oils, or fish oil is not associated with adverse effects in infants or adults. DHA from breast milk was determined to be safe up to at least 315 mg daily in infants ages 1-6 months. DHA from algae was safe at doses up to 3,290 mg/kg body weight in 90-day toxicity evaluations, and DHA from fish oil administered at doses of 1-7.5 g daily was not associated with adverse events.⁶¹

Dosage

Although average breast milk DHA concentration in Western countries is 0.34 percent, values have been shown to be as low as 0.15 percent in some populations. To provide adequate levels of DHA in breast milk for optimal infant nutrition, The International Society for the Study of Fatty Acids and Lipids recommends 300 mg daily of DHA for pregnant and lactating women.⁶²

For formula-fed infants it is suggested arachidonic acid be given with DHA at a ratio of 1.5:1 (AA:DHA). Most DHA-supplemented formulas commercially available in the United States contain between 0.15 and 0.4 percent DHA.⁶³ Recommendations recently published by international experts in the *Journal of Perinatal Medicine* state that infant formulas should include DHA levels of between 0.2- and 0.5 percent and the amount of AA should be at least equal to the DHA level. The experts also recommend at least 0.2 percent DHA plus AA is necessary to achieve functional developmental benefits.⁶⁴

Although the recommended adult dosage is 0.5-7.0 g daily, most published clinical trials have used 1-3 g daily.

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Monograph

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