



## The Role of Omega-3 Fatty Acids in Chronic Disorders: Part 2

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In part one of this publication, we reviewed recent studies investigating the apparent health benefits of the fish/fish oil – derived omega-3 fatty acids as DHA (docosahexaenoic acid, 22:6 n-3) and EPA (eicosapentaenoic acid) on the enhancement of cognitive and visual functioning during pregnancy, lactation, childhood, and throughout adult life. The present report (Part 2) will focus on recent evidence-based epidemiological studies and intervention trials of DHA/EPA omega-3 fatty acids in the prevention and/or management of chronic disorders and associated risk factors.

### 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 who consumed 2 to 4 fish servings/week and  $\geq 5$ /week, respectively<sup>1</sup>; the corresponding reduction in stroke mortality was 18% and 31%, respectively<sup>2</sup>. 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<sup>3</sup> include anti-thrombotic effects and other favorable 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 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 maintained on statin treatment for cholesterol reduction<sup>4</sup>. 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<sup>5</sup>.

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<sup>6</sup>. For the general population, the American Dietetic Association and the Dietitians of Canada recommended a daily intake of 500 mg (EPA/DHA)<sup>7</sup>.

The GISSI-Prevenzione trial from Italy<sup>8</sup> 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 fish oil supplementation in those with coronary disease<sup>9</sup>. A subsequent Japanese trial provided 1800 mg of EPA omega-3 per day compared 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<sup>10</sup>. 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<sup>11</sup> 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<sup>12</sup>. These latter intakes contrast with daily North American intakes of only 120-150 mg (EPA/DHA) daily<sup>13</sup>. The JELIS Trial observed a 20% reduction in the recurrence of stroke in patients given daily supplementation with 1.8 gm of EPA (compared to placebo)<sup>14</sup>. 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<sup>15</sup>.

Two major systematic reviews have recently been published. The first reviewed 11 studies (39,044 patients) with an average dose of (EPA+DHA) of 1.8 gm/day and a mean follow-up duration 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<sup>16</sup>. 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<sup>17</sup>. 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<sup>18</sup>.

### 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<sup>19</sup>. 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<sup>20</sup>. 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<sup>21</sup>. 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<sup>21</sup>. 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<sup>22</sup>. The anti-inflammatory effects of (EPA plus DHA) at daily doses of 5 gms/day over 3 weeks have reduced exercise-induced asthma symptomatology in athletes and asthmatic individuals<sup>23</sup>. The potential benefits of increasing 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<sup>24</sup>. 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<sup>25</sup>. There is some, but not yet conclusive evidence, that EPA may be somewhat more efficacious than DHA in managing depression<sup>26</sup>.

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<sup>27</sup>; furthermore, a clinical trial in patients with mild Alzheimer's Disease (AD) showed a delay in cognitive deterioration with omega-3 supplementation (1.7 gm DHA plus 0.6 gm EPA daily) compared to placebo. A recent trial using 900 mg DHA daily as supplementation or matching placebo for 24 weeks in 485 healthy individuals ( $\geq 55$  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<sup>28</sup>. 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<sup>29</sup>. Very recently, a population-based survey on 2956 participants ( $\geq 50$  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<sup>30</sup>.

### Summary and Conclusions

Current adult intakes of DHA plus EPA in Canada average 120–150 mg/day. The overall evidence from epidemiological studies and controlled intervention trials supports the general conclusion that higher intakes of the omega-3 fatty acids as DHA plus EPA, than currently consumed in North America, via fish/seafood, supplementation, or certain functional foods can likely reduce the onset and alleviate the impact of various clinical disorders such as cardiovascular disease, rheumatoid arthritis, certain cancers, age-related disorders, and cognitive decline.

*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](http://www.dhaomega3.org).*

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