Can Specialized Pro-resolving Mediators Deliver Benefit Originally Expected from Fish Oil?

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Abstract

Purpose of the Review Fish oil (FO) supplementation has historically been used by individuals suffering from cardiovascular disease and other inflammatory processes. However, a meta-analysis of several large randomized control trials (RCTs) suggested FO conferred no benefit in reducing cardiovascular risk. Skeptics surmised that the lack of benefit was related to FO dose or drug interactions; therefore, the widely accepted practice of FO consumption was brought into question.

Recent Findings Thereafter, Serhan et al. identified specialized pro-resolving mediators (SPMs) to be one of the bioactive components and mechanisms of action of FO. SPMs are thought to enhance resolution of inflammation, as opposed to classic anti-inflammatory agents which inhibit inflammatory pathways. Numerous diseases, including persistent Inflammation, immunosuppression, and catabolic syndrome (PICS), are rooted in a burden of chronic inflammation. SPMs are gaining traction as potential therapeutic agents used to resolve inflammation in cardiovascular disorders, inflammatory bowel disease, sepsis, pancreatitis, and acute respiratory distress syndrome (ARDS).

Summary This narrative reviews the history of FO and the various studies that made the health benefits of FO inconclusive, as well as an overview of SPMs and their use in specific disease states.

Keywords Specialized pro-resolving mediators · Fish oil · Omega-3 fatty acids · Inflammation · Persistent immunosuppression inflammation catabolic syndrome (PICS)

Introduction

Fish oil (FO), for this review, is a lipid concentration of anti-inflammatory omega-3 polyunsaturated fatty acids (PUFAs), Docosahexaenoic acid (DHA), and eicosapentaenoic acid

(EPA). FO has long been supplemented to improve cardiovascular health, but since 2005, its benefits have undergone more scrutiny. FO supplementation for cardiovascular health benefits and overall risk reduction can be traced to an epidemiologic study of Eskimos. In 1940, Berthelsen queried why an Eskimo population on Greenland had an exceedingly low rates of cardiovascular death. Berthelsen concluded the Eskimo population consumed more fish, as compared to other Greenland habitants, who consumed more “Westernized” diets. The working hypothesis was fish contained greater omega-3 fatty acids, which modified the inflammatory process resulting in reduced atherosclerosis. Berthelsen’s work led the charge to increase research to identify the linkage between FO and cardiovascular disease. Unfortunately, a meta-analysis in 2014, consisting of several large randomized control trials (RCTs), did not identify a clear benefit in modifying cardiovascular health [1]. The results of this meta-analysis, as well as several others, sidelined the supplementation of FO for cardiovascular disease even though they were not without critique:

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use of low-quality data, no evaluation of adequate dosing, and ill-defined, objective outcome parameters.

Fortunately, the discovery of new lipid mediators produced from EPA and DHA, called specialized pro-resolving mediators (SPMs), have once again shed light onto FO for therapeutic benefit. SPMs are unique derivatives of omega-3 PUFAs (DHA and EPA) that serve to “resolve” host inflammation [2, 3–5]. SPMs’ novel influence on host inflammation could potentially be the answer to the long anticipated benefits from the FO promise.

This narrative review will provide a past and present overview of FO and identify disorders and review specific disease where SPMs have been used. Specifically, we will (a) explain the mechanism of action of SPMs, (b) review literature for and against FO in cardiovascular diseases, (c) review disease processes and literature documenting SPM benefit, and (d) cogitate on the future of SPM supplementation.

Mechanism of Specialized Pro-resolving Mediators

SPMs are FO-derived pluripotent lipid modulators of inflammation. They resolve inflammation by several endogenous mechanisms, and allow for restoration of homeostasis. Once thought to be a passive process, inflammation resolution is now known to be an inducible, active, and a programmable response [5–8]. Unlike FO, SPMs exert their effect at “pico” or “nanomolar” levels, whereas the optimal therapeutic FO dose remains unknown. SPMs are further divided into three classification: resolvins, protectins, and maresin (macrophage-derived resolution mediators of inflammation) [4]. (see Fig. 1) Each has a unique structure, receptor, and mechanism of action, but all three have an anti-inflammatory, endogenous break as resolution mediators [9–14].

