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Omega-3 (Ω-3) Essential Fatty Acids

by Joseph J Collins, RN, ND.

Introduction to Ω-3

Omega-3s are one group of polyunsaturated fatty acids (PUFA) that are important for optimal health. Other PUFAs include omega-6 and omega-9 fatty acids. Omega-3 and omega-6 are essential fatty acids, while omega-9 PUFAs can be made from unsaturated fats.

In the typical Western diet the ratio of omega-6 to omega-3 essential fatty acids is typically as high as 15:1 to 16.7:1. This high omega-6/omega-3 ratio promotes the pathogenesis of many diseases, including cardiovascular disease, cancer, depression, and inflammatory and autoimmune diseases.[1,2,3,] A lower ratio improves tissue function and controls many disease states. For instance, ratio of 5:1 had a beneficial effect on patients with asthma, whereas a ratio of 10:1 had adverse consequences.[4] A ratio of 2-3:1 suppressed inflammation in patients with rheumatoid arthritis. A ratio as low as 1.4:1 has been recommended for infants.[5] Omega-3 fatty acids have anti-inflammatory effects, and reduce production of IL-1 beta, IL-2, IL-6 and TNF-alpha (tumor necrosis factor-alpha), whereas omega-6 fatty acids significantly increase the production of pro-inflammatory cytokines, like TNF-alpha.[6,3] Because inflammation is at the base of many chronic diseases, inadequate levels of omega-3 fatty acids play an important role in the manifestation of many diseases, particularly in persons with genetic variation, as for example in individuals with genetic variants of delta-6-desaturase & delta-5-desaturase.[7] Important omega-3 fatty acids in nutrition are: linolenic acid (18:3n–3; ALA), stearidonic acid (18:4n-3; SDA) eicosapentaenoic acid (20:5n–3; EPA), and docosahexaenoic acid (22:6n–3; DHA). The polyunsaturated fatty acid-linolenic acid occurs in high concentrations in flax seed, chia seed and perilla seed[8,9,10]. Stearidonic acid is a minor omega-3 fatty acid in fish, making up only about 0.5-2% of total fatty acids[11], but occurs in echium seed as 12.5% of total fatty acids.[12] Omega-3 highly unsaturated fatty acids (HUFA, ≥ 20 carbons and ≥ 3 carbon-carbon double bonds) include EPA and DHA, which may be synthesized from PUFAs or provided in oils from fish such as salmon, herring, mackerel, anchovies and sardines.

Ω-3 Definition & Nomenclature

Omega-3 fatty acids are polyunsaturated fats that the body cannot synthesize, but are essential for proper structure and function of multiple body systems. Unsaturated fats have less hydrogen molecules than saturated fats, and provide fewer calories, but are more active in various physiological processes including cell signaling, and cell membrane function and control of inflammation. Biochemically, omega-3 fatty acids are a family of polyunsaturated fatty acids which have their final double bond on the third carbon from the end, or the terminal (n) carbon bond. This may be represented as either the lower case (ϖ) or the upper case (Ω) of "omega" (which is Greek for "last"). Technically "omega-3" is "omega minus 3". In the scientific literature omega-3 may be written as ϖ-3, Ω-3 or n-3.[13] The human body cannot make omega-3 fatty acids on its own so they must be obtained from food or supplements. Omega-3 fatty acids that are important in human function include: linolenic acid (18:3n–3; ALA), stearidonic acid (18:4n-3; SDA) eicosapentaenoic acid (20:5n–3; EPA), and docosahexaenoic acid (22:6n–3; DHA). In front of the n-3 designation, the number of carbons, and the number of double bonds are represented as C:D. As such, linolenic acid an omega-3 fatty acid with 18 carbons and 3 double bonds is designated at 18:3n–3. The conversion of linolenic acid (18:3n–3) to stearidonic acid (18:4n-3) is dependent on the enzyme such as delta-6-desaturase. If delta-6-desaturase function is inadequate, longer omega-3 fatty acids such as SDA, EPA & DHA must be provided in the diet.

