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MEETING REPORT

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Expert consensus report on lipid mediators: Role in resolution of inflammation and muscle preservation

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Abstract

This meeting report presents a consensus on the biological aspects of lipid emulsions in parenteral nutrition, emphasizing the unanimous support for the integration of lipid emulsions, particularly those containing fish oil, owing to their many potential benefits beyond caloric provision. Lipid emulsions have evolved from simple energy sources to complex formulations designed to improve safety profiles and offer therapeutic benefits. The consensus highlights the critical role of omega-3 polyunsaturated fatty acids (PUFAs), notably eicosapentaenoic acid

Consensus summit experts who attended this meeting were: Magnus Bäck, Sweden; Philip Calder, UK; Sarah Cogle, USA; Valerio Chiurchiù, Italy; David Evans, USA; Leah Gramlich, Canada; Martin Hersberger, Switzerland; Stanislaw Klek, Poland; Robert Martindale, USA; Stephen McClave, USA; Bettina Mittendorfer, USA; Manpreet Mundi, USA; Maurizio Muscaritoli, Italy; Reid Nishikawa, USA; Jayshil Patel, USA; Lorenzo Pradelli, Italy; Martin Rosenthal, USA; Charles Serhan, USA; Christian Stoppe, Germany; Kelly Tappenden, USA; Dan Waitzberg, Brazil; Malissa Warren, USA; Paul Wischmeyer, USA.

(EPA) and docosahexaenoic acid (DHA), found in fish oil and other marine oils, for their anti-inflammatory properties, muscle mass preservation, and as precursors to the specialized pro-resolving mediators (SPMs). SPMs play a significant role in immune modulation, tissue repair, and the active resolution of inflammation without impairing host defense mechanisms. The panel's agreement underscores the importance of incorporating fish oil within clinical practices to facilitate recovery in conditions like surgery, critical illness, or immobility, while cautioning against therapies that might disrupt natural inflammation resolution processes. This consensus not only reaffirms the role of specific lipid components in enhancing patient outcomes, but also suggests a shift towards nutrition-based therapeutic strategies in clinical settings, advocating for the proactive evidence-based use of lipid emulsions enriched with omega-3 PUFAs. Furthermore, we should seek to apply our knowledge concerning DHA, EPA, and their SPM derivatives, to produce more informative randomized controlled trial protocols, thus allowing more authoritative clinical recommendations.

KEYWORDS

anti-inflammatory, consensus, intravenous lipid emulsion, lipid mediator, lipoxins, maresins, omega-3 fatty acids, parenteral nutrition, protectins, resolvins, sarcopenia

1 | INTRODUCTION

The role of lipid mediators in several physiological and pathological processes is of increasing interest to clinicians. For example, lipid mediators derived from polyunsaturated fatty acids (PUFAs) play a pivotal role in the endogenous regulation of inflammation and its resolution,[1] and they affect skeletal muscle mass.[2] Systemic inflammation is often dysregulated, and inflammation-driven muscle depletion can be a concern in patients requiring parenteral nutrition (PN), such as those in the intensive care unit (ICU) or requiring surgery. Given that lipids are an integral part of PN in all settings where PN is indicated, understanding the roles of fatty acids and lipid mediators in PN is critical. To this end, the International Lipids in Parenteral Nutrition Summit was held on November 3 and 4, 2022, in New Orleans, USA. The meeting was divided into two main segments. The first focuses on the basic science of emerging concepts related to mediators derived from omega-3 fatty acids, and the second addresses clinical aspects, with the aim of bridging the gap between formal guideline recommendations and actual clinical practice regarding the use of lipids in PN. The clinical discussions at the summit build on information from an earlier meeting[3] and a detailed summary of these clinical aspects will be published separately.

The focus of this manuscript is the aforementioned science session. This was attended by 23 experts, including academic scientists ($n=5$), clinical nutrition experts from academic and non-academic institutions ($n=17$) and a nutritionist ($n=1$). The authors of this manuscript comprise a subgroup of the summit attendees with a particular interest in lipid and/or lipid mediator research, including the two chairmen of the meeting (all experts attending the International Lipids in Parenteral Nutrition Summit 2022 are listed earlier in this article).

The summit format promoted interactive discussions between areas of academic evidence and clinical experience. It became apparent that the role of lipid mediators in physiological and pathological processes is a rapidly expanding field of research, with clinical data accruing for different diseases and conditions.[4,5] Research is mainly at the pre-clinical stage, and much work remains until the full therapeutic potential of lipid mediators is reached. Here, we summarize the basic principles and mechanisms promoting and, more importantly, actively resolving inflammation, and the roles of lipids in controlling the breakdown of muscle mass, as presented by experts during the summit. We bridge experimental research to clinical data, where data are available, covering different diseases and various lipid sources used in PN. In addition, we provide a set of summary statements formulated during the meeting to facilitate better understanding between research and clinical questions or applications (Table 1). These consensus statements were formulated and voted on by experts participating in the International Lipids in PN Summit 2022, as listed previously, using the same methods documented in the 2020 Lipids in PN summit.[3] The consensus

TABLE 1 Consensus statements—Biological aspects.

