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Omega-3 Fatty Acids for Health Care

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There has been a dramatic surge in interest amongst clinicians, pharmacists, dietitians, and other health professionals in the evidence-based science for omega-3 fatty acids to support human health and the prevention and management of cardiovascular disease (CVD) and other chronic disorders. The two families of polyunsaturated fatty acids in a typical Canadian diet include the omega-6 fatty acids (also known as n-6 polyunsaturates) as well as the omega-3 fatty acid family¹. The predominant types of omega-6 and omega-3 fatty acids are listed in Table 1 along with some common food sources. The 'omega' terminology refers to the location of the first of many double bonds (unsaturation sites) within the fatty acid structure upon designating the terminal carbon (methyl carbon) as number one. For example, DHA (docosahexaenoic acid, 22:6 n-3) indicates that this polyunsaturated fatty acid has 22 carbons with 6 double bonds such that the first of the latter begins with the third carbon from the methyl end. A typical Canadian diet has a very high intake of the omega-6 fatty acids (predominantly linoleic acid) at an intake level of approximately 5-6% of total energy. The omega-3 fatty acids include α -LNA (alpha-linolenic acid 18:3n-3) which is consumed at approximately 0.5% of energy or 1.2-1.5 g/person/day. EPA (eicosapentaenoic acid, 20:5, n-3) plus DHA are found predominantly in dietary fish and fish oils (or specialty foods containing these fatty acids) and are lacking from plant-based foods including the common vegetable oils. The amount of EPA plus DHA varies across different fish species and sources.

DHA (docosahexaenoic acid) in the Brain and Retina

The unique structure and physico-chemical properties of DHA underlie its role as a physiologically-essential component of the brain and retina for optimal mental performance and visual acuity, respectively^{2,3}. The high levels of DHA in neural membrane phospholipids as actively deposited particularly during the last trimester of pregnancy and during the first few months and early years of life support the important functioning of DHA⁴. There is clinical evidence indicating that infant formulas containing DHA (in contrast to conventional infant formula) provide an improved performance on the Mental Development Index in term infants⁵ and better mental development in preterm infants⁶. Very recently, a significantly better visual maturation of term infants using sweep visual evoked potential (VEP) acuity as the functional outcome was demonstrated in term infants fed long-chain polyunsaturated fatty acids (including DHA) as compared to control formula for a 12-month period⁷. These and other findings have led to DHA-containing infant formula now appearing in the Canadian marketplace. It is of interest to note that Health Canada (in 1990)⁸ and the Food and Nutrition Board in the US (in 2002)⁹ recognized that omega-3 fatty acid was of importance in providing DHA for neuronal functioning. However, both groups recommended the consumption of α -LNA (but not DHA) at a level of 0.5% of total energy. This recommendation was based in part on reported animal studies indicating some conversion of α -LNA to DHA by the complex pathway (found in the liver and elsewhere) via desaturation/elongation reactions¹⁰. However, it has become apparent that the human body has an extremely limited capacity to convert dietary α -LNA to the physiologically-essential DHA. A recent review of the many studies conducted on conversion efficiencies in humans has indicated estimated conversions ranging from non-detectable to 9%¹¹. Furthermore, it has been demonstrated that the low level of DHA in North American breast milk, which is reflective of a very modest fish consumption (containing DHA), was found not to be increased despite the consumption of high levels of α -LNA from flaxseed oil over several weeks thereby further supporting the very limited conversion to DHA¹². Finally, it should be noted that the current estimated daily intake of DHA in Canadian women of approximately 80 mg DHA/day¹ is only 1/4 the intake level (300 mg DHA/day) recommended at the 1999 Workshop at the NIH¹³ for women during pregnancy (for infant neuronal development) and lactation (to provide for DHA levels in breast milk attaining levels found in the DHA-containing infant formula). Our lab has reported the intake of 2-3 yr old children to average

only 19 mg DHA/day¹⁴; this level is markedly below daily amounts provided by the DHA-containing infant formula.