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Since linolenic acid has many health benefits in and of itself, it should also be obtained from food or supplements even if SDA, EPA & DHA supplements are taken because of inadequate delta-6-desaturase function.[14]

The Metabolic Pathway of Ω-3

The metabolic pathway for omega-3 oils is well defined. Omega-3 oils within this metabolic pathway range from 18 to 24 carbons long, and vary from 3 to 6 carbon-carbon unsaturated double bonds. The omega-3 fatty acid-linolenic acid (ALA) is an 18-carbon fatty acid that can be converted to longer chain and more unsaturated fatty acids via a series of elongation and desaturation steps. Humans actually convert little of ingested ALA to EPA because of limited delata-6 desaturase activity (the first biochemical step in the pathway).[12] Whole body conversion of ALA through the pathway to DHA is less than 5% in humans. Oxidation of dietary ALA to CO^2 accounts for about 25% of ALA in the first 24 hours and may reach 60% by 7 days.[15] To the degree that delta-6 desaturtase does function, it converts ALA to stearidonic acid (SDA) by desaturation of an additional carbon-carbon bond. Both dietary and biosynthesized SDA may be metabolized to eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA) by the actions of elongase and delt-5-desaturase with relative ease compared to further metabolism to DHA that depends on delta-6-desaturase activity followed by beta-oxidation.[16] There is some evidence that the omega-3 pathway is affected by gender based differences in hormone levels. Elongase activity appears to be enhanced by estradiol, based on studies that showed increased formation of EPA & DHA from ALA in cells exposed to estradiol.[17] Females have higher DHA concentrations than males.[18] EPA & DHA concentrations in tissue and plasma are positively associated with circulating levels of estradiol and progesterone and negatively associates with circulating levels of testosterone.[19]

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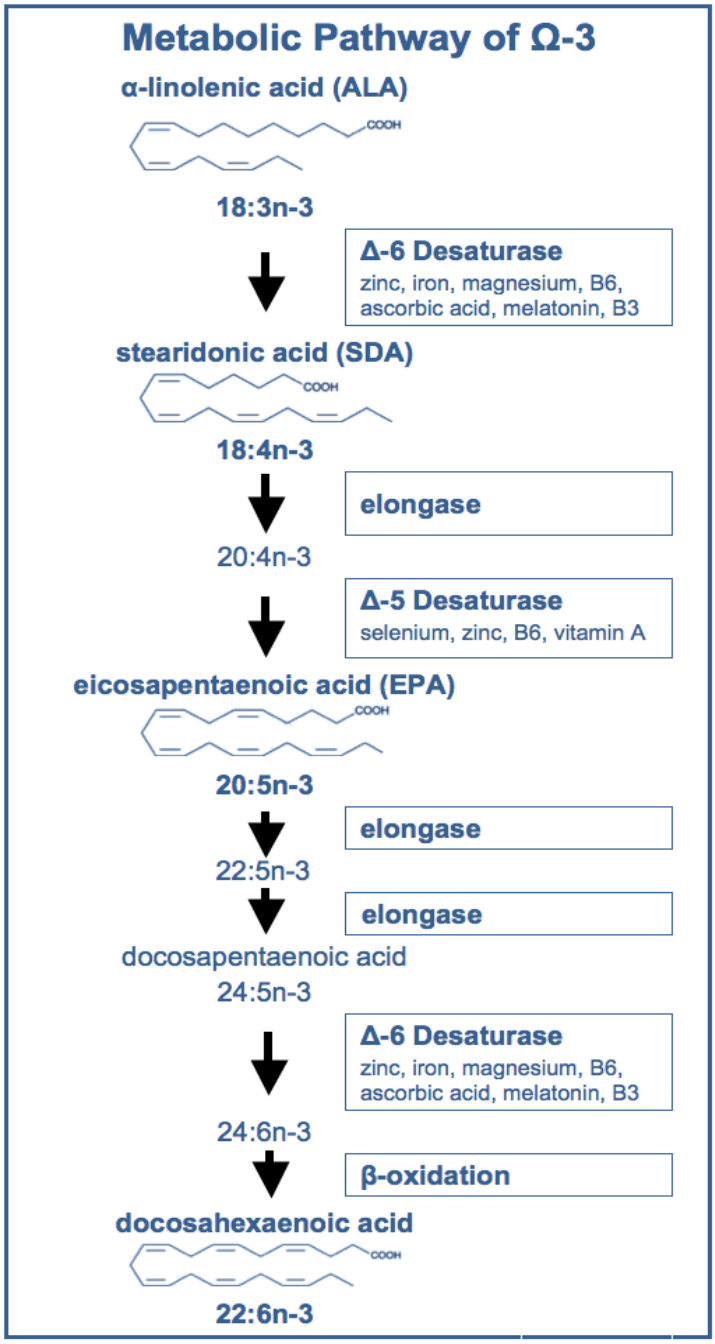