Consensus statement	Voting
1. ILEs are an integral part of parenteral nutrition. Originally, ILEs were included as an energy-dense source of calories and provided EFAs	Agree: 23 (100%) Don't agree: 0 Don't wish to answer: 0
2. Subsequent generations of ILEs include combinations of various lipid components, predominantly with the aim of improving the safety profile of ILEs. Each lipid component has its own fatty acid composition and biological effects, which may be more or less beneficial on, for example, inflammation, immunity, or metabolism	Agree: 23 (100%) Don't agree: 0 Don't wish to answer: 0
3. Fish oil is an important component of modern composite ILEs. The biological effects of fish oil can mainly be attributed to its constituent omega-3 PUFAs, EPA and DHA, which have been shown to have anti-inflammatory properties and properties enabling the preservation of skeletal muscle mass and to be precursors for mediators that promote resolution of inflammation. Based on pre-clinical data they have the potential to promote tissue repair, analgesia and insulin sensitivity	Agree: 22 (95.7%) Don't agree: 0 Don't wish to answer: 1 (4.4%)
4. Administration of ILEs containing fish oil rapidly increases EPA and DHA in plasma and subsequently in cell membranes	Agree: 23 (100%) Don't agree: 0 Don't wish to answer: 0
5. The omega-3 PUFAs EPA and DHA serve as precursors for specialized pro-resolving mediators (SPMs). Evidence continues to grow regarding the role of SPMs in immune modulation and tissue repair	Agree: 23 (100%) Don't agree: 0 Don't wish to answer: 0
6. Resolution of inflammation is an active process that is controlled by endogenous pro-resolving mediators without suppressing the host immune defenses. The omega-3 PUFAs EPA and DHA are the precursors of a SPM family including resolvins, protectins and maresins. SPMs are produced during the acute inflammatory response, promoting the resolution of inflammation, facilitating restoration of homeostasis, and supporting tissue repair	Agree: 23 (100%) Don't agree: 0 Don't wish to answer: 0
7. According to an increasing number of clinical studies, the omega-3 PUFAs EPA and DHA are linked to the preservation of skeletal muscle mass and strength. Both are important determinants of recovery from situations of accelerated muscle loss such as after surgery or immobility or in critical illness	Agree: 20 (90.9%) Don't agree: 0 Don't wish to answer: 2 (9.1%)
8. The primary means by which omega-3 PUFAs positively impact skeletal muscle mass is via the incorporation of EPA and DHA into the membranes of muscle cells and intracellular organelles. The increased content of omega-3 PUFAs in these structures may enhance anabolic signaling pathways	Agree: 20 (87.0%) Don't agree: 0 Don't wish to answer: 3 (13.0%)
9. The anabolic effects of omega-3 PUFAs EPA and DHA may be dependent on numerous factors such as daily protein intake, age, co-morbidities or general health status of a patient	Agree: 21 (95.5%) Don't agree: 0 Don't wish to answer: 1 (4.6%)
10. Clinicians should consider proactively utilizing strategies that promote resolution physiology, of which fish oil, as a source of EPA and DHA, is a key component. Clinicians should avoid therapies (such as nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, or corticosteroids) unless clinically indicated, that disrupt the active process of inflammation resolution	Agree: 18 (78.3) Don't agree: 2 (8.7%) Don't wish to answer: 3 (13.0%)

Explanations

Lipid emulsions containing fish oil: commercially available intravenous lipid emulsions (ILEs) that include fish oil as a component (e.g. SMOFlipid; also Finomel in Europe).
Fish oil contains (among others) the bioactive omega-3 PUFAs, EPA and DHA.
Omega-3 PUFA stands for omega-3 polyunsaturated fatty acids and is a group of fatty acids.
EPA (eicosapentaenoic acid) is an omega-3 PUFA.
DHA (docosahexaenoic acid) is another omega-3 PUFA.
EPA and DHA serve as precursors for bioactive lipid mediators including SPMs.
SPMs are specialized pro-resolving mediators.

Abbreviations: COX, cyclooxygenase; DHA, docosahexaenoic acid; EFA, essential fatty acid; EPA, eicosapentaenoic acid; ILE, intravenous lipid emulsion; PUFA, polyunsaturated fatty acid; SPM, specialized pro-resolving mediator.

statements represent the collective opinion of the expert panel, and are supported by scientific evidence.

1.1 | Mechanisms regulating the resolution of inflammation

Uncontrolled and/or excessive inflammation is a component of many widely occurring human conditions, including cardiovascular and neurological diseases, metabolic diseases, cancer, obesity, arthritis, hepatitis, and bacterial and viral infections including coronavirus disease 2019 (COVID-19), among others.[6–10] The key mediators of inflammation, such as vasoactive amines, prostaglandins (PGs), leukotrienes (LTs), cytokines, and chemokines, are targeted by classic anti-inflammatory drugs including steroids and nonsteroidal anti-inflammatory drugs (NSAIDS), but these approaches can be associated with undesirable side-effects including increased risk of infection or other symptoms associated with compromised immune defense.[9,11–13] Furthermore, NSAIDS can impair the resolution of inflammation via cyclooxygenase (COX)-2 inhibition.[13] Thus, there is a clear need for new, more effective approaches to control excessive inflammation. Advances regarding mechanisms of acute inflammation resolution may lead to the development of advanced therapies within this field.[14]

The acute inflammatory reaction is part of a normal immune response, and is protective, permitting injured tissue repair and the elimination of invading organisms. In good health, this process has evolved to be self-limiting (i.e. leading to the complete resolution of leukocyte infiltrates and clearance of cellular debris), enabling a return to homeostasis.[7] Until recently, resolution was considered to be a passive process, but we now know that the resolution of inflammation is a biosynthetically active programmed response that is 'turned on' and follows a highly coordinated process.[6,15,16] This realization followed exploration of the fundamental mechanisms in the resolution response from self-resolving inflammatory exudates, resulting in the discovery of the superfamily of pro-resolving lipid mediators. These are now collectively termed specialized pro-resolving mediators (SPMs) owing to their highly specialized cellular functions in the resolution of inflammation and tissue injury, microbial clearance, and reducing pain.[15,17,18] SPMs are potent endogenous bioactive compounds that are biosynthesized from PUFA precursors such as arachidonic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).[17,19] The main classes of SPMs are the omega-6 arachidonic acid-derived lipoxins, and omega-3 EPA- and DHA-derived resolvins, protectins and maresins.[5,9]

The structure of most SPMs has been established and total organic synthesis performed, allowing confirmation of their potent pro-resolving mechanisms in vitro and in pre-clinical in vivo disease models.[7,17] SPMs activate resolution of inflammation in human and other mammalian models in a wide variety of organs and tissues, including the eye, heart, cardiovascular vessels, muscle, kidney, central nervous system, lungs, skin, and the gastrointestinal tract.[17] Endogenous SPM biosynthesis involves cell–cell interactions and is largely facilitated by lipoxygenases.[20] On maturation of an acute inflammatory response, pro-inflammatory products accumulate such as PGs, LTs, and hydroxy acids, favoring a phenomenon known as lipid mediator class switching.[21,22] This switching towards the production of SPMs results in SPM synthesis via pathways that are distinct from those involved in the generation of pro-inflammatory lipid mediators.[21] A quantitative definition of resolution was deemed critical to pinpoint the biosynthesis and actions of SPMs, and also to dissect the effect of drugs and infection on resolution.[23] Thus, focusing on polymorphonuclear neutrophils (PMNs) and macrophages, quantitative resolution indices were developed for these cells and their actions in tissues.[23] SPMs have a defined mode of action in which they limit the magnitude and duration of the acute inflammatory response.[6] In part, this is because SPMs stimulate macrophage phagocytosis/efferocytosis (i.e. the engulfment of dead cells by phagocytes such as macrophages: a highly intricate process that ultimately allows for the recycling of cellular products, reduction of persistent inflammation, limitation of tissue necrosis and promotion of tissue repair), as well as dampening the production of pro-inflammatory factors.[24–26]

