DHA/EPA Omega-3 Fatty Acids for Human Health and Chronic Disorders

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Introduction

North American diets contain relatively high levels of polyunsaturated fats (fatty acids) representing approximately 5% of total energy intakes with 85% of the polyunsaturated fatty acids (PUFA) being consumed as the omega-6 PUFA (also known as n-6 PUFA) [1]. The latter are consumed mostly as linoleic acid via common vegetable oils plus minor amounts of arachidonic acid in animal-based food products. The so-called omega-3 PUFA (n-3 PUFA) typically represent only 10-15% of the total PUFA intake with approximately 90% of the omega-3 PUFA being consumed (approximately 1.5 gm daily) as the short-chain omega-3 fatty acid known as LNA (alpha-linolenic acid) as found in plant food sources such as soybean oil, canola oil, flax, English walnuts, others. The fish/fish oil-based omega-3 fatty acids represent very minor components (approximately 10%) of the total omega-3 intakes. These long-chain omega-3 fatty acids consist of EPA (eicosapentaenoic acid, 20:5 n-3) plus DHA (docosahexaenoic acid, 22:6 n-3) and are found in varying amounts and ratios in fish/seafood with lesser amounts being consumed in other animal-based foods or processed foods wherein DHA/EPA are added. The metabolic conversion of dietary LNA in the liver to EPA/DHA is both highly variable between individuals and very limited with overall efficiencies in adults (females

plus males) for LNA to DHA averaging only 3-4% [2]. Thus, the direct consumption of pre-formed DHA/EPA in foods/diets is the most direct means for their provision to the body for health. Typical adult intakes of EPA plus DHA (combined) in North America range from 100-150 mg/day which reflects very modest fish intakes of approximately one serving every 7-10 days. Much higher intakes are found (approaching 1200 mg/day) in certain countries such as Japan which have very high fish/seafood consumption. The present report will attempt to update the reader on recent evidence-based studies which focus on the potential health benefits of DHA/EPA omega-3 when consumed as fish/seafood, fish/algal oils, functional foods, and/or via supplementation in healthy or risk populations.

Omega-3 Fatty Acids during Pregnancy and Lactation

Docosahexaenoic acid (DHA) is recognized as a physiologically-essential fatty acid in the brain and retina of the eye where it is found in high levels as the predominant member of the omega-3 fatty acids found in the cell membranes therein. The high level of DHA, with its special structural and physical-chemical properties, supports optimal cognitive performance and visual acuity in the brain and retina, respectively, via the mediation of nerve transmission and other critical functions. DHA accumulates in neural and other tissues throughout pregnancy with the last trimester being a particularly active period of growth and neurodevelopment for the infant. DHA continues to accrue at a high rate via lactation during early infant development after birth in nervous and other tissues with the amount of DHA in the brain increasing approximately 30-fold from about 24 weeks of gestation to about 2 years of age [3].

The ALSPAC study [4] found a significantly higher risk of sub-optimal outcomes for various development parameters (verbal IQ, behaviours) up to 8 yrs later in those children from mothers who consumed no seafood as compared to those consuming 340 gms or more per week during pregnancy (340 gms /week estimated to provide an average of approx. 160 mg DHA/day). A recent Spanish study suggested that moderately high intakes of fish during pregnancy may benefit neurodevelopment in children at age 4 years [5]. Daily intake levels of 294 mg DHA as enhanced via supplementation by mothers (versus only 80 mg/day) were found to significantly improve infant visual acuity at four but not six months of age [6]. The PERLIP project (as charged by the European Commission) has recommended that pregnant women should aim to achieve an average intake of at least 200 mg DHA/day [7] which contrasts with an average intake of only 82 mg/day for pregnant North American women as directly assessed [2]. Very recently, a randomized controlled trial from Australia reported that DHA supplementation (800 mg DHA plus 100 mg EPA daily) during the last half of pregnancy did not reduce postpartum depression in the mothers or selected measures of cognitive and language development in children as assessed at 18 months [8]. However, the frequency of preterm babies (<34 weeks) was significantly lower in the DHA-supplemented group (by 52 %) relative to the control (placebo group) and of low birth weight infants (lower by 36%) and the need for admission to intensive care (lower by 45%).

Omega-3 Fatty Acids during Infancy, Childhood and Adolescence

Some controlled clinical trials in full-term infants have indicated that the presence of DHA in breast milk at higher levels or in infant formula (eg., approx. 0.32 % of milk fat which is close to the worldwide human milk level) results in improved cognitive and

visual outcomes [9]. A literature review has supported an overall improvement in visual developments in term infants fed formula providing at least 100 mg daily [10] which can be expected by breast milk or infant formula having approx. 0.35 % of milk fatty acids as DHA. Recently, the World Association of Perinatal Medicine recommended that lactating women consume at least 200 mg DHA/day [11] while the earlier ISSFAL-supported NIH Workshop advised at least 300 mg DHA/day. Such intakes can be expected to yield levels of approx. 0.30-0.35 % DHA in breast milk fat.