Delta-6-Desaturase (D6D) & Delta-5-Desaturase (D5D)

Delta-6-desaturase is a membrane-bound enzyme that is one of the two rate-limiting enzymes for the biosynthesis of polyunsaturated fatty acids.[20,21,22] In the omega-3 pathway, it is required for the bioconversion of linolenic acid (18:3n–3) to stearidonic acid (18:4n-3), and is partially involved in the bioconversion of 24:5n-3 to 22:6n-3. Delta-5-desaturase is required for the conversion of 20:4n-3 to 20:5n–3 (EPA). Delta-6 desaturase activity may be adversely affected by low levels of zinc, iron, magnesium, vitamin B6, ascorbic acid, melatonin, and possibly vitamin B3.[23,24,25] Proper function of

delta-5-desaturase is dependent on adequate levels of selenium, zinc, vitamin B6 and vitamin A.[26,27,28,24,29,30,25] Women are more able to convert alpha-linolenic acid to docosahexaenoic acid than are men.[31] However the age related decline in beta-6 desaturation was greater in women than in men.[32,23] Increased visceral fat correlates with increased D6D, reflecting the actions of increased insulin due to insulin resistance, but there is also decreases D5D activity[33], explaining why low levels of EPA & DHA are observed in humans with increased BMI, waist circumference, or hip circumference.[34] Of interest, DHEA increases delta-6-desaturase activity and lowers the n-6/n-3 ratio in humans.[35,36] It should also be noted that in addition to nutrition, hormones, and dietary excess, genetic factors also play an important role in regulating the biosynthesis of omega-3 fatty acids. Several studies have reported an association between single nucleotide polymorphisms (SNPs) in the two desaturase encoding genes; fatty acid desaturase 1 (FADS1, encoding Delta-5-desaturase) and fatty acid desaturase 2 (FADS2, encoding Delta-6-desaturase) and blood levels of omega-3 fatty acids.[37,38] Eighteen polymorphisms have been identified in the FADS1, FADS2 gene cluster, which is located on a region of chromosome 11 that is found to be linked with atopy and other complex diseases.[7] Since delta-5-desaturase and delta-6-desaturase are the most important enzymes in the omega-3 pathway these polymorphisms of FADS1, FADS2 have a significant impact on lipid metabolism, and can influence infant intellectual development, neurological conditions, inflammatory diseases, and metabolic disease as well as cardiovascular diseases.[39] Based on genetic variation, individuals may require different amounts of dietary omega-3 essential fatty acids to achieve comparable biological effects.[40]

Alpha-linolenic Acid (ALA)

18:3n-3

Alpha-linolenic acid (linolenic acid; ALA) is a plant based omega-3 polyunsaturated fatty acids (PUFA) that occurs in high concentrations in flax seed[8], chia[9] and perilla.[10] The linolenic acid PUFA omega-3 may be metabolized into HUFA omega-3s (highly unsaturated fatty acids, which have 20 or more carbons and 3 or more carbon-carbon double bonds) ALA, along with its longer chain metabolites, may play an important role in many physiological functions. Potential benefits of ALA, independent of its conversion to HUFAs include cardioprotective effects, modulation of the inflammatory response, and a positive impact on both central nervous system function and behavior.[14] ALA conversion to HUFA omega-3 metabolites is approximately 6% to 21% for EPA and 3.8% to 9% for DHA, with lower conversion in men and in adults on a diet high in saturated fat, and higher conversions in women of reproductive age.[41,42] However, the omega-3 PUFA linolenic acid has physiological properties in and of itself even if it is not converted to the omega-3 HUFAs EPA & DHA. A 2007 study revealed that diets high in linolenic acid were associated with a decreased risk of MI regardless of FADS2 genotype, even though there is lower tissue EPA. It is likely that high levels of ALA mask any potential cardiovascular risk associated with defect in the transcription of the gene.[20] Indeed, dietary ALA has been associated with a lower rate of fatal and nonfatal coronary events.[43] The reduced risk of cardiovascular disease with alpha-linolenic acid may be in part due to an anti-hypertensive effect that can lower both systolic and diastolic blood pressure.[44] This blood pressure-lowering mechanism of dietary alpha-linolenic acid may be involved in the reduction of ACE activity and mRNA expression.[45] The anti-arrhythmic properties of linolenic acid have been demonstrated in a number of studies, including an observed anti-arrhythmic effect of in women of postmenopause age.[46,47,48] The cardioprotective effects of ALA can benefit both healthy individuals and patients with coronary heart disease.[49] A diet rich on ALA may be good alternative for people who seldom eat fish and only take small amounts of fish oils.[50] The anti-inflammatory properties of linolenic acid may also extend beyond the cardiovascular system. Preliminary research demonstrates that alpha-linolenic acid can reduce ischemic brain damage, provides neuronal protection, enhances brain plasticity, and maintains the frontal cortex and pituitary gland.[52,53] In postmenopausal patients with primary breast cancer a diet rich in linolenic acid demonstrated significant reductions in tumor growth and in HER2 oncogene expression at the transcriptional level.[54] ALA alone might also be responsible for growth-inhibitory and proapoptotic effects on estrogen-positive breast cancer cells by affecting both anti-proliferative pathways and the proapoptotic pathways.[55]