SPMs have demonstrated potent pro-resolving actions in a range of disease models, and thus many related resolution-targeted drug development opportunities are currently being studied.[4] A number of approaches may be considered to actively resolve inflammation. These include SPM receptor agonists, stable SPM mimetics, synthetic resolvins and other SPMs, increased availability of SPM substrates (e.g. EPA and DHA) or intermediates, as well as nanomedicines to deliver SPMs and their analogues.[4] Focussing on increased availability of substrates such as EPA and DHA, it is notable that endogenous production of SPMs is favored by the higher EPA and DHA status brought about by increased supply of these fatty acids.[27,28] This may explain some of the biological effects of fish oil, which is an important component of modern composite lipid emulsions used in PN. Fish oil is a rich source of omega-3 PUFAs, EPA and DHA, which are precursors for SPMs (Table 1, consensus statements 3 and 5). Furthermore, administration of lipid emulsions containing fish oil rapidly increases EPA and DHA in plasma and subsequently in cell membranes (Table 1, consensus

statement 4). It is also important to note that the resolution of inflammation is a biosynthetically active process partially controlled by SPMs, without suppressing host immune defenses (Table 1, consensus statement 6). Clinicians may thus consider using strategies that promote, rather than disrupt, inflammation resolution physiology (Table 1, consensus statement 10). A simplified overview of the acute inflammatory response and its resolution or progression to chronic/excessive inflammation is shown in Figure 1.[4,28–30]

1.2 | Stimulating the resolution of inflammation via omega-3 PUFAs: Examples from different diseases

As mentioned previously, one objective of the summit was to bridge between experimental research and clinical data. To do this, a range of diseases and conditions were discussed that have parallels to situations where PN is used. For each of these diseases/conditions discussed, some basic disease-specific pathophysiological insights are provided in this section, focusing on inflammatory mechanisms, resolution of inflammation, and including a short summary of current pre-clinical and clinical data.

1.2.1 | Cardiovascular diseases: Focus on atherosclerosis and aortic valve stenosis

Atherosclerosis is an inflammatory disease involving the arterial intima, in which the balance of inflammatory and inflammation-resolving mechanisms dictates the final clinical outcome.[29] Inadequate resolution of inflammation ultimately results in the formation of lesions with a necrotic lipid core and thinning of the protective collagen cap, which are hallmarks of atherosclerotic plaque vulnerability and potentially poor clinical outcomes (e.g. acute cardiovascular and cerebrovascular events).[29,31,32] The imbalance between resolving and inflammatory mediators in atherosclerosis results in defective resolution of inflammation, tissue injury, and damage-associated molecular pattern (DAMP)-mediated inflammation.[29] SPMs have shown therapeutic potential in promoting the resolution of inflammation in cardiovascular disease, given that many SPMs have shown atheroprotective actions and promise for cardioprotection with reduction of tissue fibrosis in animal models.[26] Studies in humans and in mice have found a low ratio of pro-resolving lipid mediators (such as resolvin D1) to inflammatory LTs in advanced compared with early atherosclerotic plaques.[33] Furthermore, administration of resolvin D1 to mice during plaque progression restored the resolvin D1:LTB4 ratio to that of less advanced lesions and promoted plaque stability.[33] In addition, the ratio between the pro-resolving and inflammatory lipid mediators resolvin D1 and LTB4 in human saliva can predict carotid intima thickness in cardiovascular disease.[34]

In humans, the direct use of SPMs has been proposed as an approach to suppressing the formation of clinically dangerous atherosclerotic lesions or even treating atherosclerosis (e.g. the targeted delivery of SPM to atherosclerotic plaques with the use of nanoparticles or biodegradable vascular wraps).[26] Another therapeutic approach could be to increase the supply of SPM precursor lipids (i.e. the use of fish oil/omega-3 PUFAs). However, meta-analyses of

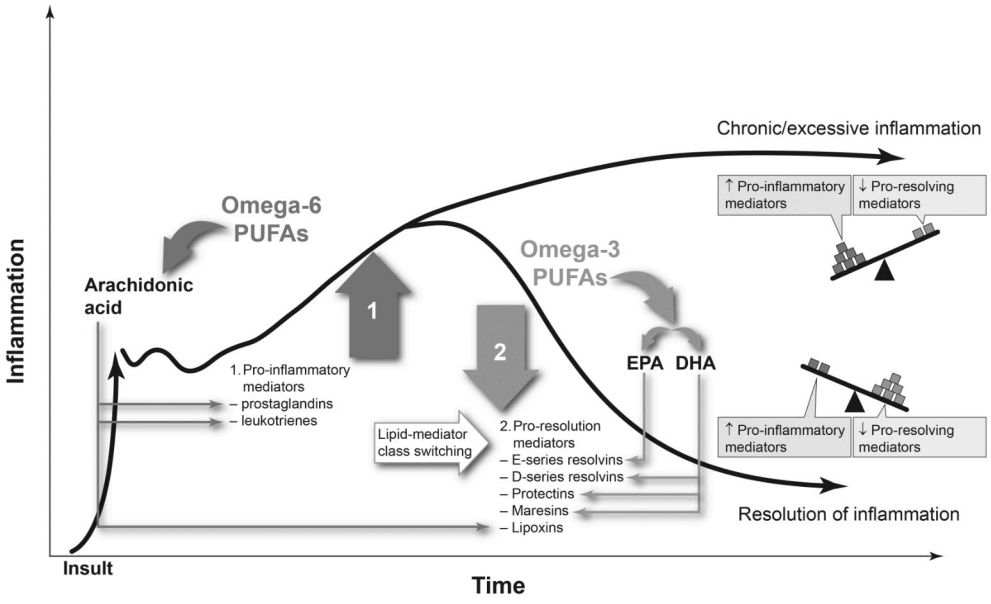

FIGURE 1 The acute inflammatory response and its resolution or progression to chronic/excessive inflammation.[4,28–30]

oral omega-3 PUFA supplementation studies in patients at high risk of (or with) advanced cardiovascular disease have shown mixed results. Some showed no reduction in risk for myocardial infarction (MI) with omega-3 PUFAs,[35] but another more recent meta-analysis revealed a relative 8% lower risk of MI, with higher omega-3 PUFA doses offering the greatest protection.[36] Most recently, a meta-analysis updated these results, incorporating the latest clinical trials, and reported that oral omega-3 PUFA supplementation resulted in a significant 9% reduction in the odds of non-fatal MI.[37] Interestingly, the authors also found a dose-dependent risk reduction of non-fatal MI with increasing EPA dosage, regardless of DHA intake.[37] These results show that it is important to continue to focus on further optimization of omega-3 PUFA supplementation formulation and dose to stimulate SPM formation, as well as considering the most appropriate target populations (e.g. primary versus secondary prevention, lipid profiles, comorbidities, and medication use).[29]