Charles Serhan was the first to describe SPMs, and their impact on inflammation resolution [5, 7, 14–17]. Through further research, Serhan and colleagues have demonstrated that SPMs enhance macrophage efferocytosis (clearing of cellular debris) to eliminate the source of inflammation [18]. Furthermore, SPMs induce a class shift of macrophages from an M1 to M2 phenotypes, which is a programmed immunologic response to promote a shift from a TH1 (pro-inflammation) to a TH2 (pro-resolution) cytokine milieu [19, 20]. SPMs not only stimulate macrophages to clear debris, but also enhance clearing bacteria and apoptotic cells [7, 21, 22]. Levy et al. demonstrated improved clearance of bacteremia, viremia, and fungemia with higher concentrations of resolvins [23]. These mechanisms temper inflammation through two principles [1]: by increasing of the clearance of organisms and debris responsible for ongoing inflammation and [2] by cessation of the host response to injury of polymorphonuclear (PMNs) infiltration to local tissue responsible for continued inflammation [6, 8, 14, 21, 24]. For example, the various end-products such as resolvins E1 and D2 and protectin D1 all are

capable of inhibiting trans-epithelial migration of neutrophils. Many of the biologic actions of SPMs are mediated via specific G-protein-coupled receptors [4, 25].

Therefore, SPMs decrease dysregulated inflammation through an immunologic mechanism, thus promoting catabasis, but also function in host defense, pain modulation, organ protection, tissue remodeling, and potentially limiting acute organ dysfunction by reducing leukocyte-mediated tissue damage (ischemic-reperfusion injury) and fibrosis [2, 4, 26–30]. Though this is a wide application for SPMs to modulate numerous host processes, we will focus on disease-specific uses for FO and SPMs.

FO and Cardiovascular Disease

FO was once heralded as the key dietary component of Eskimos, which provided cardiovascular health benefits. Patients were advised to take FO for various chronic inflammatory processes, including atherosclerosis and cardiovascular disease, inflammatory bowel disease, psoriasis, multiple sclerosis, rheumatoid arthritis, or lupus [31–33]. In 2002, the American Heart Association endorsed FO for the secondary prevention of heart disease [34]. Oral FO supplementation works to increase both plasma and cell-membrane EPA and DHA levels [35, 36]. Unfortunately, blood DHA and EPA levels poorly correlate with reducing cardiovascular risk.

Ultimately, the negative meta-analyses for FO use in cardiovascular disease contradicted the prevailing practice that all patients with or at-risk should consume FO [37–42]. The evidentiary base contradicting FO benefit included: 6 meta-analyses, 17 double-blind RCTs, and 1 open label RCT that largely demonstrated no benefit [1]. There were only two meta-analyses that posed some benefit of FO supplementation for cardiovascular risk reduction, as secondary (not primary) risk reduction. Studer et al. demonstrated benefit summarizing RCTs that used FO as the single, lipid-lowering agent. They identified 97 trials that reported mortality outcomes after exclusion criteria were applied. In this study, omega-3 fatty acids lowered mortality through secondary cardiovascular risk reduction (OR 0.77), but insufficient evidence for primary risk reduction was not significant [37]. Leon and colleagues, in the second meta-analysis to show any benefit, demonstrated the FO decreased cardiac death, but again as a secondary endpoint and not primary [39]. The other cardiac events analyzed by Leon et al. showed no benefit: ventricular arrhythmia, sudden cardiac death, and mortality. The remaining four meta-analyses concluded no benefit for primary or secondary cardiovascular risk reduction.

Similar to cardiovascular risk reduction, other pathologic states have found inconclusive evidence to support supplementation. Fish oils have also been studied in adult respiratory distress syndrome (ARDS), where supplementation with FO still remains controversial. Early studies found omega-3 fatty

Fig. 1 Bioactive profile of specialized pro-resolving mediators (Serhan. The American Journal of Pathology. October 2010: Vol. 177, Issue 4; Fig. 3). Used with permission from Elsevier

acids to have benefit in the setting of ARDS, but an ARDS network trial in 2011 studying omega-3 fatty acids and antioxidant supplementation was stopped early for futility, as there was no benefit for the primary endpoint of ventilator free days [43]. A meta-analysis of omega-3 supplementation determined results was inconsistent and inconclusive to recommend enteral omega-3 supplementation to all ARDS patients [43–45]. It has been speculated that the reason the ARDS network trial failed to show benefit was threefold: (1) the omega-3 (along with other substrate) was given as a twice daily bolus without controlling for the background nutrition, (2) the nutrition historically had skewed ratio of omega-3:omega-6 ratio in favor of pro-inflammatory lipid diets, and (3) there was slight imbalance of age, APACHE III score, PaO₂:FIO₂ ratio, and minute ventilation favoring the control group [43, 46, 47]. For cardiovascular health and ARDS, among others, there are several factors, as well as heterogeneity of the populations that can influence results of trials, which could answer why the literature on FO is inconclusive [38, 40–42].