Stearidonic Acid (SDA)

18:4n-3

Stearidonic acid (SDA) is an omega-3 long chain polyunsaturated fatty acid (PUFA) that occurs naturally in small amounts in fish and other seafood where it typically makes up about 0.5-2% of the total fatty acids, compared to the 15-20% contributed by EPA & DHA, but may be as high as 7% SDA in mackerel. By weight, echium oil from *Echium plantagineum* is the richest commercially available plant source of SDA at approximately 12.5%.[12] Echium oil, from the plant Echium plantagineum, is an excellent vegetarian source of stearidonic acid. Human studies have revealed that stearidonic acid may be used as a precursor to increase the EPA content of human lipids, and is much more effective than alpha-linolenic acid.[56,57] Compared to alpha-linolenic acid, stearidonic acid is 3 to 5 times more effective at increasing tissue EPA in erythrocyte and plasma phospholipids.[16,58] Even though stearidonic acid is valuable as a precursor to eicosapentaenoic acid (EPA), there is increasing evidence that stearidonic acid has beneficial biological effects independent of its conversion to HUFAs.[11] Stearidonic acid appears to possess hypotriglyceridemic properties typically associated with fish oils. Echium oil taken for 4 weeks resulted in a 21% decrease in triglyceride levels in adults.[59] Echium oil rich in stearidoninc acid provides a botanical alternative to fish oil for reduction of plasma Triglyceride concentrations. One way in which Echium oil may reduce plasma Triglyceride concentrations is by reducing hepatic Triglyceride synthesis and secretion.[60] The anti-inflammatory properties of echium oil and other oils containing stearidonicacid is due to a number of mechanisms independent of its conversion to EPA.[12] Stearidonic acid is

more effective than alpha-linolenic acid in decreasing the intracellular omega-6/omega-3 ratio. Stearidonic acid is more potent than alpha-linolenic acid suppressing the expression of the COX-2 gene which can result in decreased inflammation.[57] Stearidonic acid also reduces synthesis of leukotrienes which can also reduce inflammation.[61] In addition, stearidonic acid also competes with endogenous arachidonate metabolism, resulting in decreased inflammation as well as weak inhibition of platelet aggregation.[62] Stearidonic acid can also interfere with biosynthesis of 2-series prostaglandins from arachidonic acid, in effect lowering inflammation as well as attenuating prostaglandin dependent tumorigenesis.[63,64]

Eicosapentaenoic Acid (EPA)