The accretion of DHA in the brain progressively increases in the cerebral cortex up to 18 years of age [12]. The evidence for the potential benefits of DHA/EPA supplementation in healthy children older than 2 years of age is generally promising in some studies but not yet conclusive. By supplementing healthy 4-year-old children with 400 mg DHA (or placebo) per day for 4 months, the higher blood levels of DHA which resulted were significantly and positively associated with improved scores on the Peabody Picture Vocabulary Test (a test of listening comprehension for the spoken word in Standard English) [13]. Another recent study on older children (10-12 years of age) which provided 400 or 800 mg supplemental DHA per day for 8 weeks did not find any significant beneficial effect on brain function in healthy children [14]. A formulated functional food (bread spread containing fish flour from a marine source) providing an average intake of 182 mg per day of DHA and EPA combined over 6 months was recently reported to moderately improve the learning ability and memory of children ages 7-9 years [15]. Various studies using DHA and EPA supplementation in attention-deficit-hyperactivity disorder have been inconsistent [16] while preliminary investigations on

childhood depression [17] and neurological outcomes in children with phenylketonuria [18] have been encouraging.

Our lab has determined fatty acid intakes in a population of Canadian children aged 4-8 years by direct diet quantitation [19]. Very low intakes of DHA and EPA were found averaging 54 and 38 mg/child/day, respectively. Only 22 % of the children met the suggested adequate intake (DHA plus EPA) based on the Dietary Reference Intakes from the Institute of Medicine (Washington, DC) and only 51 % met the recommended intakes for long-chain omega-3 fatty acids for children from Australia and New Zealand. The wide 'nutrition gap' between actual versus recommended intakes of DHA and EPA for young children emphasizes the need to recommend increased consumption of appropriate fish and seafood, fortified foods, and possibly supplements containing DHA and EPA.

Cardiovascular Health

Reviews of various cohort studies (on over 200,000 subjects combined with a 12-13 year follow-up) indicated an overall 23% and 38% reduction in coronary heart disease (CHD) mortality for those consuming 2 to 4 fish servings/week and $\geq$ 5/week, respectively [20]; the corresponding reduction in stroke mortality was 18 % and 31 %, respectively [21]. Two servings per week would provide approximately 250 mg (EPA/DHA) daily on average while 5-7 fish servings per week would be expected to provide approximately 650-900 mg daily. The numerous mechanisms for the cardioprotective effects of EPA/DHA as reviewed [22] include anti-thrombotic effects and other favourable effects on the haemostatic system, reduction in malignant ventricular arrhythmias (via enrichment of cardiac lipids in EPA/DHA), improved endothelial relaxation, inhibitory effects on atherosclerosis and inflammation and, of particular risk

importance, blood triglyceride-lowering in the fasted and postprandial state independent of cholesterol-lowering. Three grams of EPA + DHA per day typically can result in reductions in fasting triglyceride levels of 25-30 % within a 3-4 week period with significant reductions being seen (in the fasted and postprandial state) in a high proportion of patients who are being maintained on statin treatment for cholesterol reduction [23]. Clinical reports have also indicated that EPA/DHA supplementation enhanced plaque stabilization, reduced the induction of ventricular tachycardia, moderately reduced the resting heart rate, and provided favorable cardiac autonomic changes. A recent review concluded that EPA/DHA supplementation offers benefits in type 2 diabetes mainly in terms of dyslipidemia [24].

Data from the U.S. National Center for Health Statistics on lifestyle-related preventable causes of death estimated that insufficient intakes of EPA/DHA omega-3 fatty acid from seafood were responsible for approximately 72,000 – 96,000 preventable deaths per year in the United States [25]. For the general population, the American Dietetic Association and the Dietitians of Canada recommended a daily intake of 500 mg (EPA/DHA) [26].

The GISSI-Prevenzione trial from Italy [27] on 11,324 patients who had experienced a myocardial infarction indicated that, in the presence of a Mediterranean-type diet as well as treatment with various cardiovascular medications, those patients receiving approximately 900 mg/day of EPA/DHA over the subsequent 3.5 years exhibited a marked reduction in overall cardiovascular death and a 45% reduction in sudden cardiac death. The American Heart Association advises a daily intake of 900 mg (EPA/DHA) from fish or via fish oil supplementation in those with coronary disease [28]. A subsequent

Japanese trial provided 1800 mg of EPA omega-3 per day relative to a placebo (control) supplementation in over 18,000 hypercholesterolemic patients who were being treated with statins for elevated blood cholesterol levels but were free of known CHD [29]. The risk for major coronary events (including sudden cardiac death plus fatal/nonfatal myocardial infarction plus other nonfatal events including nonstable angina, angioplasty, stenting, and bypass surgery) after a 4.6 yr follow-up was found to be reduced by approximately 20% in all patients including those with a history of coronary artery disease. Upon analyses of patient sub-sets within the total group, these investigators reported [30] dramatic reductions in the cumulative incidence of major coronary events (by 53 %) with EPA supplementation in those having elevated fasting triglyceride levels (equal or greater than 150 mg/100 mL) along with lower HDL-cholesterol levels (less than 40 mg/100mL). It is noteworthy that the EPA supplementation was in addition to expected Japanese intakes of 900-1500 mg (EPA/DHA) daily from several servings of fish/ seafood [31]. These latter intakes contrast with daily North American intakes of only 120-150 mg (EPA/DHA) daily [32]. The JELIS Trial observed a 20 % reduction in the recurrence of stroke in patients given daily supplementation with 1.8 gm of EPA (relative to placebo) [33]. A moderate-statistically-significant relative risk reduction of 9 % in total mortality associated with treatment using 1 gm daily of EPA/DHA omega-3 has been reported in patients with heart failure [34].

