Resolving inflammation by using nutrition therapy: roles for specialized proresolving mediators

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Purpose of review
Inflammation is a unifying component of many of the diseases that afflict Western civilizations. Nutrition therapy and, in particular, essential fatty acid supplementation is one of the approaches that is currently in use for the treatment and management of many inflammatory conditions. The purpose of the present review is to discuss the recent literature in light of the discovery that essential fatty acids are converted by the body to a novel genus of lipid mediators, termed specialized proresolving mediators (SPMs).

Recent findings
The SPM genus is composed of four mediator families – the lipoxins, resolvins, protectins, and maresins. These molecules potently and stereoselectively promote the termination of inflammation, tissue repair, and regeneration. Recent studies indicate that in disease, SPM production becomes dysregulated giving rise to a status of failed resolution. Of note, several studies found that omega-3 fatty acid supplementation, at doses within the recommended daily allowance, led to increases in several SPM families that correlate with enhanced white blood cell responses in humans and reduced inflammation in mice.

Summary
Given the potent biological actions of SPM in organ protection and promoting bacterial clearance, nutritional therapies enriched in omega-3 fatty acids hold promise as a potential co-therapy approach when coupled with functional lipid mediator profiling.

Keywords
chronic inflammation, essential fatty acids, immunity, resolution pharmacology, specialized proresolving mediators

INTRODUCTION

Resolution of acute inflammation is a protective, highly coordinated cellular and biochemical process that paves the way for repairing and regeneration of damaged tissues and re-establishment of host function. This fundamental process orchestrated by a novel genus of lipid mediators, termed specialized proresolving mediators (SPMs), consists of the essential fatty acid (EFA)-derived lipoxins, resolvins, protectins, and maresins. These molecules are enzymatically produced in many organs in the human body at levels commensurate with their biological actions (Fig. 1) and carry defined stereochemistries that are central for their bioactions (for a detailed review on the biosynthetic mechanisms see [17,18]). The biological actions of these novel mediators in controlling inflammation are distinct to current therapeutics. Indeed, whereas drugs in clinical use are designed to inhibit inflammation and block leukocytic recruitment, SPMs act by counter-regulating the production of proinflammatory mediators (cytokines, chemokines, and inflammatory eicosanoids), limiting leukocytic infiltration and promoting leukocyte phenotype switch (for a detailed review see [19]). Therefore, these molecules do not prevent inflammation, but rather avert it from becoming uncontrolled and thus promote its termination. In addition, recent studies demonstrate that they actively promote tissue repair and regeneration in the context of infection [20]. Given the potent biological actions of these molecules

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KEY POINTS

- SPMs are produced via stereoselective enzymatic conversion of EFAs.
- EFA supplementation is associated with increased SPM and improved outcomes in experimental systems and humans.
- Functional lipid mediator profiling represents a novel and predictive approach to determine the efficacy of EFA supplementation.

understanding how their biosynthetic pathways become dysregulated during chronic inflammatory diseases and the impact of EFA supplementation on increasing their endogenous production will provide novel and effective ways in nutrition therapy.

Despite the potent actions of SPM and the role of EFA in their biosynthesis, clinical nutrition in the context of the ICU is somewhat limited. The scope of the present review is to discuss recent literature and the current preclinical and clinical evidence as it pertains to the role of SPM in mediating the host-protective actions of EFA supplementation in both health and disease with the aim to identify potential areas for future translation research of EFA nutrition in an ICU context. We will also review the utility of functional lipid mediator profiling in determining the functional impact of immune nutrition, which may help provide a mechanistic basis for the apparently discordant results on the effectiveness of EFA supplementation in the treatment of inflammatory conditions (Fig. 2).

PROTECTIVE ACTIONS OF SPECIALIZED PRORESOLVING MEDIATORS AND OMEGA-3 ESSENTIAL FATTY ACIDS IN PRECLINICAL SETTINGS

Arthritis

Arthritis is a prototypical chronic inflammatory disease characterized by unabated inflammation that leads to joint destruction and is associated with increased risk of cardiovascular disease. Metabololipidomic profiling of arthritic joints from ω-3 EFA-supplemented mice identified elevated levels of SPM including resolvin D1 (7S,8R,17S-trihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid) [9]. When tested in a murine model of inflammatory arthritis, the stable epimer 17*R*-resolvin D1 significantly attenuated arthritis severity, cachexia, hind-paw edema, and paw leukocyte infiltration, and shortened the remission interval. Furthermore, 17*R*-resolvin D1 exhibited novel tissue-protective functions including stimulation of chondrocyte matrix production and protection from cartilage degradation [9]. Resolvin D1 also displayed protective effects in osteoarthritis pathophysiology.