20:5n-3

Eicosapentaenoic acid (EPA) is an omega-3 highly unsaturated fatty acid that may be biosynthesized from plant source PUFAs or obtained directly through oils from oily fish such as salmon, herring, mackerel, anchovies and sardines, or in cod liver oil. About 6% to 21% of the PUFA alpha-linolenic acid is converted to EPA, and possibly less based on some studies.[41,42] The benefits of eicosapentaenoic acid rich foods or supplements are in large part due to its anti-inflammatory actions. Intake of EPA rich fish oil results in partial replacement of anti-inflammatory actions in cell membranes by EPA.[65] This is beneficial because arachidonic acid is the precursor of 2-series prostaglandins and 4-series leukotrienes, which are highly-active mediators of inflammation. Increased EPA results in increased levels of 3-series prostaglandins, which are relatively anti-inflammatory. Animal and human studies have shown that dietary fish oil results in suppressed production of pro-inflammatory cytokines and can decrease adhesion molecule expression. Clinical studies have reported that oral fish oil supplementation has beneficial effects in rheumatoid arthritis and among some patients with asthma, supporting the idea that the n-3 PUFA in fish oil are anti-inflammatory.[66] In general, eicosanoids derived from EPA are less potent inducers of inflammation, blood vessel constriction, and coagulation than eicosanoids derived from arachidonic acid.[67] EPA can also result in increased resolvin E1 (RvE1), an anti-inflammatory lipid mediator derived from the eicosapentaenoic acid that has been shown to be involved in resolving inflammation.[68] Rheumatoid arthritis improvement with EPA may be due to various actions including the production of less inflammatory eicosanoids, the reduction of pro-inflammatory cytokines, and the inhibition of the activation of T lymphocytes and of catabolic enzymes.[69] EPA can also suppress the proliferation of synoviocytes and decrease the synovial hyperplasia that is thought to be a major cause of destruction of cartilage and bone.[70] EPA can also decrease the muscle wasting associated with Rheumatoid arthritis.[71] Asthma with exercise-induced bronchoconstriction is significantly improved when 3.2g of eicosapentaenoic acid and 2.0g of docohexaenoic acid was taken for 3 weeks.[72] This improvement may be due to the actions of EPA derived resolving E1, which both decreases production of the pro-inflammatory cytokines and increases the production of the counter-regulatory mediators.[73] Cardiovascular benefits specific to increased EPA intake include decreased LDL cholesterol, reduced unstable angina and non-fatal coronary events, and reduced in major coronary events, in patients taking 1800 mg of EPA/day, with an average BMI of 24.[74] Researchers concluded that EPA is a promising treatment for prevention of major coronary events, and especially non-fatal coronary events, in hypercholesterolaemic patients. EPA also significantly reduces the levels of plasma triglycerides and may increase the levels of high-density lipoproteins.[75] Alzheimer's disease and cognitive decline may be prevented with regular intake of fish oil.[76] In a 2008 study, the 65 out of 1,214 participants who developed dementia had lower concentrations of EPA at baseline.[77] Metabolic syndrome patients have significantly lower levels of age and BMI-adjusted eicosapentaenoic acid.[78] Metabolic syndrome conversion to type 2 diabetes is reduced by EPA and/or DHA consumption.[79] EPA reduces the frequency of cardiovascular disease development in metabolic syndrome[80]. Analysis of desaturase enzyme activity and metabolic syndrome reveals that dietary intake of EPA can play an important role in preventing abdominal obesity and the development of metabolic syndrome.[81] The effective management of metabolic syndrome is in part due to its ability to modulate low-grade inflammation.[82,83] Other inflammatory and autoimmune diseases in humans that benefit from supplementation with fish oils include Crohn's disease, ulcerative colitis, psoriasis, lupus erythematosus, multiple sclerosis and migraine headaches.[84]

Docosahexaenoic Acid (DHA)

22:6n-3

Docosahexaenoic Acid (DHA) is an omega-3 highly unsaturated fatty acid that may be biosynthesized from eicosapentaenoic acid (EPA) or obtained directly through oils from oily fish such as salmon, herring, mackerel, anchovies and sardines, or in cod liver oil. Only 4% to 9% of the PUFA omega-3 alpha-linolenic acid is converted to the HUFA omega-3 DHA.[41,42] The benefits of DHA may, for the most part be attributed towards its ability to improve cell membrane functions and cellular signaling. DHA is greater than that of EPA in increasing plasma membrane fluidity of vascular endothelial cells.[85] The greater effect of DHA may be due to its ability to influence functions of membrane-bound proteins such as receptors, ion channels, and various enzymes, which may affect downstream signaling pathways after receptor stimulation or expression of ion channel proteins.[86] The improved cellular signaling may be why DHA appears to have unique beneficial effects on cardiovascular health and may be effective in preventing or treating senile dementia, depression and certain visual dysfunction and other conditions.[87] Cardiovascular benefits attributed to consumption of omega-3 rich fish oil may be due to the effects of DHA in specific applications. It appears that supplemented DHA has a greater ability to reduce ambulatory blood pressure and heart rate in mildly hyperlipidemic men than does EPA.[10,45,44,50] This may be because men have a relatively lower ability to convert alpha-linolenic acid to docosahexaenoic acid.[31] In both genders, DHA may be a more effective anti-thrombotic agent than EPA.[88] DHA increases LDL particle size in type 2 diabetic patients, which decreases the susceptibility of LDL to glycation and oxidation and lower