In addition to direct omega-3 PUFA supplementation, the activity of fatty-acid desaturases (FADS) also determines PUFA levels. In turn, FADS activity is influenced by polymorphisms in the genes encoding the FADS proteins. Thus, the relationship between FADS polymorphisms and increased atrial stiffness (an independent predictor of premature mortality and cardiovascular events), has recently been explored.[38] Results showed an association of *FADS1* genotype with arterial stiffness, an effect that was mitigated by higher oral omega-3 PUFA intake.[38] As such, these findings may allow the identification of responders and non-responders to omega-3 PUFA supplementation, opening the way for personalized cardiovascular prevention through dietary counseling. It is also interesting to note that a Mendelian randomization study exploring relationships between plasma phospholipid fatty-acid levels and cardiovascular disease showed that levels of several fatty acids were driven by the *FADS1* genotype in six out 15 cardiovascular diseases investigated (aortic aneurism, aortic valve stenosis, large artery stroke, venous thromboembolism, ischemic stroke and coronary artery disease).[39] In addition, experiments by Plunde et al. supported the association between the *FADS1* genotype and lower risk for aortic stenosis, by showing that DHA levels were decreased in calcified versus non-calcified aortic valve tissue in a genotype-dependent manner.[40] Thus, DHA and DHA-derived SPMs may contribute to a protective effect in aortic stenosis,[40] and upregulation of the LT-forming 5-lipoxygenase pathway in human aortic valves correlates with the severity of stenosis.[41] Moreover, human stenotic aortic valves have been shown to contain decreased omega-3 PUFA levels, and that omega-3 PUFA decreased aortic valve calcification in murine models.[42] Furthermore, the pro-resolving lipid mediator resolvin E1, derived from EPA, exerted protective effects on valvular interstitial cell calcification and valvular inflammation.[42] Thus, resolvin E1 and its receptor ChemR23 have emerged as a key axis in the inhibition of aortic valve stenosis progression, and may represent a novel therapeutic opportunity for evaluation in patients with this condition.[42,43] In particular, the potential beneficial effects of omega-3 PUFA supplementation in aortic valve stenosis warrant further investigation in clinical trials.[43]

1.2.2 | COVID-19

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Infection can trigger an immune response with local pulmonary inflammation, which in the most severe cases may lead to a systemic hyperinflammatory reaction, acute respiratory distress syndrome, and cardiac failure.[44] This uncontrolled systemic inflammation is associated with cytokine release syndrome or 'cytokine storm' (e.g. increased levels of inflammatory cytokines such as interleukin [IL]-6, IL-8, IL-17, IL-1β, and tumor necrosis factor [TNF]-α).[45] In addition, there may be an 'eicosanoid storm' component during uncontrolled systemic inflammation, caused by increased levels of pro-inflammatory lipid mediators derived from the omega-6 PUFA arachidonic acid, including prostanoids (prostaglandins and thromboxane), formed by the COX pathway, and the LTs and cysteinyl LTs, formed by the 5-lipoxygenase pathway.[30] The uncontrolled immune response observed in severe COVID-19 represents the archetype for failed resolution of inflammation, and thus there may be a therapeutic role for omega-3 fatty acids to promote the formation of SPMs and to resolve inflammation in these infections.[30]

The Resolving Inflammatory Storm in COVID-19 Patients by Omega-3 PUFA (COVID-Omega-F) study—a single-blind, randomized, placebo-controlled feasibility trial—was conducted to establish whether intravenous omega-3 PUFA supplementation was a possible treatment option in COVID-19.[30,46] Hospitalized COVID-19 patients ($n = 22$) were given 2 mL/kg of either placebo (0.9% saline) or fish oil (Omegaven®, Fresenius Kabi, 10 g of fish oil per 100 mL) intravenously for 5 days. Fish oil treatment was associated with a beneficial cellular immune response, increased pro-resolving mediator precursor levels, decreased leukotoxin-diols, decreased immunothrombosis (bidirectional interaction process between the innate immune pathway and coagulation), and enhanced phagocytosis.[46,47] Larger studies are needed to determine

whether these results can be translated into better clinical outcomes.

1.2.3 | Neurological diseases: Multiple sclerosis

Although the brain has long been considered an immunoprivileged organ, uncontrolled inflammation and failed resolution of inflammation is also a common feature of neurodegenerative disorders (e.g. multiple sclerosis [MS], Alzheimer's disease [AareD], and Parkinson's disease [PD]).[48,49] Inflammation within the central nervous system (CNS), termed neuroinflammation, can indeed occur and is similar in many ways to inflammation in the rest of the body insomuch as peripheral blood leukocytes can infiltrate brain parenchyma and can sustain the activation of resident immune cells (i.e. microglia) or other glial cells, eventually damaging neurological functions and resulting in neurodegeneration.[48] Likewise, neuroinflammation is kept in homeostatic balance by an active resolution process orchestrated by SPMs, ultimately leading to the avoidance of neurodegeneration and the subsequent development and/or progression of neurodegenerative disease. However, relatively little is known currently concerning neuroinflammation resolution within the CNS, including the anatomical and cellular source of CNS SPMs.[48]