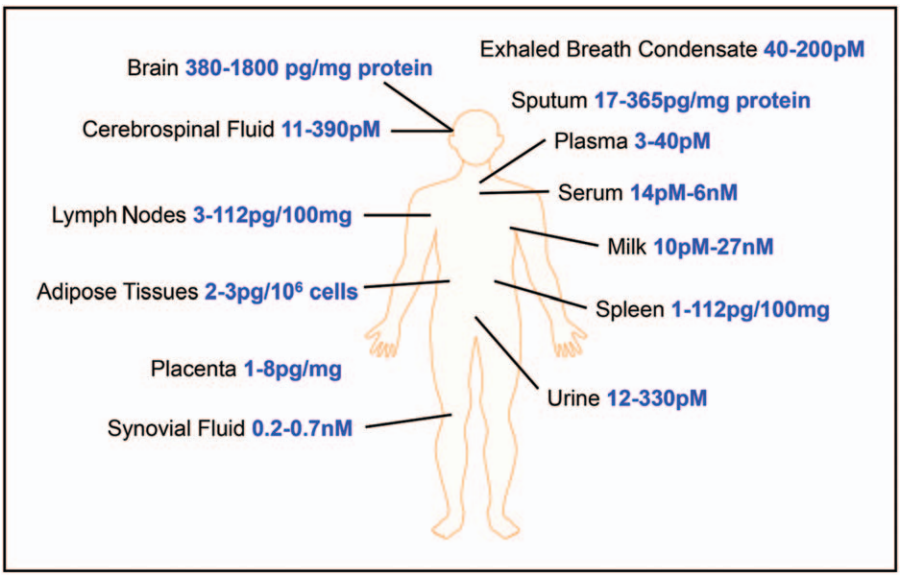

FIGURE 1. Specialized proresolving mediators (SPMs) are produced in human organs and tissues. This figure provides a nonexhaustive list of lipid mediator levels identified in inflamed and noninflamed human tissues including brain [1], cerebrospinal fluid [2,3], lymph nodes [4], adipose tissues [5], placenta [6], synovial fluids [7–9], exhaled breath condensate [10], sputum [11], plasma [4,12], serum [2,4,13], milk [14,15], spleen [4], and urine [16], along with the ranges that these mediators were identified in each tissue or organ system. The biological actions for the identified mediators with human primary cells are in the femtomolar to nanomolar ranges.