the progression of endothelial dysfunction in type 2 diabetic patients.[89] The increased activity of membrane-bound enzymes and transporters induced by DHA and the concomitant increase in lipid fluidity may be one of the mechanisms involved in DHA-induced clearance of plasma cholesterol.[90] Alzheimer's patients with DHA in the top quartile have a 47% lower risk of developing dementia than those in the bottom quartile.[76] Increased intake of DHA can correct the DHA deficiency seen in Alzheimer's patients.[77] Supplementation restores brain DHA levels, enhances learning and memory tasks in aged animals, and significantly reduces beta amyloid, plaques, and tau in transgenic AD models.[91] Depressive disorders may be due to relative deficiency of docosahexaenoic acid, the principal omega-3 fatty acid in brain gray matter, which has neurotrophic and neuroprotective properties. DHA deficiency may increase vulnerability to neuronal atrophy in the prefrontal cortex of patients with affective disorders, such as unipolar and bipolar depression.[92] It is believe that DHA deficiency may increase vulnerability to recurrent affective disorders because the prefrontal cortex modulates multiple limbic structures involved in affective regulation. Attention-deficit/hyperactivity disorder (ADHD) is a pervasive neurobehavioral disorder affecting approximately 5% of children and adolescents and 3% of adults. The prefrontal cortex (PFC) may play the most critical role in the expression of ADHD.[93] When healthy boys aged (8-10 y/o) received DHA at a dosage of 400 or 1200 mg/day for eight weeks, erythrocyte membrane DHA composition increased by 47% (low does or 70% high-dose). The erythrocyte DHA composition was positively correlated with dorsolateral prefrontal cortex activation and with alterations in functional activity in cortical attention networks during sustained attention in healthy boys.[94] A double blind study in patients with ADHD revealed a statistically significant improvement based on parent reports, with a subgroup also showing significant improvement based on clinical assessment.[95] Metabolism of omega-3 fatty acids may be impaired in individuals with ADHD, who may require higher intake of omega-3 fatty acids.[96] Visual processing and optimal retinal function are dependent on DHA content to maintain membrane fluidity and permeability, and the associated enzyme and transport activities.[97] Inadequate tissue levels of DHA is associated with alterations in retinal function. Tissue DHA status affects retinal cell signaling mechanisms involved in phototransduction enhancing activation of membrane bound retinal proteins and possibly by supporting rhodopsin regeneration. Visual processing deficits have been ameliorated with DHA supplementation in some cases.[98] Rheumatoid arthritis patients taking dietary supplements of fish oil exhibit improvements in clinical parameters of disease activity from baseline, including the number of tender joints, and these improvements are associated with significant decreases in levels of IL-1 beta from baseline. Some patients who take fish oil are able to discontinue NSAIDs without experiencing a disease flare.[99]

Bioavailability of Omega-3

Encapsulated Fish Oils

For individuals not consuming fish rich in omega-3 fatty acids twice a week, encapsulated fish oils provide an option. In spite of the fact that they are two very different matrixes, consuming 1 to 2 encapsulated fish oils on a daily bases was effective as eating oily fish twice a week. In a comparative study the total daily average was 95 mg of EPA and 390 mg of DHA. Whether omega-3 fatty acids are consumed from oil-rich fish or fish-oil capsules on a regular bases for 16 weeks, there was no difference in the effect on the major long-chain omega-3 fatty acids. As such, encapsulated fish oils have a bioavailability similar to oily fish.[100] As expected, daily intake of encapsulated fish oils resulted in fewer fluctuations than consuming oily fish twice a week. The frequency of fishy aftertaste was higher in persons taking the capsules than in those eating oily fish. The fishy after taste is most often considered "mildly unpleasant." The unpleasant taste may be diminished by taking the fish before meals with a large glass of water 30 minutes before meals, to diminish stomach retention time, based on clinical experience. Enteric-coated fish oil can be beneficial for both decreasing the unpleasant after taste and as therapeutic intervention for patients with inflammatory bowel disease. Enteric-coated fish oil increases remission, and decreases relapse in both adult and children with Crohn's disease.[101,102] All subjects taking the enteric-coated fish oil also attained higher levels of EPA and DHA demonstrated by RBC fatty acid analysis.[103]