Chronic inflammation is a key pathological feature of MS, and thus peripheral blood of patients with different clinical phases of MS and healthy volunteers was analyzed using targeted-metabololipidomics.[50] This revealed defects in the inflammation resolution pathway in MS, with each MS disease state associated with distinct lipid mediator profiles correlating significantly with disease severity. For example, MS patients during a relapse (representing an acute neuroinflammatory demyelinating reaction) or those with a progressive disease course, had high levels of eicosanoids, with most pro-resolving lipid mediators significantly reduced or below limits of detection.[50] Moreover, SPM biosynthetic enzymes and receptors were found to be expressed differentially in MS patients according to clinical disease phase.[50] In a blood–brain barrier model, significantly reduced SPMs in relapsing MS patients (e.g. lipoxin A_4, lipoxin B_4, resolvin D1, and protectin D1) reduced MS-derived monocyte activation and cytokine production from monocytes obtained from such patients as well as inhibiting monocyte transendothelial migration.[50] Thus, SPMs have the potential to become not only novel blood biomarkers for MS diagnosis, but also putative novel tools to limit MS pathogenesis at several clinical disease stages. For example, further work has been conducted using an experimental autoimmune encephalomyelitis murine model of MS, as well as in vivo and in isolated human T cells from healthy donors and patients with relapsing–remitting MS.[51] This showed that lipoxin A_4, a pro-resolving lipid mediator, attenuates neuro-inflammation by modulating T-cell responses and modifies the spinal cord lipidome. Therefore, lipoxin A_4-mediated amelioration of neuroinflammation is a potential strategy to foster resolution of neuroinflammation and perhaps to modulate MS pathogenesis and disease progression.[51]

1.2.4 | Neurological diseases other than MS

Any advances within the field of MS may also have ramifications for other neurological fields. For instance, impaired cognition is a major clinical symptom of MS, being present in more than 50% of patients,[52] and neuroinflammation is also thought to play a causal role in this and other disorders with cognitive and/or motor symptoms, including other neurodegenerative diseases like AD and PD, as well as perioperative neurocognitive disorders.[53] Indeed, neuroinflammation can often complicate postoperative recovery, and this has been reflected in postoperative changes in lipid mediator levels from cerebrospinal fluid (CSF) samples.[53] As such, there may be a rationale for an increased supply of omega-3 fatty acids during the post-operative period to help protect against perioperative neurocognitive disorders.

Preclinical studies from both AD and PD animal models have indicated a dysregulation of SPMs and their receptors in these neurological disorders.[49,54] For instance, in AD the levels of several families of SPMs are reduced in post-mortem human brain tissues (i.e. in the hippocampus and entorhinal cortex) of patients with AD[55,56] and in transgenic animal models of AD.[57–60] Recently, the first lipidomic profiling of cerebrospinal fluid in AD was undertaken to simultaneously analyze both SPMs and pro-inflammatory eicosanoids in patients with cognitive impairment, ranging from subjective impairment to a diagnosis of AD, and correlated to cognition, CSF tau, and β-amyloid.[61] In this study, resolvins D1, D4, and E4, protectin 1, and maresin 1, were lower in AD and/or cases of mild cognitive impairment, compared with patients with spinal cord injuries. Furthermore, levels of resolvin D1 showed a negative correlation with p-tau levels, while resolvin D4 negatively correlated with AD tangle biomarkers, and positive correlations with cognitive test scores were observed for both SPMs and their precursor fatty acids.[61] A 6-month randomized, double-blind, placebo-controlled clinical trial of DHA/EPA supplements has been conducted in patients with AD.[62] After treatment, levels of resolvin D1 and lipoxin A_4 in

peripheral blood mononuclear cells (PBMCs) remained unchanged, suggesting that omega-3 supplementation may have prevented a reduction in SPMs.[62] A similar result was obtained in another clinical trial in human patients affected by mild cognitive impairment and pre-mild cognitive impairment conditions, whereby the supplementation with omega-3 fatty acids and antioxidants led to increased levels of resolvin D1 in macrophage cultures isolated from PBMCs.[63]

SPMs may have a neuroprotective role in AD by altering the expression of pro-inflammatory genes, modulating macrophage and microglia function, as well as clearing β-amyloid aggregation/deposits, and promoting resolution of neuroinflammation.[49] In PD, data suggest SPMs are able to cross the blood–brain barrier, inhibit microglial activation and decrease inflammatory marker levels,[64] perhaps as a result of downregulating nuclear factor kappa B (NFκB) signaling pathways.[49] Moreover, several in vivo and in vitro studies have shown potential benefits following administration of SPMs for both of these neurodegenerative disorders. For example, Krashia et al. used a rodent transgenic humanized model for PD to show that treatment with resolvin D1 prevented central and peripheral inflammation, while also preventing dopaminergic neuronal dysfunction and motor deficits.[64] Furthermore, the same study also demonstrated significantly lower levels of resolvin D1 in both the cerebrospinal fluid and plasma of patients with early PD compared with healthy age-matched controls. As SPMs may prevent or resolve chronic neuroinflammation, future research should include focused, translational efforts to investigate SPMs as an add-on (in addition to standard treatment) or as standalone agents in patients with neurodegenerative disorders.[49]

1.3 | Lipid mediator profiles after treatment with intravenous lipid emulsions (pre-clinical data)

Lipid emulsions are an integral part of PN, supplying an energy-dense source of calories and essential fatty acids (Table 1, consensus statement 1). Developments in lipid emulsions used for PN have resulted in increased complexity and choice of lipids, with each component differing in fatty-acid composition and potential biological effects (Table 1, consensus statement 2). Thus, the choice of lipid emulsion used for PN has become an important decision, particularly given very promising results from meta-analyses showing benefits for PN containing omega-3 PUFAs including significantly reduced lengths of hospital and ICU stays, as well as reduced incidence of infection or sepsis.[65] Moreover, these clinical observations have a sound scientific basis founded on inflammation resolution physiology and the key roles played by EPA and DHA within this active process, as mentioned previously (Table 1, consensus statement 10). In healthy volunteers in whom an inflammatory reaction has been provoked (via lipopolysaccharide inhalation), the infusion of fish-oil lipid emulsions induced a rapid increase in free- and cell-bound EPA and DHA levels, counterbalancing arachidonic acid, whereas a soybean oil lipid emulsion infusion did not induce this shift in the fatty-acid profile.[66] More detailed information was derived from a murine model of PN, which investigated whether PN with lipid emulsions containing higher concentrations of omega-3 PUFAs had more favorable effects than those low in omega-3 PUFAs.[67] Mice were given 7 days' PN with either fish oil (Omegaven; omega-6:omega-3 ratio of 1:8) or soybean oil (Intralipid; omega-6:omega-3 ratio of 7:1), with control groups given either a standard oral (chow) diet or chow diet plus intravenous saline. Only PN with soybean oil resulted in significantly increased IL-6 levels, indicating liver inflammation, while the fish-oil group had reduced inflammation (significantly lower levels of both monocyte chemoattractant protein (MCP)-1 than the saline control and IL-1α than the Intralipid group). Predictably, both PN groups had higher plasma insulin concentrations than for the controls, but glucagon and glucagon-like peptide-1 (GLP-1) levels were significantly higher in those given soybean oil than the fish-oil group, indicating reduced insulin sensitivity with soybean oil.[67] Finally, omega-3 lipid emulsions given orally in murine peritonitis and sepsis models resulted in accelerated resolution of inflammation, reducing pro-inflammatory and enhancing anti-inflammatory mediators, and stopping neutrophil infiltration.[68] Also, omega-3 strongly reduced classical monocytes and increased the non-classical monocyte/macrophage recruitment and increased efferocytosis of apoptotic PMNs.[68] Moreover, these phagocyte responses were 5-lipoxygenase and 12/15-lipoxygenase dependent.[68] Omega-3 lipids also protected against hypothermia and weight loss, and enhanced survival in murine polymicrobial sepsis.[68] Together, these results show that omega-3 lipids can control key innate protective mechanisms during the onset and the resolution of acute inflammation and may promote survival in sepsis.[68]