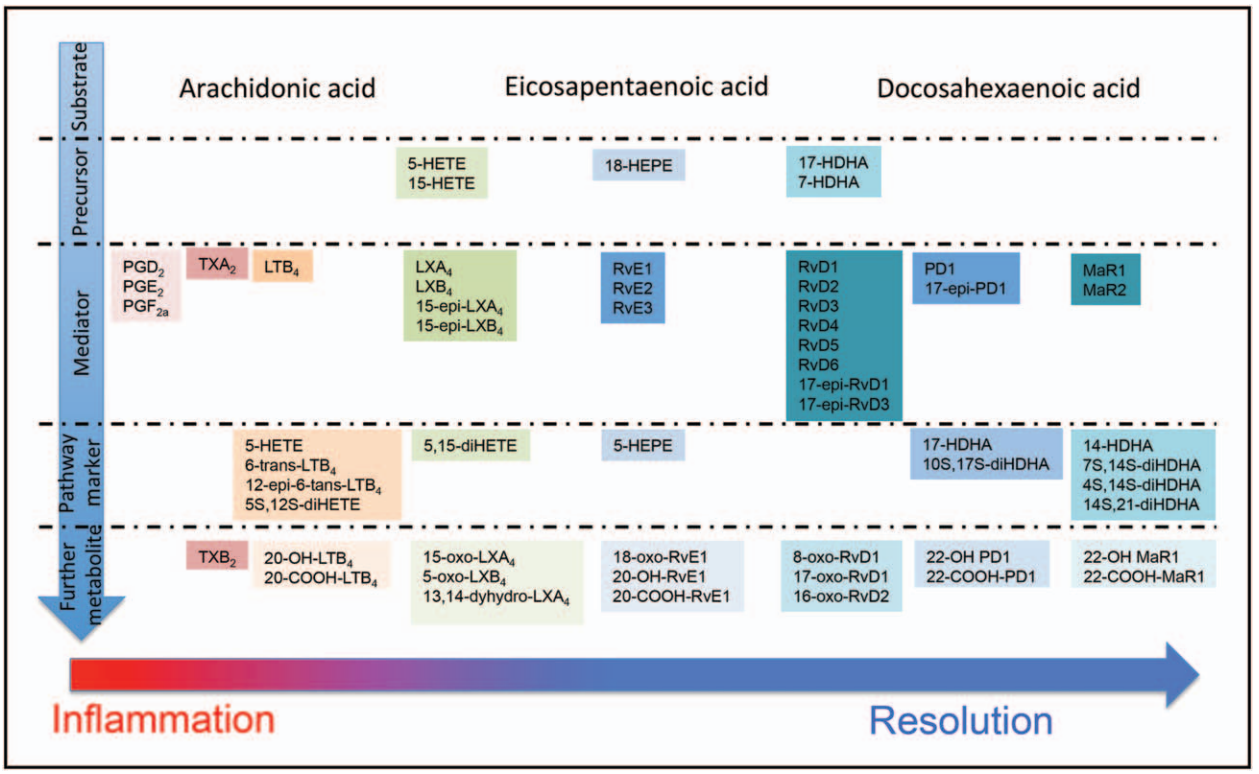

FIGURE 2. Functional lipid mediator profiling provides a snapshot of the flux down of each of the major bioactive metabolomes. This figure illustrates three of the four major lipid mediator bioactive metabolomes. Molecules illustrated here represent the flux down of each of the biosynthetic metabolomes from substrate to bioactive mediator to further metabolites. Measuring the levels of these molecules in tissues provides a snapshot of the dynamic biochemical processes occurring at the site and therefore provides an insight into the inflammation-resolution status. LT, leukotriene; LX, lipoxin; MaR, maresin; PD, protectin; PG, prostaglandin; Rv, resolvin; and Tx, thromboxane.

Resolvin D1 counteracted interleukin (IL)-1β-induced cyclooxygenase (COX)-2, prostaglandin E_2 (9-oxo-11α,15S-dihydroxy-5Z,13E-prostadienoic acid), inducible nitric oxide synthase, nitric oxide, and matrix metalloproteinase-13 in human osteoarthritis chondrocytes via suppression of nuclear factor-kappa B (NF-κB)/p65, p38/mitogen-activated protein kinase and c-Jun N-terminal kinase1/2, and prevented human neutrophil elastase-induced cell apoptosis and oxidative stress [21].

Pain is a major symptom of arthritis and related conditions that can significantly affect the quality of a patient's life. Fish oil supplementation significantly reduced subchronic inflammatory pain induced by intraplantar injection of complete freunds adjuvant into rat hind paws. In these experiments, different doses of eicosapentaenoic acid (460–690 mg) and docosahexaenoic acid (300–540 mg) were found to reduce pain. Protection was associated with reduced tumor necrosis factor-alpha (TNF-α) and increased levels of resolvin D1 in supplemented groups, thereby indicating that EFA supplementation may regulate pain via SPM production [22].

Saturated fatty acids such as palmitate can cause muscle atrophy, which in turn may contribute to a debilitating loss of functional independence. A recent finding indicates that docosahexaenoic acid, the biosynthetic precursor of the D-series resolvins, including resolvin D1 and 17R-resolvin D1, prevents the catabolic effects of palmitate-induced protein degradation by restoring protein kinase B/Forkhead box O-signaling [23]. These studies provide mechanistic substance for the benefits of ω-3 eicosapentaenoic acid supplementation in symptoms associated with arthritis and by limiting the amount of pain relief patients require.

Actions in promoting the clearance of bacterial and viral infections

With the rising incidence in sepsis, which is prone to antibiotic resistance, there is an emphasis in identifying novel therapeutics to combat this fatal condition. Mice fed a high-fat diet (HFD) rich in ω-3 eicosapentaenoic acid for 8 weeks prior to inoculation with *Staphylococcus aureus* had

decreased bacterial loads and better survival compared to those fed a HFD rich in saturated fatty acids. Administering doses as low as 1 or 10 ng of resolvin D1 or resolvin D2 (7S,16R,17S-trihydroxy-4Z,8E,10Z,12E,14E,19Z-docosahexaenoic acid) to mice given a HFD rich in saturated fatty acid diet for 8 weeks also gave significant protection, increased survival, and reduced bacterial loads [24]. Recently, a receptor for RvD2 G-protein coupled receptor 18 (GPR18) was identified using unbiased GPRβ-arrestin-based screening and functional sensing systems [25]. The binding affinity of resolvin D1 was approximately 10 nmol/l, consistent with its bioactive concentration range. In *Escherichia coli* and *S. aureus* infections, resolvin D1 limited polymononuclear (PMN) infiltration, enhanced bacterial clearance, and accelerated resolution. These actions were lost in GPR18-deficient mice, providing evidence for a novel resolvin D2-GPR18 resolution axis that stimulates phagocyte functions to control bacterial infections and protect the host [25].

