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A Revolution in Omega-3 Fatty Acid Research

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Decades of observational research have supported an association between omega-3 fatty acid (OM3FA) intake and a lower rate of cardiovascular events (1). However, with the exception of Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione (GISSI-P), multiple randomized trials of mixtures of largely low doses of omega-3 fatty acids provided neutral overall results (2). Particular subgroups or secondary endpoints did show promise, but certainly nothing definitive (2). Then came the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), which proved in a large cardiovascular outcome trial that a high dose, of a purified ethyl ester of eicosapentaenoic acid (EPA) in patients at elevated cardiac risk significantly reduced a variety of ischemic endpoints, including death from cardiovascular causes, in a largely Western population (3-9). This followed the earlier randomized, but open-label, Japan EPA Lipid Intervention Study (JELIS) trial which had also found significant benefit in a mixed primary and secondary prevention population, in this case with a medium dose of a purified ethyl ester in a Japanese population (with higher baseline levels of EPA) (10). The benefits appeared to be largely related to achieved levels of EPA. Effect of Vascepa on Progression of Coronary Atherosclerosis in Persons With Elevated Triglycerides (200–499) on Statin Therapy (EVAPORATE) showed significant, favorable effects on measures of plaque volume and composition on noninvasive computed tomography with icosapent ethyl versus placebo, echoing what had been observed with EPA in the open-label Combination Therapy of Eicosapentaenoic Acid and Pitavastatin for Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography (CHERRY) trial which had used invasive intravascular ultrasound (11-13). Thus, the case for EPA provision by means of prescription-grade medication is now firmly established.

In this issue of the *Journal*, Lázaro and colleagues evaluated dietary impact of OM3FAs in 944 consecutive patients with ST-segment elevation MI (STEMI) (14). They examined the proportion of EPA in serum phosphatidylcholine (PC), which estimates the amount of recent dietary EPA consumption. They found that the serum-PC EPA levels at the time of STEMI were associated with a significantly lower incidence of major adverse cardiovascular events (MACE) at 3-years follow-up. They also found that alpha-linolenic acid (ALA) levels were associated with a lower incidence of all-cause mortality.

The study by Lázaro et al enrolled patients with STEMI (14). However, the results likely apply to all patients with atherosclerosis or at high risk for it. Interestingly, in a recent study of coronary artery calcification (CAC), low levels of EPA and another omega-3 fatty acid called docosahexaenoic acid (DHA) were associated with early-onset coronary atherosclerosis which was independent of age, sex, or statin use (15).

The biology of OM3FAs is complex, and our understanding is rapidly evolving (16). Essential OM3FAs are obtained by the diet from plant sources (such as chia seeds, flax seeds, and walnuts) enriched in ALA. As indicated in the **Figure**, ALA must first be converted to EPA through three independent reactions before converting to DHA after an additional four reactions. By contrast, EPA and DHA can be directly obtained from marine sources (such as oily fish) to avoid these complex conversion steps required of ALA. Indeed, the conversion of ALA to EPA before converting to DHA is inefficient, especially in patients consuming a typical Western diet rich in processed foods, animal fats, and popular cooking oils (corn, soybean, sunflower, rapeseed) that contain O6FAs. Therefore, direct dietary intake of OM3FAs from foods rich in EPA and DHA are of the most benefit, but in patients with cardiovascular disease, even these sources are inadequate to achieve consistent and therapeutic levels in the blood required for the beneficial outcomes reported in REDUCE-IT. The OM3FA dietary supplements remain unproven with respect to reducing cardiovascular risk, and oxidation of these highly unsaturated oils during isolation, storage, and encapsulation may undo any potential benefit as demonstrated by independent laboratory studies (17).

For those with fish or seafood allergy, or who for religious or ethical reasons are vegetarian or vegan and extend this to prohibit consumption of marine-derived medicinal products, ALA may provide a suitable alternative. However, as noted above, the conversion of ALA to EPA is very inefficient with a rate of only approximately 5–20%, with higher, estrogen-dependent rates only among healthy younger women. Thus, ALA may not be a sufficient substitute for direct dietary sources of EPA and related long chain fatty acids. Beyond the implications for drug development, lessons learned from this study likely also apply to dietary guidance. Walnuts, flax seeds, chia seeds, and leafy green vegetables are some examples of foods rich in ALA content. Nuts, such as walnuts, seeds, and leafy green vegetables have been associated with cardiovascular benefits in multiple studies, and within the world of nutritional epidemiology, the results are extremely robust. Indeed, certain observations from this study by Lázaro et al could be confounded by the beneficial elements of such diets that are also rich in ALA and EPA (14).

REDUCE-IT has ushered in a new era in cardiovascular prevention, with what will likely be the first of several therapeutics (18). Ongoing research will examine the potential of higher doses of EPA than what was used in REDUCE-IT, as well as investigation of non-cardiovascular applications. We are witnessing a resurgence in OM3FA research – basic science, nutritional, epidemiology, and randomized trials. Cardiovascular benefits of other active metabolites and derivatives of EPA, and different OM3FAs such as docosapentaenoic acid (DPA) and ALA, will also be explored in the years to come (19). While such research is ongoing, based on findings such as from by Lázaro et al, it makes sense to counsel patients to increase their intake of foods rich in OM3FAs such as EPA and ALA in place of less healthy sources of calories, as well as to implement use of prescription EPA in patients who have approved indications.

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Figure. Pathway for biosynthetic conversion of ALA to EPA, DPA, and DHA. Alpha(α)-linolenic acid (ALA) is enzymatically converted to the omega-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA), by a series of endoplasmic reticulum proteins. The final step is DHA synthesis, and that involves peroxisomal β-oxidation to remove the 2-carbon acetyl-CoA from its precursor. The biosynthesis pathway involves desaturases encoded by the FADS1 and FADS2 genes, respectively. The fatty acid elongation steps are carried out by elongases that are encoded by the EVOLV1 and EVOLV2 genes. Specialized pro-resolving mediators (SPMs) comprise chemical mediators designated resolvins of the E series derived from EPA and resolvins of the D series - protectins, and maresins - generated from DPA and DHA. The PUFAs are converted to SPMs and other bioactive lipids (eicosanoids, docosanoids) by various enzymes including cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP). These products mediate cell signaling, gene expression, and potent anti-inflammatory effects. There are dietary sources for ALA that are plant-based (such as chia seeds, flax seeds, and walnuts), while EPA, DPA, and DHA can be obtained from marine sources (such as oily fish).

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