Editorial

Omega-3 polyunsaturated fatty acids: new evidence supports cardiovascular benefits

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Introduction

A notable public health controversy during the past decade has been whether omega-3 (n-3) polyunsaturated fatty acids (PUFA) are beneficial in either the prevention or treatment of cardiovascular disease (CVD), chiefly in coronary heart disease (CHD), in arrhythmias, particularly atrial fibrillation, and in relation to surgery. Both proponents and opponents have substantial evidence to support their views. Since CVD is the leading cause of death in the world, less toxic and dietary approaches have considerable appeal. As a result, even though about half of Americans eat less fish than is recommended, supplemental "fish oil" is used by 8.9% of the American population, with a market in excess of US$32 billion worldwide. Therefore, the question of whether the benefits of this investment are supported by science is relevant to cardiology societies and public health officials in formulating evidence-based policies—and to consumers in guiding their decisions.

Background

Long-chain n-3 PUFA derived from marine sources have been extensively studied, but despite the research, the answer to this question has been elusive. Even in the face of conflicting evidence, popularity continues, with widespread availability, extremely low toxicity, and the tantalizing possibility of improvements in several conditions. Cognitive benefits associated with omega-3 PUFA are also supported by evidence, although a Cochrane study reported no effect; dementia studies, however, suffer from similar flaws as those in cardiology, as is discussed below. Omega-3 PUFA are termed "essential" because they cannot be synthesized by humans. Authorities frequently note the change of ratios of dietary n-6 to n-3 PUFA from about 1:1 in Paleolithic man to the current ratio of 20:1. The hypothesis that this change has contributed to current epidemics of degenerative diseases may be partially correct, although the topic is far more complex. While a related controversy exists about the extent this trend contributes to CHD, and how this fits with some properties of n-6 PUFA, the change in ratios is generally considered negative. The multiple chronic diseases that plague humans today are associated with systemic inflammation, and indeed, with the prevalent "Western diet" (1). A number of anti-inflammatory properties of n-3 PUFA have been identified, together with many molecular mechanisms of potential clinical importance (2-4).

Cardioprotective actions attributed to n-3 PUFA are likely the result of a web of positive interactions that include not only anti-inflammatory effects, but also antiatherogenic and antiarrhythmic properties, although their pleiotropic effects also include antithrombotic, antihypertensive, antimitogenic, antioxidant, and favorable actions upon lipid profiles (5). In addition, benefits include improvements in endothelial and autonomic system function, enhanced heart rate variability, and faster heart rate recovery after exercise. While several publications convincingly identify a reduction in lethal arrhythmias and the rate of sudden death, others do not (6).

Clinical associations of these agents arise from their

highly conserved anatomic and physiological roles in maintaining bilayer membrane fluidity, to change positions of binding sites and caveolae, optimize signaling, and influence ion channels and calcium regulatory proteins. Metabolic regulatory actions are partly mediated through nuclear receptor modulation. Binding of omega-3 PUFA to the G protein coupled receptor GPR120 and activation of the anti-inflammatory transcription factor peroxisome proliferator activated receptor gamma (PPAR-γ) alters membrane phospholipid composition, remodels lipid rafts, and improves insulin sensitivity; they are all linked events that contribute to lowering the inflammatory load (6). Inhibition of nuclear factor-kappa B (NF-κB) activity is one important anti-inflammatory mediator of n-3 PUFA (2). In recent years, local n-3 PUFA metabolites called specialized pro-resolving mediators (SPMs), including resolvins, protectins, and maresins [together with arachidonic acid-derived (n-6) lipoxins] have received considerable attention because of their active and necessary role in the resolution of inflammation (7). Defective resolution of inflammation impairs efferocytosis, the process of identification and removal of apoptotic debris from lesions, which promotes plaque instability. One can readily appreciate the importance of prolonged exposure to benefit maximally from any improvements in this slow-moving, but highly-regulated event.