Recent studies demonstrate that SPMs are also effective in regulating response to viral infections including influenza. Influenza viruses remain a critical global health concern and more effective vaccines are needed. Mice immunized with ovalbumin (OVA) and 17-hydroxy-4Z,7Z,10Z,13Z,15E,19Z-docosahexaenoic acid (17-HDHA) or with H1N1-derived hemagglutinin protein plus 17-HDHA increased antigen-specific antibody titers [26]. Importantly, the 17-HDHA-mediated increase in antibody production was more protective against live pH1N1 influenza infection, implicating SPM as useful for a potential new vaccine.

Adipose and metabolic syndrome

Fat-1 transgenic mice express the *Caenorhabditis elegans* (*C. elegans*) enzyme that converts ω-6 into ω-3 EFA, and are therefore used as an experimental tool to assess if higher ratios of ω-3 : ω-6 EFA contribute to protective responses in various conditions. It was recently reported that Fat-1 transgenic mice are protected from obesity, fasting hyperglycemia, glucose intolerance, and adipose tissue inflammation [27].

Dietary intervention with ω-3 EFA was shown to curb inflammatory and oxidative stress markers related with metabolic syndrome. This was associated with a modulation of lipoxygenase (LOX) and COX activities, reducing proinflammatory arachidonic acid-derived eicosanoids and oxidative stress biomarkers from eicosapentaenoic acid and docosahexaenoic acid [28]. In a separate study, treatment with 467 mg/g eicosapentaenoic acid and 365 mg/g docosahexaenoic acid for 20 weeks prevented renal failure associated with metabolic syndrome, which was associated with decreased triglyceride levels and augmented levels of protectin D1 (10R,17S-dihydroxy-4Z,7Z,11E,13E,15Z,19Z-docosahexaenoic acid), resolvin D1, and resolvin D2 [29].

A selective increase in levels of anti-inflammatory and proresolving lipid mediators in white adipose tissue was observed in mice fed a HFD for 5 weeks that was supplemented with ω-3 EFA (4.3 mg eicosapentaenoic acid/14.7 mg docosahexaenoic acid per gram of diet), reflecting either their association with adipocytes or with stromal vascular cells that gave elevated expression of protectin D1 [30].

In a model of diabetic neuropathy, dietary fish oil supplementation for 6 weeks or RvD1 administration (1 ng/g body weight) improved thermal hypoalgesia, motor and sensory nerve conduction velocities, innervation of the cornea and skin, and the retinal ganglion cell complex [31]. Resolvin D1 also stimulated neurite outgrowth from primary cultures of dorsal root ganglion neurons [31].

Cardiovascular inflammation

Essential fatty acid supplementation has for long been associated with improved outcomes in cardiovascular disease. Recent studies demonstrate that ω-EFA supplementation may lead to improved outcomes following myocardial infarction (MI). The role of SPM in mediating these protective actions was tested by blocking enzymes involved in their biosynthesis, COX-2 and 15-LOX. Rats fed a ω-3 EFA rich diet for 10 days before MI and given inhibitors displayed larger infarct sizes than ω-3 diet alone. Moreover, resolvin D1 administration gave significant cardioprotection in these animals, providing evidence for the role of these mediators in observed cardioprotective actions of ω-3 EFA supplementation [32]. In addition, supplementation of apolipoprotein E null mice with a diet enriched (0.70%) in ω-3 EFA was protective against proinflammatory and oxidative stress responses following short-term infusion with angiotensin II, which was also associated with elevated plasma resolvin D1 levels [33].