Optimal FO dose, timing, route of delivery, and composition are unknown [48]. The physiologic impact of oral omega-3 PUFA on disease processes varies and depends upon factors

such as prior diet and genotype [49]. Outcomes from several studies were potentially confounded by co-interventions, such as co-administration of FO and other supplements, making it difficult to attribute any outcome to FO. Additionally, omega-3 and omega-6 fatty acids compete for enzymes responsible for conversion to bio-inactive mediators, which do not have pro-resolving activity [50, 51]. It is the bioactive mediators, or SPMs, that are much more potent than FO. From a mechanistic and pharmacologic standpoint, this may explain why SPMs deliver the benefit that FO cannot [2, 6, 8, 52–55]. The enzymes necessary to convert FO to SPMs have roles in other enzymatic pathways, which may divert the catalysis away and prevents omega-3 fatty acids from actualizing their therapeutic constituents. Aging may further complicate the process by reducing the host biosynthetic potential [56–59]. Finally, limited oral FO bioavailability may attenuate adequate systemic concentrations needed to produce therapeutic effects [60]. Understanding these limitations is crucial to exploring novel methods to optimize dose, delivery, bioavailability, and biosynthetic optimization.

To overcome one of these limitations, parenteral omega-3 supplementation has been shown to be more beneficial than oral. A meta-analysis by Manzanares et al. concluded that

parenteral omega-3 fatty acid supplementation significantly reduced infections, and trended towards reduced mechanical ventilator free days and reduced hospital length of stay [61–64]. Additionally, Pluess and Pittet et al. in two different studies demonstrated that intravenous FO emulsion, given as two doses of 0.5 g/kg of Omegaven (non-FDA-approved lipid emulsion: Fresenius Kabi, Illinois), altered platelet phospholipid composition, blunted the fever curve, and enhanced the neuroendocrine/inflammatory response to endotoxin in healthy subjects [65, 66]. These studies show that parenteral FO may provide benefit in reducing the inflammatory response that was not seen with oral supplementation and cardiovascular risk reduction.

Currently, there is one FDA approved-parenteral supplement that provides increased concentration of FO compared to competitive brands such as Intralipids (Baxter, Illinois). This supplement is known as SMOF lipid (Soy, Medium chain fatty acids, Olive oil, and Fish oil), which has a more balanced ratio of omega-6: omega-3 of 2.5:1 (Fresenius Kabi, Illinois). Intralipid, on the other hand, continues to produce ratios in the range of 6:1, largely promoting a pro-inflammatory parenteral formula. Ultimately, FO supplementation may play a role in various pathophysiologic states. There is inconsistent literature supporting its benefit, likely due to heterogeneity in dose, timing, and route of delivery.

More recently, oral omega-3 fatty acids have shown some improved benefit to individual organ systems in the setting of multiple trauma, head injury, hyperdynamic states, and major surgery [43, 67–69]. Data from human RCTs have demonstrated partial attenuation of the metabolic response, reversal or minimization of lean body tissue loss, prevention of oxidative injury, and positive modulation of the inflammatory response with omega-3 fatty acids [32, 70]. Taking into account and understanding the influence of several key variables, such as dosing, route of delivery, timing, and composition, may ultimately allow researchers to develop better study strategies going forward. The results of these trials may hold promise and foster improved outcomes with FO supplementation.

Specialized Pro-resolving Mediators and Specific Disease States

SPMs have been shown to attenuate the inflammatory response in numerous acute and chronic illnesses. These include cardiovascular disease, inflammatory bowel disease, stroke, asthma, sepsis, periodontal infection, critical illness, and ARDS [9, 32, 71–78]. In a small study of 6 patients, Elajami et al. concluded that patients with coronary artery disease lack specific SPMs and when restored, promote macrophage clearance of blood clots and slowed disease progression [79]. Upchurch and colleagues demonstrated SPMs decreased aneurysm formation and reduce rupture risk in a murine model of abdominal aortic aneurysm. In the same murine model, the

D resolvin class of SPMs were shown to decrease local expansion of the abdominal aorta through shifting of macrophages from M1 to M2, the latter hypothesized to be protective. (58) Furthermore, clinical evidence suggests the magnitude of inflammation is related to outcomes in conditions, such as stroke, myocardial infarction, and peripheral vascular disease. Post-intervention with SPMs in these disorders has demonstrated reduced inflammatory biomarkers, including high-sensitivity C-reactive protein (hsCRP), fibrinogen, serum amyloid A, interleukin (IL)-1, IL-6, and TNF-alpha [80–92].