The role of SPMs in PN with different lipid emulsions was investigated by developing an analytical method to quantify 58 pro-inflammatory and pro-resolving lipid mediators in plasma, determine preliminary reference ranges for healthy adolescents, and subsequently determine how PN lipid emulsions influence lipid mediator concentrations in plasma using the murine model of PN.[69] The results showed that PN with fish oil leads to a less inflammatory lipid mediator profile in mice than PN with Intralipid. Thus, compared with mice given

soybean oil, PN with fish oil resulted in significantly increased EPA- and DHA-derived SPMs such as maresins 1 and 2, protectin D1, protectin DX, and resolvin D5, and decreased inflammatory lipid mediators such as LTB4 and PGD2.[69] A further study investigating these aspects in the murine model of PN found that fish oil shifts the lipid mediator profile towards omega-3 PUFA-based lipid mediators in the liver and that SPMs (including resolvin D1, maresin 1 and 2, and protectin D1 and DX), were higher in the livers of mice given fish oil compared with those given soybean oil.[70] Moreover, the murine spleen was identified as a rich source of lipid mediators and SPM formation, as lipid mediator concentrations were approximately 25-fold higher in the spleen than in the liver.[70] Finally, a variety of different research groups have demonstrated that interventions with SPMs resolvin D1, maresin 1, and protectin DX improved insulin sensitivity in obese diabetic mice,[71–73] suggesting a role for these SPMs in the improved insulin sensitivity with fish oil in the PN murine model.[67]

1.4 | Effects of omega-3 polyunsaturated fatty acids in the prevention of muscle depletion

Sarcopenia is primarily an age-related progressive loss of skeletal muscle mass and strength and reduction in physical performance.[74,75] Sarcopenia is more common in older populations that are physically inactive and those with chronic diseases, compared with healthy older adults.[74] The decline in muscle mass starts from approximately 40 years of age onwards.[74] Symptoms or signs of sarcopenia are increased incidence of falls, feeling weak, slow walking speed, difficulty rising from a chair and/or weight loss/muscle wasting.[75]

An increasing number of clinical studies have suggested that omega-3 PUFAs are linked to the preservation of skeletal muscle mass and strength, which are important determinants of recovery from situations of accelerated muscle loss, such as after surgery, a period of immobility, or during critical illness (Table 1, consensus statement 7). A cross-sectional retrospective cohort study found that an increase in grip strength of 0.43 kg in men and 0.48 kg in women was observed for each additional portion of fatty fish consumed per week.[76] Grip strength measurement is used to identify low muscle strength in cases of sarcopenia, and is a powerful predictor of poor patient outcomes (e.g. duration of hospital stay, health-related quality of life, and death).[75] Animal experiments have also shown that diets high in omega-3 PUFAs can enhance insulin-sensitive aspects of protein metabolism and the activation of protein anabolic signaling (anabolic effect) in cattle[77] and in rats.[78] Similar effects have been observed in humans. For example, a trial involving older adults randomly assigned to receive either 4 g/day omega-3 PUFAs or corn oil orally for 8 weeks showed that omega-3 PUFAs alone increased muscle anabolic signaling activity and the insulin/amino acid-mediated increase in muscle protein synthesis.[79] Further studies in healthy older adults have shown that oral omega-3 PUFA supplementation can increase muscle mass and function compared with a control group given corn oil.[80] Over the 6-month trial duration, omega-3 PUFA supplementation (4 g/day) resulted in significant increases in thigh muscle volume, hand-grip strength, and one-repetition maximum muscle strength compared with the control group.[80] These results have been confirmed and extended in recent randomized controlled studies, also in older adults and in which 4 g of omega-3 PUFAs were given per day, leading to increased muscle mass and function.[81,82] A recent systematic review and meta-analysis has examined oral omega-3 PUFA supplementation, with or without resistance exercise training, on muscle mass and function in older adults.[83] Sixteen studies were included, and this meta-analysis revealed significant benefits for lower body strength, timed-up-and-go, and 30-second sit-to-stand performance.

Omega-3 supplementation has also been shown to have beneficial effects in sarcopenia that is not related purely to increased age. For example, omega-3 PUFA supplementation has been found to attenuate skeletal muscle disuse atrophy in young women who underwent 2 weeks of unilateral limb immobilization followed by 2 weeks return to normal activity.[84] Starting 4 weeks before immobilization, participants consumed either 5 g/day of omega-3 fatty acids or an isoenergetic quantity of sunflower oil (control). Muscle mass was reduced significantly in the control group, but not in those receiving omega-3 PUFAs.[84] Moreover, myofibrillar protein synthesis was higher in the omega-3 group compared with the control group at all times. Patients with esophageal cancer undergoing esophagectomy, were randomized to receive either standard enteral nutrition (EN) or a formula enriched with EPA for 5 days preoperatively (orally) and 21 days postoperatively (jejunostomy).[85] EPA supplemented early EN was associated with the preservation of lean body mass post esophagectomy compared with standard EN, with which patients lost significant amounts of fat-free mass.[85]