Another major mechanism of cardioprotection by n-3 PUFA includes a reduction in plasma triglyceride levels. Nearly half of adult Americans have either diabetes or prediabetes, and there is also growing evidence that triglyceride-rich lipoproteins, which are typically elevated in these conditions, cause CVD. Whether omega-3 PUFA will find a wider role in lowering triglyceride levels in this population remains to be seen.

All the above considered, both plausible mechanistic and evidence-based arguments could be drafted, at least to elevate the association of n-3 PUFA with cardiometabolic risk factors and outcomes from a naïve hypothesis to one with possible merit (8-10). However, CHD is a complex disease which develops over decades, and the integration of putative processes of n-3 PUFA presents a formidable challenge. Hence, studies of short duration have limited clinical relevance and generalizability. In large part, the marked heterogeneity in study methodologies, preparations and doses of n-3 PUFA used, as well as biological, dietary and environmental variation, among other difficulties, has precluded comparisons of effects and conclusions. For instance, human studies have included insufficient numbers of participants with diverse medical histories, ages, ethnicities, comorbidities, and many covariates that were not controlled. Preparations used varied in freshness, quality, rates of auto-oxidation, strength, ratios of eicosapentaenoic acid (EPA) (20:5n-3) to docosahexaenoic acid (DHA) (22:6n-3), as well as the durations of exposure. Most were observational studies of varying power, which, of course, cannot establish any causal relationship. As a result, ongoing mixed reports have been the source of more confusion than clarity (11).

While it is not the intent to review these papers here, a number of recent reviews amply illustrate the common theme of methodological deficiencies in omega-3 research (12-18). In addition, there is an outstanding resource from the Agency for Health Care Research and Quality which catalogs most of the primary studies (19).

Results in a new meta-analysis

An alliance of researchers from 16 countries, the Fatty acids and Outcomes Research Consortium (FORCE), combined resources to study particular risk factors and outcomes in CVD. In one of their projects under discussion in this communication, studies [prospective (cohort, nested case-control) or retrospective] were chosen in which blood or tissue levels of n-3 PUFA were available (20). A total of 45,637 healthy participants (mean age 59 years, 63% male) within 19 studies were enrolled, and were later evaluated for development of incident total CHD, nonfatal and fatal CHD; results were centrally pooled using random-effects meta-analysis. There were 7,973 people who developed an initial myocardial infarction (MI), resulting in 2,781 deaths and 7,157 nonfatal MIs.

In this meta-analysis, EPA, DHA, docosapentaenoic acid (DPA) (22:5n-3), and α-linolenic acid (ALA) (18:3n-3), a shorter chain omega-3 fat found in plants, were analyzed. For most n-3 CV effects, ALA is believed to be weaker than EPA; shared properties are not fully characterized, although benefits of ALA consumption alone are well-recognized. While ALA can be elongated to the potent long-chain relatives, this process is extremely inefficient, on the order of 2–5% (on the lower end for the longer DHA), and conversion is impaired in patients with cardiometabolic disease. Not only do the long chain n-3 PUFA compete with their n-6 counterparts for incorporation into membranes, they also compete for active sites on two enzymes responsible for their metabolism. When the ratio of ingested n-6 linoleic to n-3 ALA is high, there is a

corresponding fall in elongation of the latter (differences also occur because of other factors: gene activities, nuclear transcription factor expression, etc.). Importantly, the standard American diet is relatively high in processed n-6 PUFA vegetable oils. The leading such oils consumed are soybean, canola, palm, and corn oil, followed by lesser amounts of cottonseed-, sunflower-, and safflower-oils, all of which are produced using refinement (crushing and extraction with solvent), bleaching, and deodorization under high temperatures, which reduces n-3 content.

Standardized, individual-level analyses were conducted using harmonized models, exposures, outcomes, and covariates. All n-3 PUFA were reported as weight percentage of total FA in total plasma, phospholipids, cholesterol esters, and in adipose tissue. Heterogeneity was analyzed by age, sex, race, diabetes, statins, aspirin, n-6 levels, and *FADS* desaturase genes.