It is hypothesized that the inflammatory resolution deficit, or ability to get back to homeostasis in advanced atherosclerosis, is lost. Ho et al. demonstrated that circulating levels of aspirin-induced lipoxin A4, an SPM, were significantly lower in patients with symptomatic peripheral arterial disease compared to healthy controls, which inversely correlated with clinical severity [35, 52]. Similar findings have been observed in patients with coronary artery disease and cerebrovascular disease [79, 93]. Expanding on these findings, Conte et al. are currently investigating increasing FO dose to achieve higher SPM levels to evaluate the dose and role as a therapy in patients with atherosclerotic disease in two multi-center RCTs (Omega-SPM-DOSE and Omega-SPM-PAD). Currently, studies support SPMs as pharmaconutrition to provide immune-enhancing function for inflammation resolution. The available evidence suggests SPMs may have an increasing role in treating patients with acute and chronic inflammation. Clinical trials are underway, the results of which may better inform us of the use of SPMs.

Pro-resolving Mediators and the Future

Multiple organ failure (MOF) after sepsis has plagued intensive care units (ICUs) for the past 40 years. With recent ICU advances, early sepsis mortality is low and more ICU patients are surviving despite MOF. Unfortunately, sepsis survivors are now progressing into chronic critical illness (CCI) with a new MOF phenotype called the Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS) [94, 95]. Currently, there are no effective interventions for CCI-PICS and long-term outcomes for this growing epidemic are dismal [96].

When normal protective host responses to infection become excessive, the resulting systemic inflammatory response syndrome (SIRS) can cause a clinical trajectory of refractory shock, fulminant MOF, and early in-hospital death. Until recently, this was a common clinical scenario occurring in > 35% of sepsis patients. However, over the last decade as the result of unprecedented quality improvements to identify sepsis early and provide rapid evidence-based care, early in-hospital mortality has decreased substantially and late onset MOF deaths in the ICU has largely disappeared.

Unfortunately, many sepsis survivors are now progressing into CCI. Based on substantial laboratory and clinical research data, the CCI-PICS paradigm was proposed as a mechanistic framework in which to explain the increased incidence of CCI in surgical ICUs. As SIRS resolves, roughly 60% of the sepsis survivors exhibit “rapid recovery” (RAP, defined as < 14 days in ICU) of their organ dysfunction and achieve “immune homeostasis.” Unfortunately, the remaining 40% develop CCI (defined > 14 days in ICU with persistent, low-grade organ dysfunction) [96–99]. Ongoing studies show these patients have evidence of PICS as demonstrated by (a) persistent inflammation (increased inflammatory cytokines interleukin [IL]-6 and IL-8) and expansion of myeloid-derived suppressor cells (MDCs), (b) immunosuppression (lymphopenia and increased soluble programmed death-ligand 1 [sPDL-1]) requiring frequent treatment of nosocomial infections, and (c) catabolism with muscle wasting and cachexia (similar to cancer and other chronic inflammatory diseases) [100, 101].

SPMs could be an adjunctive therapeutic agent for the PICS population to promote resolution of the irregular inflammatory cascade and possibly prevent patients with CCI from progressing to the full-blown PICS phenotype. Hypothetically, SPM would break the persistently active innate immune response stimulating a self-perpetual cycle of inflammation driven by endogenous DAMPs and exogenous PAMPs. Through inflammation resolution, SPMs would decrease the amount of energy diverted to sustaining PICS, thus allowing the host to potentially become anabolic and returning the patient to physiologic homeostasis [102, 103•].

Further research is needed to delineate the novel role of SPMs in PICS nutrition, as these lipid mediators are likely to be only one agent in the armamentarium of a multi-modality therapeutic approach for PICS that would reduce inflammation while promoting anabolism and improved functional status.

Conclusions

Systemic administration of SPMs or augmentation of their biosynthetic pathways may provide a novel approach to improve outcomes of vascular disorders. SPM mechanism of action could explain some of the cardio-protective benefits derived from dietary intake of their precursor omega-3 fatty acids (DHA and EPA) [50]. Currently, cumulative clinical trial results of omega-3 fatty acids in the cardiovascular setting are conflicting [34, 48]. The body of literature for the beneficial effects of SPMs continues to evolve. Numerous acute and chronic conditions are plagued by inflammation. Animal data inform us of SPM dose, target, mechanism, and host interactions to quell inflammation. These highly conserved lipid mediators are certainly promising; however, clinical human trials

using SPMs are needed to better elucidate and inform us of their therapeutic benefits.

Compliance with Ethical Standards

Conflict of Interest Martin Rosental, Kyle Staton, Robert Martindale, Frederick Moore, and Gilbert Upchurch Jr. declare that they have no conflict of interest. Jayshit Patel reports being a speaker for Nestle.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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