Emulsified Omega-3 Fatty Acids

Pre-emulsification of an oil mixture prior to ingestion increases the absorption of longer chain highly unsaturated fatty acids (especially eicosapentaenoic acid and docosahexaenoic acid) but does not affect absorption of shorter chain less saturated fatty acids, suggesting that pre-emulsification of fish oils may be a useful means of boosting absorption of these beneficial fatty acids.[104] It has also been observed that bioavailability of omega-3 fatty acids is significantly increased when EPA & DHA are incorporated into an emulsion.[105] A new delivery system consisting of a microemulsion of DHA and EPA in a proprietary chewable gelatin matrix has been shown to significantly increase the absorption of EPA and DHA. This enhanced absorption was evidenced by the change from baseline of the plasma concentrations of EPA and DHA based on 26 hour area under curve (AUC), and by 26 hour maximum concentration (Cmax) when compared to fish oil triglycerides delivered in softgel capsules. The chewable gelatin matrix resulted in increased AUC of EPA by an additional 44.9% compared to fish oil delivered in softgel capsules and an increased Cmax of EPA by an additional 100.4% compared to fish oil delivered in softgel capsules. For DHA alone, the increase in AUC for DHA was not statistically significant when compared to fish oil delivered in softgel capsules, but the Cmax for DHA was statistically greater, with the increased Cmax of DHA an additional 115.8% greater compared to fish oil delivered in softgel capsules. For EPA & DHA delivered together, the bioavailability of EPA+DHA delivered within a gelatin matrix is significantly increased by 43.3% compared to fish oil

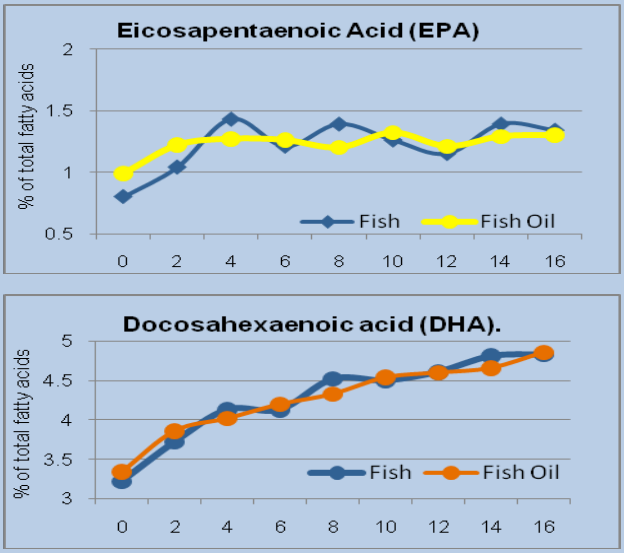
delivered in softgel capsules triglycerides based on (AUC) data. When Cmax data is analyzed, the bioavailability of EPA+DHA delivered within a gelatin matrix is greater by 105.6% when compared to fish oil delivered in softgel capsules.[106]