α -LNA and Cardiovascular Disease

The Lyon Diet Heart Study¹⁵ indicated the benefit of the Mediterranean, α -LNA-rich diet, in the secondary prevention of coronary heart disease (CHD). While the diet contained numerous cardioprotective components, the specific role of α -LNA could not be unequivocally proven. A very recent review of prospective cohort studies via meta-analysis indicated that higher intakes of α -LNA might reduce heart disease mortality by 20% although an apparent increased risk of prostate cancer in men with higher intakes was of concern¹⁶. This association between α -LNA and prostate cancer risk has recently been challenged¹⁷. In contrast to α -LNA intakes, increased dietary intakes of the fish-derived EPA/DHA have been associated with a lower risk of prostate cancer in a large prospective study over 14 years¹⁸. The protective effect for CHD with increasing intakes of α -LNA (up to 2-3 g/day), especially for men with an increased risk of heart disease, who are consuming very little EPA/DHA, would probably outweigh any potential negative effects on balance. Interestingly, a recently-published prospective study concluded that α -LNA may particularly reduce CHD risk when seafood-based EPA/DHA intakes are low (<100 mg/day) but not when the latter intakes are about 100 mg/day¹⁹. It is noteworthy that the average Canadian consumes approximately 130 mg/day of EPA/DHA combined¹ which reflects an average fish consumption of approximately one fish serving per week.

EPA/DHA and Cardiovascular Disease

Numerous epidemiological and controlled-intervention trials have supported highly beneficial effects of EPA/DHA from fish and fish oils in decreasing cardiac mortality and the favourable modification of numerous risk factors for CVD independent of blood cholesterol-lowering²⁰. Recent meta-analysis of cohort studies (on over 200,000 subjects combined with a 12-13 year follow-up) indicated an overall 23% and 38% reduction in CHD mortality for those consuming 2-4 servings/week and ≥ 5 /week, respectively²¹; the corresponding reduction in stroke mortality was 18% and 31%, respectively²². The Multiple Risk Factor Intervention Trial in the U.S. indicated that increasing intakes over 10.5 years of EPA/DHA (up to 665 mg/day) from fish were associated with a markedly reduced risk of cardiac-related mortality²³. The numerous mechanisms for the cardioprotective effects of EPA/DHA as

reviewed²⁰ have included anti-thrombotic effects and other effects on the haemostatic system, reduction in malignant ventricular arrhythmias (via enrichment of cardiac lipids in omega-3 fatty acids), improved endothelial relaxation, inhibitory effects on atherosclerosis and inflammation (altered eicosanoid synthesis, suppressed production of inflammatory cytokines, etc), and blood triglyceride-lowering in the fasted and postprandial state independent of cholesterol-lowering. Recent clinical reports have indicated that EPA/DHA supplementation enhanced the stability of atherosclerotic plaques²⁴, reduced the induction of ventricular tachycardia²⁵, moderately reduced the resting heart rate²⁶, and provided favourable cardiac autonomic changes²⁷. It is anticipated that future research will further clarify the optimal therapeutic doses and durations of EPA/DHA supplementation in target patient groups with compromised cardiovascular functioning. Measurements of EPA+DHA levels in blood serum phospholipid have indicated a 70% lower risk of fatal ischemic heart disease in those with higher concentrations²⁸. MDS Diagnostic Services provide such test measurements when requested by a physician in Canada.