Unresolved inflammation contributes to heart failure following MI. When resolvin D1 was administered alone or incorporated into liposomes, this led to improved fractional shortening after MI. The levels of resolvin D1, resolvin D2, maresin 1 (7R,14S-dihydroxy-4Z,8E,10E,12Z,16Z,19Z-docosahexaenoic) acid, and lipoxin A_4 (5S,6R,15S-trihydroxy-7E,9E,11Z,13E-eicosatetraenoic acid) were increased in spleens from RvD1-injected mice 5 days after MI, and also increased expression of its receptor ALX/FPR2. RvD1 reduced profibrotic genes and collagen deposition in the heart, leading to reduced

post-MI fibrosis and thereby reducing the risk of heart failure [34].

Studies in rats given high-fat, high-cholesterol diet for 8 weeks with or without docosahexaenoic acid (3 g/day) demonstrated that docosahexaenoic acid supplementation gave lower arterial blood pressure and heart rates, and prevented aortic wall thickening. Aortic tissue analysis revealed an increase in docosahexaenoic acid-to-arachidonic acid ratio and enhanced production of resolvin D2 and resolvin D3 (4S,11R,17S-trihydroxy-5Z,7E,9E,13Z,15E,19Z-docosahexaenoic acid) [35]. In a mouse model of carotid ligation, resolvin D2 or maresin 1 treatment significantly attenuated neointima formation measured at day 14, indicating a protective role of SPM in vascular remodeling [36].

Neuroprotection

Transient global cerebral ischemia, which can result from cardiac arrest or cardiovascular surgery, can cause neuronal death and cognitive defects. Currently, there are no effective preventions or treatments for this condition. Fat-1 transgenic mice were protected from neuronal loss and cognitive deficits induced by global ischemic insult, which correlated with increased production of resolvin D1, suppressed NF-κB activation, and reduced generation of proinflammatory mediators in the hippocampus [37]. In separate studies, resolvin D1 administration in experimental autoimmune encephalomyelitis decreased disease progression by suppressing autoreactive T cells and inducing an M2 phenotype of monocytes/macrophages and resident brain microglial cells [38].

Recent studies also demonstrate that eicosapentaenoic acid consumption in the early stage of social isolation suppresses hyperglycemia and hypertriglyceridemia associated with insulin resistance without altering food intake or body weight [39]. Docosahexaenoic acid is important for brain function, and clinical data indicate that docosahexaenoic acid can improve cognition in very early stages of Alzheimer's disease [40]. Local delivery of docosahexaenoic acid to the brain has proved possible using systemically administered low-density lipoprotein nanoparticles combined with pulsed focused ultrasound exposures. This treatment modality led to increased levels of resolvin D1 in the brain [41].

Lung inflammation

Neutrophil-mediated acute lung injury from ischemia/reperfusion (I/R) remains a major cause of morbidity and mortality in critical care medicine. Lung A549 cells incubated with eicosapentaenoic acid or docosahexaenoic acid followed by lipopolysaccharide increased levels of maresin 1 and protectin D1 [42]. In mice, low-dose inhaled carbon monoxide (125–250 ppm) or resolvin D1 (250–500 ng) reduced PMN-mediated lung injury, neutrophil–platelet interactions, and production of cysteinyl leukotrienes and thromboxane B_2 (9α,11,15S-trihydroxy-5Z,13E-thrombadienoic acid) during ischemia reperfusion [42]. Maresin 1 was recently found to display potent broncho-protective actions, significantly decreasing bronchoalveolar lavage neutrophil infiltration and proinflammatory mediators in a model of dust exposure. In addition, maresin 1 was produced during early stages of acid induced inflammation [43] and during the resolution phase of allergic inflammation [44] and promoted the resolution of disease.

Ageing

Ageing is associated with an overt inflammatory phenotype and physiological decline. In a self-resolving model of peritonitis, aged mice had delayed resolution and reduced SPMs. Ex-vivo incubation of human monocytes eicosapentaenoic acid : docosahexaenoic acid reprogrammed their lipid mediator phenotype, significantly up-regulating SPM production. When these cells were administered to mice at the peak of inflammation, resolution of acute inflammation was accelerated. Administration of nano-proresolving medicines carrying aspirin-triggered resolvin D1 and resolvin D3 to aged mice also reduced inflammation [45]. Neuroprotective properties of fish oil were assessed in brains of young (3 months) and aged (24 months) mice. Docosahexaenoic acid levels were significantly lower in blood and brains of aged mice, which were compensated by fish oil administration [46]. Together, these results demonstrate a failure in resolution pathways associated with ageing that may be improved by ω-3 EFA supplementation.