Disturbed protein metabolism and impaired muscle health have been observed in chronic obstructive pulmonary disease (COPD), and a randomized double-blind trial investigated whether daily omega-3 PUFA supplementation could improve protein homeostasis

in patients with moderate-to-severe COPD.[86] Patients were randomized to receive gel capsules containing either a high dose (3.5 g) of EPA + DHA, a low dose (2.0 g) of EPA + DHA, or a placebo (olive oil) for 4 weeks. Oral intake of omega-3 PUFAs improved post-absorptive protein metabolism and enhanced the anabolic response to feeding in patients with COPD, partly in a dose-dependent manner, indicating a more positive daily protein homeostasis. Daily doses up to 3.5 g EPA and DHA were well tolerated and resulted in protein gain in patients with COPD.[86] A recent meta-analysis of clinical trials also support the positive effects of supplementation with omega-3 PUFAs on muscle mass and strength in patients with sarcopenia and cancer, COPD, or in healthy individuals after a fatiguing exercise bout.[87]

The results discussed in this section show that intake of omega-3 PUFAs has the potential to enhance skeletal muscle anabolism, but the magnitude of this effect is dependent upon factors such as protein intake, amount of resistance exercise, patient age, co-morbidities and general health status (Table 1, consensus statement 9). Several molecular mechanisms may mediate improved skeletal muscle protein turnover and functionality with omega-3 PUFA intake (Figure 2).[2,88] The primary means by which omega-3 PUFAs improve skeletal muscle mass is via the incorporation of EPA and DHA into membrane phospholipids of the sarcolemma and intracellular organelles, and the increased omega-3 PUFA content in these structures may enhance anabolic signaling pathways (Table 1, consensus statement 8). However, the exact mechanisms whereby these pathways are modified remain unknown.[2]

1.5 | Lipid mediators in health and disease: New frontiers and research opportunities

Throughout this manuscript, we have illustrated mechanisms through which omega-3 PUFA SPM metabolites act to improve outcome in many pathologies, and plausible rationales that exist to further explore these mechanisms and ideally scrutinize their therapeutic potential and/or the role of SPMs as biomarkers. Regardless of the enormous progress made, there are many challenges to overcome. There is a long pathway from the current state of knowledge to an approved 'SPM therapeutic agent', an evidence-based 'precision nutrient', or a biomarker to reliably predict or monitor an intervention response. Such advances may enable truly personalized medicine and/or nutrition. Nevertheless, accumulating evidence indicates that lipid mediators derived from omega-3 PUFAs play a pivotal role in the endogenous regulation and resolution of inflammation,[1] and they affect skeletal muscle mass.[2,84] Importantly, immune modulation and tissue repair involving SPMs occur without compromising host defense (contrary to many anti-inflammatory medicines in common use).[4,9] The question arises whether some of this known physiology can already be used to improve current clinical practice. From a public health perspective, the consumption of fish or seafood as part of a balanced diet is broadly advised to promote 'heart health' with one or two servings of seafood a week reducing the risk of congestive heart failure, coronary heart disease, ischemic stroke, and sudden cardiac death, especially when the seafood replaces less healthy foods.[89] For other areas in the interest of public health such as cancer prevention, rheumatoid arthritis, AD, dementia, or cognitive function, evidence is scant and additional data are required before similar recommendations could be made.[89,90]

The formulation and dose of omega-3 PUFAs may also require further optimization, as mentioned in the section on cardiovascular diseases. There are signals that dosing may differ for EPA and DHA,[37] and may also depend on underlying health issues. For instance, numerous clinical studies have investigated the effect of omega-3 PUFAs at fairly high doses of approximately 4–5 g/day.[37,79,80,84] Considerably lower EPA and DHA doses have been used for pain. A dose of 250 mg/day (EPA + DHA) led to promising results in a small study in patients with chronic pain,[91] and isolated SPMs have shown analgesic effects at a dose 1000-times lower than morphine doses in experimental models,[19] bringing us into a microgram range. The development of reliable, sensitive and practical quantification methods is another prerequisite for advancing research on lipid mediators for various diseases. Such a method allowing the quantification of numerous proinflammatory and pro-resolving lipid mediators in plasma could now be available,[69] but few hospital laboratories are currently performing these analyses.

The Lipid in Parenteral Nutrition Summit formed the impetus for this review, and as such many of the aspects mentioned thus far are, in one way or another, relevant in situations where PN is indicated. For instance, uncontrolled inflammation is often a concern during acute situations such as during critical illness or after major surgery,[1,3,92] and there may also be a persistent inflammatory environment during long-term PN, particularly in older patients or in patients with multiple co-morbidities.[93,94] Neurocognitive disorders,[53] accelerated muscle mass loss,[2] or pain,[95] are unwarranted 'side effects' of surgery and/or critical illness, which may be favorably affected by pro-resolving lipid mediators. Lipids are an integral part of PN in all settings where PN is required. Hence, patients requiring PN may receive omega-3 PUFAs such as EPA and DHA when they are given lipid