The GISSI-Prevenzione trial from Italy²⁹ 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. In their dietary guidelines, the American Heart Association (AHA) recommends two servings of fatty fish per week for healthy individuals and daily fish consumption for those with CHD^{30,31}. The AHA advises consideration of a fish oil supplement to provide 900 mg/day of EPA/DHA combined for CHD patients not consuming one fatty fish meal per day. This daily intake of EPA/DHA is below that of many people living in Japan¹⁰ and is approximately one-half that of the Inuit population in Northern Quebec³². The AHA has recommended 2-4 g EPA/DHA/day under physician care for patients needing triglyceride-lowering³⁰. Such levels of supplementation have been found to lower fasting triglyceride levels by 15-35% in many trials. The Food and Drug Administration (FDA) in the U.S. considers up to 3 g EPA/DHA/day to be generally safe for the majority of the population. Higher doses (3-5 g/day) that might be used for triglyceride management in patients with marked hypertriglyceridemia need careful physician

supervision since excessive bleeding might possibly occur in a few individuals. A recent extensive and systematic review of 97 randomized, controlled trials on various antilipidemic agents indicated an overall reduction in cardiac mortality by 22% with statin use and 32% with omega-3 fatty acids³³.

EPA/DHA Supplementation and Other Chronic Disorders

While lesser in number relative to cardiovascular-related studies, a small number of trials have indicated a beneficial effect of EPA/DHA supplementation in patients with major depressive and other psychiatric disorders²⁰. Regular users of fish oil supplements (mean age of 64 yrs) were found to exhibit higher cognitive functioning than non-users; better cognitive aging also correlated with higher levels of EPA/DHA in the blood biomarker³⁴. The very recent Oxford-Durham study, a randomized, controlled trial of dietary supplementation using EPA/DHA from fish oil in children with developmental coordination disorder, demonstrated a significant improvement for active treatment vs. placebo in reading, spelling, and behaviour after 3 months³⁵. The anti-inflammatory and immune-modulating effects of EPA/DHA as demonstrated in controlled clinical trials are considered to underlie the clinically important benefits seen in various trials on omega-3 supplementation in rheumatoid arthritis, certain inflammatory bowel disorders, and some inflammatory skin conditions such as atopic dermatitis and psoriasis^{36,37}. It should be noted that EPA/DHA was employed as a complementary nutraceutical therapeutic in many of the latter studies with effects often seen at levels of 3 g/day over 3-4 months in duration.

Conclusion

It appears that DHA intakes during pregnancy, lactation, and amongst young children in North America are well below evidence-based targets for supporting optimal neuronal and visual functioning during growth and development. The FDA recommends that women who are pregnant or nursing and young children eliminate shark, swordfish, king mackerel, and golden snapper from their diets while limiting their consumption of other fish to 3 servings/week to minimize exposure to methyl-mercury. Alternative sources of DHA include DHA-containing functional foods now appearing in the

market place including eggs, dairy produce, others. For some, supplementation can provide intakes of DHA (along with EPA) which are devoid of risk levels of contaminants. An accessible website is available to provide information on EPA/DHA levels as well as contaminant levels in commercial supplements by brand name (www.ifosprogram.com). The AHA has recommended increasing fish intake to 2 and 7 servings

per week for healthy individuals and those with CHD, respectively. The EPA/DHA target of 900 mg/day for CHD patients can be reached by daily fatty fish consumption, functional foods enriched in EPA/DHA, and/or with high quality supplementation. The informed health professional can expect to see a surge in the use of omega-3 therapeutics as both alternative and complementary strategies in the health care system.

Table 1. Listing of Polyunsaturated Fatty Acids and some Common Food Sources

| Fatty Acid | Food Source |
|---|--|
| (i) Omega-6 Types | |
| LA, linoleic acid, 18:2 ω 6 (18:2 n-6) | Vegetable oils (corn, safflower, sunflower, soybean), animal meats |
| AA, arachidonic acid, 20:4 ω 6 (20:4 n-6) | Animal sources only (meat, eggs) |
| (ii) Omega-3 Types | |
| α -LNA, alpha-linolenic acid, 18:3 ω 3 (18:3 n-3) | Flaxseed, canola oil, English walnuts, specialty eggs |
| EPA, eicosapentaenoic acid, 20:5 ω 3 (20:5 n-3) | Fish, fish oils, marine sources |
| DHA, docosahexaenoic acid, 22:6 ω 3 (22:6 n-3) | Fish, fish oils, specialty egg/dairy products |

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