In multivariable-adjusted analyses, for every 1-standard deviation (SD) rise in the n-3 biomarkers, there was an association with a lower risk of fatal CHD, with relative risks (RR) as follows: ALA, 0.91 (95% CI, 0.84–0.98); DPA, 0.90 (95% CI, 0.85–0.96), and DHA, 0.90 (95% CI, 0.84–0.96). Of the three biomarkers, only DPA was linked to a lower risk of total CHD (RR, 0.94; 95% CI, 0.90–0.99), and there were no significant associations with nonfatal MI per 1 SD.

The upper quintiles of EPA and DHA were associated with a lower risk of nonfatal MI: RR, 0.71 (95% CI, 0.56–0.90) *vs.* 0.87 (95% CI, 0.78–0.97), respectively. In addition, highest quintiles of DPA and DHA were associated with a lower risk of fatal CHD [DPA (RR, 0.76; 95% CI, 0.65–0.90) and DHA (RR, 0.77; 95% CI, 0.6–0.89)].

These results indicate that in a multinational free-living population and independent of age, sex, n-6 PUFA (linoleic acid 18:2n-6) and arachidonic acid (20:4n-6) levels, presence of diabetes and use of aspirin or statins, *in vivo* levels of ALA, DPA, and DHA were associated with a lower incidence of fatal CHD. All told, the effect size was about ~9% fall per 1 SD rise in these concentrations. Most encouraging was the effect of ALA, with implications for the potential utility for plant sources of this substance. DPA is chiefly derived from endogenous, rather than dietary, sources.

This well-conducted study had many strengths. The size ensured a much greater number of events than others. In addition, analysis was prespecified, using individual-level data in each study. Standardized definitions and modeling for all variables and operations made comparisons meaningful. Inclusion criteria minimized reverse causation, and the number of studies included made publication bias unlikely. Since participants were excluded if they had a prior history of CHD, angina, coronary revascularization, the data apply more to the population at large. Limitations inherent in using subjective estimates of fish or fish oil intake were eliminated by using actual *in vivo* levels.

These data strongly support the notion that increased n-3 PUFA intake may lower risk of CHD events, especially fatal myocardial infarction. This is good news, since there is little risk in following this path, and many individuals in modern society do not consume sufficient n-3 PUFA fats (21). Finally, benefits are to be expected even in those already taking statin drugs or aspirin, in contrast to what was previously suspected, and in diabetic patients.

Whether or not these effects can be translated to the use of n-3 supplements was not examined in this meta-analysis. However, it is reasonable to assume that similar benefits will accompany higher levels, independent of the source, and also to conclude that elevating lower levels may be beneficial. Unfortunately, the questions of purity and quality of supplements, as well as mislabeling and potential consumer misinterpretation of contents remain challenges. On the other hand, concerns about fish contamination with polychlorinated biphenyls (PCBs), chlordane, dioxins, and dichlorodiphenyltrichloroethane (DDT) are evident in fish advisories, and lay articles about fish misidentification have also appeared.

For patients who fulfill the criteria, prescription omega-3 PUFA are available as icosapent ethyl, omega-3-acid ethyl esters, omega-3-acid ethyl esters A, and omega-3-carboxylic acids, but they are not FDA approved for the findings in this trial. Over-the-counter omega-3 PUFA are not interchangeable with prescription drugs, and this is particularly true of the newer formulations.

Further studies in progress will add to the evidence base, but may not definitively quell all disagreement. In the interim, the data in this meta-analysis highlight the recommendations of both the American Heart Association and the Harvard School of Public Health concerning fish consumption. Professionals should encourage their patients to be informed and aware of both benefits and risks of using omega-3 agents. Patients at high risk for CVD, with diabetes, or who have already suffered events, should always consult with their physicians beforehand.

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