PROTECTIVE ACTIONS OF SPECIALIZED PRORESOLVING MEDIATORS AND OMEGA-3 ESSENTIAL FATTY ACIDS IN HUMANS

Neuroprotection

The effects of ω-3 EFA supplementation (4–17 months) was assessed in a small group of patients with minor cognitive impairment (MCI) and showed increased monocyte phagocytosis of amyloid-beta (Aβ). Additionally, resolvin D1, which stimulates Aβ phagocytosis, increased in 80% of

patients with MCI and pre-MCI. This study shows significant immune and biochemical effects of ω-3 EFA supplementation in MCI patients. However, cognitive benefits remain to be tested in a clinical trial [47▪▪].

Alzheimer's disease is associated with brain inflammation and reduced levels of SPMs. In a randomized, double-blind, placebo-controlled clinical trial on Alzheimer's disease patients, 1.7 g docosahexaenoic acid and 0.6 g EPA were administered daily for 6 months. Plasma levels of arachidonic acid decreased, and docosahexaenoic acid and eicosapentaenoic acid levels increased. Analysis of supernatants from peripheral blood mononuclear cells incubated with Aβ1–40 showed unchanged levels of the SPMs lipoxin A_4 and resolvin D1 in the ω-3 EFA-supplemented group. In the placebo group, there was a significant decrease in the levels of these SPMs, which corresponded to cognitive changes, suggesting a role for EFA supplementation in protection from cognitive decline [48].

Metabolic syndrome/obesity

In a recent clinical trial, the effect of ω-3 EFA supplementation (2.4 g/day for 4 weeks with aspirin 300 mg/day during the past 7 days) on volunteers with metabolic syndrome, which is associated with chronic low-grade inflammation, was assessed. SPM precursors/pathway markers 18-hydroxy-5Z,8Z, 11Z,14Z,16E-eicosapentaenoic acid (18-HEPE), 17-HDHA, and 14S-hydroxy-4Z,7Z,10Z,12E,16Z,19Z-docosahexaenoic acid (14-HDHA) were increased after ω-3 PUFA supplementation. However, these were significantly attenuated in the metabolic syndrome group [49▪▪]. ω-3 EFAs may also reduce low-grade inflammation associated with obesity. Indeed, obese women given a supplementation with 1.8 g/day of eicosapentaenoic acid and docosahexaenoic acid for 3 months showed a significant decrease in inflammatory markers including monocyte chemoattractant protein-1, and high sensitivity C-reactive protein, fasting triglycerides, and insulin. This correlated with increased plasma levels of resolvins and an up-regulation of the resolvin D1 receptor [50].

Healthy volunteers

Specialized proresolving mediator amounts in their bioactive ranges have been identified in a large number of organ systems including spleen [4], brain [1], and urine [16] (Fig. 1), and may be involved in a number of physiological processes. Using functional lipid mediator profiling to measure flux down, each of the major bioactive metabolomes plasma SPM rapidly increase (within 4 h) with ω-3 EFA (docosahexaenoic acid/eicosapentaenoic acid) and aspirin intake, which also correlated with increased *E. coli* phagocytosis in whole blood [4]. Moreover, recent studies demonstrate that ω-3 DPA supplementation (7 days) in healthy volunteers increased plasma resolvin $D5_{n\text{-}3\ DPA}$ (7S,17S-dihydroxy-8E,10Z,13Z, 15E,19Z docosapentaenoic acid and maresin 1), compared with volunteers given EPA or placebo (olive oil) [51▪]. These suggest that ω-3 EFA supplementation may have beneficial actions in healthy volunteers by up-regulating systemic SPM levels.

CONCLUSION

Recent advances in our understanding of resolution mechanisms and SPM regulation by EFA supplementation set the stage for a better understanding of the apparently discordant results obtained in clinical settings with nutritional therapies. The potent biological actions that SPM exert in regulating the host response to both infectious and sterile inflammation imply that EFA supplementation hold great potential in treating patients within the ICU. In order to ensure that this potential is fulfilled, future clinical studies assessing the clinical utility of EFA supplementation in regulating processes within inflammation need to take into consideration several factors. These include obtaining empirical evidence for the doses to be used, identifying the optimal supplement composition (including ratios of essential fatty acids, and also other components present) and the form of the EFA that is being utilized (i.e. methylester, ethylester, triglycerides, etc.) since this will influence their bioavailability and pharmacodynamics. Thus, given the potent actions of SPM and their endogenous protective roles in human disease, functional lipid mediator profiling represents a new and exciting approach for empirically defining optimal dosing and formulations for EFA supplements for designing effective nutritional therapies.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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