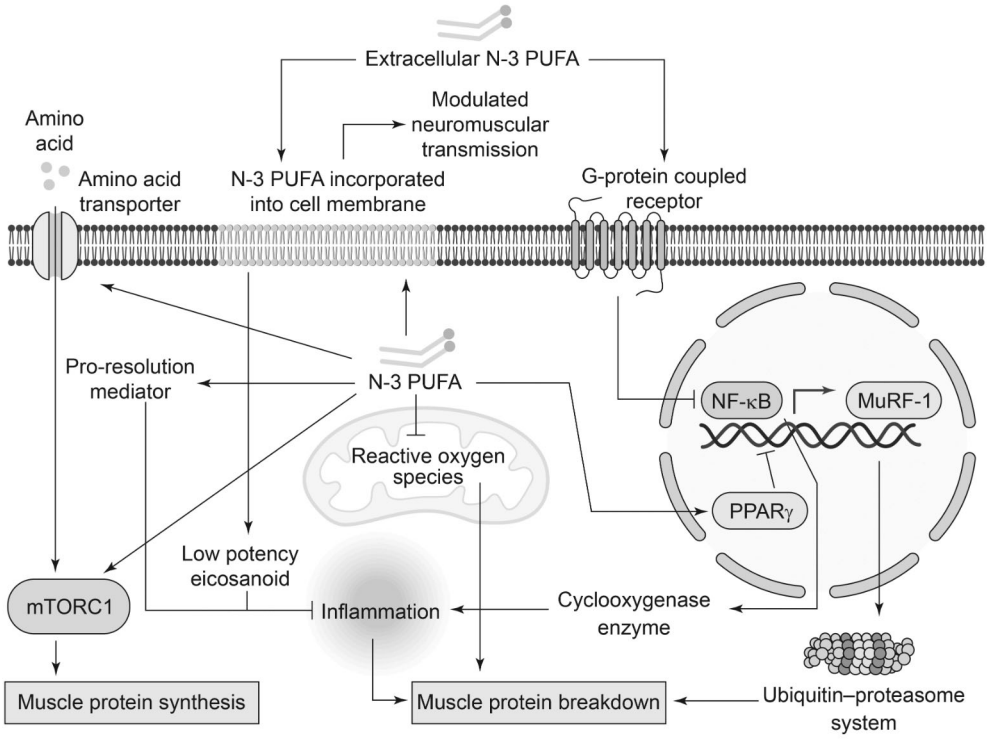

FIGURE 2 Schematic illustration of some proposed molecular mechanisms of action of omega-3 fatty acids in skeletal muscle. These are (1) reducing inflammation; (2) increasing muscle protein synthesis through the mTORC-1 pathway; (3) decreasing muscle protein breakdown via the ubiquitin–proteasome system (UPS) and autophagy lysosome system (ALS); (4) improving mitochondrial function; (5) increasing cellular amino acid transport; and (6) optimizing membrane fluidity. Adapted from Therdyothin A, Phiphopthatsanee N, Isanejad M. The effect of omega-3 fatty acids on sarcopenia: mechanism of action and potential efficacy. *Marine Drugs* 2023; 21 (7): 399.[88] MuRF1, muscle ring finger-1; mTORC-1, mechanistic target of rapamycin complex-1; NF-κB, nuclear factor kappa B; PPARγ, peroxisome proliferator-activated receptor gamma; PUFA, polyunsaturated fatty acid.

emulsions containing fish oil (as part of a mixed-oil lipid emulsion) as recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) for surgical or critically ill patients,[96–98] and the Canadian Critical Care Nutrition Organization for critically ill patients.[99] In these populations, the inclusion of fish oil into the PN regimen compared with PN formulations without fish oil has been associated with favorable effects on markers of inflammation, immune or liver function, reduced risk of infections and sepsis, and shorter duration of hospital and/or intensive care unit.[65,100–104] In other areas (i.e. during long-term PN)[105] more robust evidence may be needed before firm recommendations could be considered regarding the use of fish oil in PN.

Finally, we would also like to consider the source of omega-3 PUFAs. Fish oil is the main natural source of omega-3 PUFAs, EPA and DHA, but alternative omega-3 PUFA sources should be explored for the following reasons. Current marine supplies may not meet anticipated high market omega-3 PUFA demands if the therapeutic potential of SPMs is realized. Increased fishing may not be the answer. Overfishing reduces species' survivability and diversity and can disrupt ecosystems.[106] Moreover, the accumulation of persistent organic pollutants within the marine food chain can pose a risk to human health.[106,107] Therefore, it is important to consider the development of non-marine sources of omega-3 PUFAs before this becomes a limiting factor in access to novel therapies requiring this resource.[108]

2 | SUMMARY

The presentations, discussions, and consensus statements from the International Lipids in PN Summit 2022 have provided insight into the science of this complex field. Inflammatory processes play a key role in many diseases and conditions, and until comparatively recently inflammation resolution was considered a passive process. We now know that inflammation resolution is a biosynthetically active and highly coordinated process that can be 'turned on'. The very long-chain omega-3 PUFAs, EPA and DHA, are key participants in inflammation resolution as they are precursors for SPMs such as resolvins, protectins, and maresins. SPMs have distinct roles in resolving inflammation and the return to

homeostasis, acting without compromising host defense (contrary to many anti-inflammatory medicines in common use). Although much progress has been made, the biological effects of SPMs remain largely experimental, and much work remains until their full therapeutic potential is reached such as the concept of evidence-based personalized precision nutrition for a specific lipid.[4,5] Nevertheless, some clinical data are available that may be relevant to clinical practice. For instance, excessive acute or chronic inflammation is often a concern in situations where PN is required, and lipid emulsions are an integral part of PN. The fatty-acid composition of lipids used in PN may affect the promotion or resolution of inflammation. The precursors for mediators that promote resolution of inflammation, DHA and EPA, are usually derived from marine (i.e. fish) sources, and thus fish oil has become an important component of modern composite lipid emulsions used in PN. Compared with lipid emulsions without fish oil, the inclusion of fish oil into the PN regimen has been associated with favorable effects on markers of inflammation, immune or liver function, and reduced risk of infections and sepsis, and shorter duration of hospital and/or ICU stays in various populations requiring PN. EPA and DHA have also been associated with properties enabling the preservation of skeletal muscle mass. However, there is still inadequate clinical evidence, particularly for the direct use of SPMs as therapeutic agents, and there is a need to identify the best doses, timings, and suitable indications.

AUTHOR CONTRIBUTIONS

All authors participated in the summit and conceived the research. The manuscript was drafted by Dr Richard Clark. All authors read and revised the manuscript, and approved the final version.

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DISCLOSURES

C. N. Serhan is an inventor on patents covering the structures and use of the resolvins, protectins, maresins, and related mimetics, that are assigned to Brigham & Women's Hospital and are manged to prevent conflict of interest; some are licensed by BWH for clinical development programs.

M. Bäck has received speaker and consultant fees to his institution from Amarin, Amgen, Fresenius Kabi, Heel, and Novartis.

V. Chiurchiù has received speaker's honoraria from Fresenius Kabi.

M. Hersberger has a patent filed for a sustainable omega-3 PUFA-rich lipid emulsion and has received travel expenses from Fresenius Kabi for the International Lipids in Parenteral Nutrition Summit 2022.

B. Mittendorfer has received speaker's honoraria from Fresenius Kabi.

P. C. Calder has acted as an advisor to and received speaker's honoraria from Fresenius Kabi, B. Braun, and Baxter Healthcare.

D. L. Waitzberg has acted as an advisor to and received speaker's honoraria from Nestlé, Takeda, Pepsico and Sanofi.

C. Stoppe has received consultancy honoraria from Abiomed, Baxter, B. Braun, and DMS, and speaker honoraria from Baxter, B. Braun, and Fresenius Kabi.

S. Klek has received speaker's honoraria from Baxter, B. Braun, Fresenius Kabi, Nestle, Nutricia, Shire, and Vipharm and acted as an advisory board member for Fresenius Kabi, Shire, and Tracheron.

R. G. Martindale served as an educational consultant for Fresenius Kabi and Nestlé.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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