Two major systematic reviews have recently been published. The first reported upon 11 studies (39,044 patients) with an average dose of (EPA+DHA) of 1.8 gm/day and a mean duration of follow-up of 2.2 yr wherein omega-3 supplementation significantly reduced the overall risk of cardiovascular deaths by 13 % with the authors

recommending that such dietary supplementation should be considered in the secondary prevention of cardiovascular events [35]. A second independent review reported upon 12 studies overall and concluded that fish oil supplementation was associated with a significant reduction (by 20 %) from cardiac causes [36]. Very recently, a multi-center trial from the Netherlands reported that modest additional intakes of only 226 mg of EPA combined with 150 mg of DHA (in addition to LNA) did not significantly reduce the rate of major cardiovascular events among patients with a previous myocardial infarction who were receiving appropriate pharmaceutical therapy [37].

Cancer, Inflammatory, Mental , and Age-related Disorders

While a review of earlier cohort studies have indicated a slight reduction in colorectal cancer risk in those with the highest intake of fish containing DHA/EPA, a more recent 22-year prospective study in American men (Physicians' Health Study) found a 37 % and 26 % lower risk for colorectal cancer for those with the highest quartile of fish and omega-3 intakes, respectively, as compared to the lowest [38]. Very recently, the six-year follow-up results on 35,016 postmenopausal women who were free of a history of breast cancer at entry have been reported from the cancer research center in Seattle indicating a 32 % reduced risk of breast cancer amongst users of fish oil supplements [39]. Omega-3 supplementation with DHA/EPA versus placebo has been evaluated in various disease states where inflammatory components and the immune response play a key role. In general, the overall clinical benefits in patients with inflammatory bowel disease have been rather limited but much more promising in the case of rheumatoid arthritis [40]. Numerous randomized, placebo-controlled , double-blind studies in such patient groups using treatments of approximately 3 gms (EPA plus DHA) daily over an approximate

duration of 4 months have found improved clinical symptoms including reduced morning stiffness, joint pain, swelling, fatigue , along with a reduced need for anti-inflammatory medication in some patients [40]. The mechanisms of action attributed to EPA/DHA include a suppression in the generation of pro-inflammatory eicosanoids (derived from arachidonic acid), cytokines, and other bioactive agents in addition to the formation of anti-inflammatory resolvins and protectins from EPA/DHA [41]. The anti-inflammatory effects of (EPA plus DHA) at daily doses of 5 gms/day over 3 weeks have reduced exercise-induced asthma symptomology in athletes and asthmatic individuals [42]. The potential benefits of enhancing EPA/DHA intakes and status have been extensively researched in relation to depressive disorders. The placebo-controlled, double-blind trial from Israel on children (average age of 10 yrs) with major depressive disorder reported a marked reduction of greater than 50% in the Children's Depression Rating Scale within 4 weeks for the majority receiving 400 mg EPA plus 200 mg DHA daily [17]. A recent major review of published trials has concluded that EPA/DHA omega-3 supplementation at varied doses appears to provide beneficial support on depressed mood in individuals with diagnosed depressive illness but not in those without such a diagnosis [43]. There is some, but not yet conclusive evidence, that EPA may be somewhat more efficacious than DHA in managing depression [44].

There is fairly substantial epidemiological evidence to indicate that increased consumption of fish containing DHA over extended time periods can significantly reduce age-related cognitive decline [45]; furthermore, a clinical trial in patients with very mild but not more advanced AD (Alzheimer's Disease) indicated a delay in cognitive deterioration with omega-3 supplementation (1.7 gm DHA plus 0.6 gm EPA daily) relative to placebo.

A recent trial using 900 mg DHA daily as supplementation or matching placebo for 24 weeks in 485 healthy individuals (≥55 yrs) showed a reduction in errors on a visuospatial learning and episodic memory test in the omega-3 group which represented a net improvement and benefit of 3 years cognitively when compared to age-associated norms [46]. Interestingly, higher dietary intakes of DHA omega-3 in the Age-Related Eye Disease Study were associated with a lower risk for progression to advanced macular degeneration [47]. Very recently, a population-based survey on 2956 participants (≥50 yrs) found an inverse relation between fish (including long-chain omega-3) intakes and hearing loss thereby suggesting that dietary intervention with DHA/EPA could prevent or delay the development of age-related hearing loss [48].

Professor Bruce Holub provides ongoing updates on forthcoming evidence-based research on DHA/EPA omega-3 in health and disease which can be freely-accessed via the DHA/EPA Omega-3 Institute at www.dhaomega3.org.

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