Adjuvent & Integrative use of Omega-3

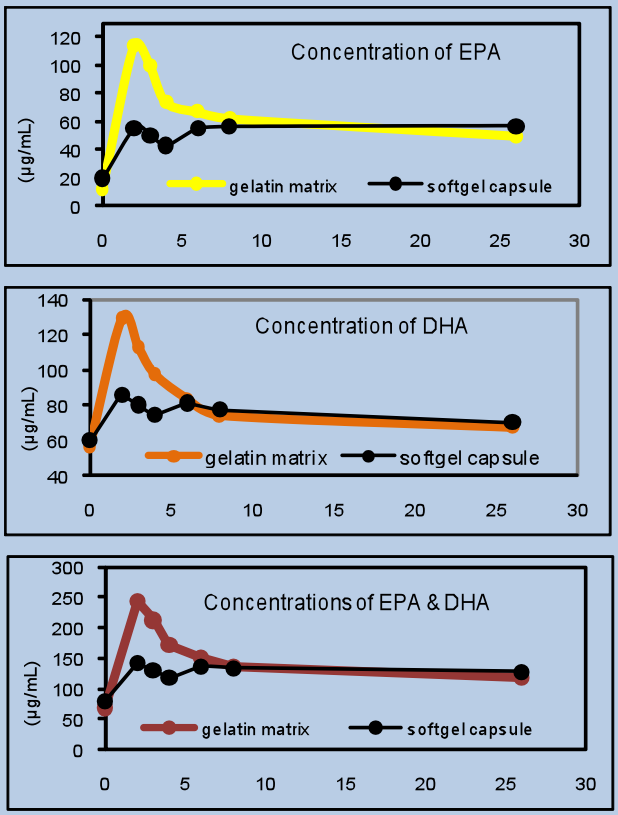
Omega-3 fatty acids may also be used as an adjuvant to drug therapies to work synergistically, potentiate the effects, or decreasing toxicity of drug therapies. Hypertensive therapy in which fish oil was used with propranolol was more effective than propranolol or fish oil alone.[107] The combined administration of fish oil and nifedipine possesses favorable anti-hypertensive and metabolic properties in hypertensive males with elevated lipid levels.[108] Rheumatoid arthritis patients consuming n-3 dietary supplements were able to lower or discontinue their background doses of nonsteroidal anti-inflammatory drugs such as indomethacin or disease-modifying anti-rheumatic drugs.[109,110] Some patients who take fish oil are able to discontinue NSAIDs without experiencing a disease flare.[99] Hyperlipidemia treated with fish oil in addition to statin therapy, such as pravastatin or simvastatin may be preferable to multiple drug combinations for the treatment of combined hyperlipidaemia, in individuals with prior coronary events.[111,112] Since HMG-CoA reductase inhibitors may increase the synthesis of metabolites from arachidonic acid in patients with hyperlipidemia the addition of fish oil is more effective for the prevention of coronary heart disease than HMG-CoA reductase inhibitors alone.[113,114] Other conditions in which omega-3 fatty acids have been shown to have synergistic effects with drugs include depression[115,116], Alzheimer's disease[117], cancer[118,119,120] and Crohn's disease.[121,122,123] Noting that omega-3 fatty acids play a dominant role in inflammation as well as receptor function, there is evidence that their use will extend into mainstream medical care, including hospitalized and surgical patients.[124] A recent study of 182 patients found that high-dose fish oil is safe in combination with aspirin and clopidogrel and does not increase the risk of bleeding compared with that seen with aspirin and clopidogrel alone.[125] An earlier study of 260 patients taking 4 g fish-oil concentrate per day and either aspirin (300 mg/day) or warfarin (INR goal: 2.5-4.2), noted that no excess of bleeding episodes could be attributed to the use of fish oil given in addition to either aspirin or warfarin, and that no long-term effects by fish oil on parameters of coagulation and fibrinolysis were seen.[126] Concerns about the putative bleeding risks associated with omega-3 supplementation may be relieved as ongoing research continues.

Omega-3 Dosage Guidelines

Patients taking higher dosages of omega-3 fatty acids for longer time intervals have the more pronounced clinical benefits than patients taking lower dosages associated with protection of function. As little as 20 mg/kg/day of omega-3 PUFA is necessary to reduces mortality due to coronary heart disease[127], and as little as 11 mg/kg/day is needed to maintain DHA levels in liver and brain phospholipids.[128] However, higher dosages are more effective for restoring lost function. Based on human studies, the therapeutic dosage, based on body weight, for autoimmune inflammatory diseases such as rheumatoid arthritis is at least 30 mg/kg/day of fish oil for 6 to 8 months.[129] Increasing the dosage to 40 mg/kg/day improves clinical outcomes in less than four months.[130] In another study,



16 weeks of fish feeding versus fish oil capsule and the proportion of total fatty acids present as EPA and DHA compiled from data.[100]



Plasma concentrations at 2, 3, 4, 6, 8 and 26 hours after 5 gram single dose omega-3 fatty acids administered in the form of gelatin matrix or triglycerides in as softgel capsules.[106]

patients ingesting 54 mg/kg EPA and 36 mg/kg DHA per day had significant clinical improvement in 12 weeks compared to patients taking 27 mg/kg (EPA) and 18 mg/kg (DHA) per day, who saw similar improvement after 24 weeks. Dosages may vary based upon clinical condition. An increase in tissue DHA levels in cystic fibrosis patients aged 14 to 43 can be achieved by supplementing for six weeks with 70 mg/kg/d DHA.[131] Alpha-linolenic acid (ALA) dosages cited in the literature range from 1.2 to 4.1 grams per day.[132,133,134,135,136]

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