Nutrition 65 (2019) 39–43

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Editorial opinion

Polyunsaturated fatty acids and sepsis

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Sepsis is a systemic inflammatory response syndrome that occurs during severe infection, sometimes after major surgery and injury, and kills >200 000 individuals in the United States annually [1]. Prognosis of sepsis depends on the severity of organ dysfunction [1–3]. Some of the mechanisms that contribute to the pathogenesis of sepsis include bacterial toxins such as lipopolysaccharide (LPS), inflammatory mediators secreted by neutrophils, macrophages, and T cells; endothelial injury; disturbed homeostasis; and microcirculatory failure. Sepsis induces defects in innate immunity and excessive lymphocyte apoptosis [3]. Clinical trials employing agents that block the inflammatory cascade such as corticosteroids, antiendotoxin antibodies, tumor necrosis factor (TNF) antagonists, and interleukin (IL)-1 receptor antagonists have failed to be of benefit in sepsis, suggesting the original belief that sepsis is due to uncontrolled inflammation, which is invalid. Sepsis may present in the form of two distinct clinical syndromes—acute septic shock and severe sepsis. Acute septic shock syndrome occurs suddenly, with the patient dying within 24 to 48 h, and some of these patients may develop severe sepsis. On the other hand, severe sepsis is characterized by signs of systemic inflammation and organ dysfunction, including abnormalities in body temperature, heart rate, respiratory rate, and leukocyte count; elevated liver enzymes; and altered cerebral function. Severe sepsis runs a protracted course over several weeks and patients succumb to the disease slowly or may eventually recover. It is possible that sepsis is due to an initial exacerbated inflammatory response as a result of robust activation of the innate immune arm (proinflammatory), whereas the adaptive immune response is obliterated (immune suppression). The initial hyperinflammatory response may lead to progressive development of subsequent immunosuppression [4]. These results suggest that inappropriate initial hyperinflammatory response followed by subsequent immunosuppression results in failure of resolution of tissue injury, restoration of normal homeostasis that leads to significant morbidity or mortality.

In general, acute organ dysfunction most commonly affects the respiratory and cardiovascular systems. Respiratory manifestations include acute respiratory distress syndrome (ARDS), whereas cardiovascular compromise is seen as hypotension or an elevated serum lactate level. It is noteworthy that even after adequate volume expansion, hypotension generally persists that may demand the use of vasopressors, and myocardial dysfunction persists [2,5].

In sepsis, the brain and kidneys often are affected. Central nervous system (CNS) dysfunction is typically seen as obtundation or delirium with imaging studies (magnetic resonance imaging and computed tomography scans) showing no focal lesions, whereas electroencephalography may reveal findings that are consistent with non-focal encephalopathy. Polyneuropathy and myopathy are also common in sepsis, especially in those who had a prolonged stay in the intensive care unit [2]. In the light of these central nervous system dysfunction manifestations described in sepsis, the findings reported by Petronilho et al. [6] that fish oil-enriched lipid emulsion diminishes the brain dysfunction after polymicrobial sepsis in the rat by reducing inflammatory and oxidative stress is not only interesting but also suggests its potential clinical effect or application. In their study, Petronilho et al. used the caecal ligation and perforation rat model that causes polymicrobial sepsis. The prevention of cognitive impairment in this model was accompanied by increases in hippocampus and prefrontal cortex brain-derived neurotrophic factor (BDNF) in addition changes in antioxidants, cytokines, lipid peroxides, and nitrite/nitrate concentrations. Despite these important and interesting findings, the authors of this study did not measure the levels of eicosapentaenoic acid or docosahexaenoic acid (EPA/DHA) and their metabolites in the plasma, brain, and other organs to know how much of the supplemented fish oil components were actually incorporated in these tissues and organs. It is important to know whether it is the EPA or the DHA or their specific metabolites that are responsible for the beneficial actions reported.

Fish oil is a mixture of various fatty acids; however, in general, its beneficial actions are attributed to its EPA/DHA content. This is a misnomer because, depending on the source and quality of the fish oil used, its content of EPA/DHA is highly variable. Ordinary fish oil present in the brand MaxEPA capsules contains ~18% EPA and ~13% DHA and variable amounts of oleic acid (OA, 18:1 ω-9), linoleic acid (LA, 18:2 ω-6), α-linolenic acid (ALA, 18:3 ω-3), and small amounts of arachidonic acid (AA, 20:4 ω-6). In contrast, concentrated fish oil contains ~17% OA, ~2.8% LA, ~5% ALA, ~5% AA, ~31% EPA, and ~21% DHA. In addition, fish oil also may contain several other saturated fatty acids to the extent of 30% to 40% of its total content of fatty acids [7,8]. Thus, depending on the source of fish oil, its fatty acid content may show a wide variation. Despite

Re. "Fish oil-rich lipid emulsion modulates neuroinflammation and prevents long-term cognitive dysfunction after sepsis"

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https://doi.org/10.1016/j.nut.2019.02.016

this variation in fatty acid content, almost no studies have discussed what could be the influence the monounsaturated fatty acids and saturated fatty acids (SFAs) present in the fish oils used. This is rather surprising because SFAs and monounsaturated fatty acids form a major percentage of fish oil fatty acid content. One way this issue could be addressed is by measuring the fatty acid content of various tissues and plasma before and after fish oil supplementation and correlating the changes in the fatty acid contents to the observed phenomena. Despite such an effort, there might still be no clearcut answer as to the influence of various fatty acids present in the fish oil on the phenomena under study as different fatty acids may have different and sometimes diametrically opposite actions. Hence, studies using pure individual fatty acids present in fish oil and delineating which fatty acid is responsible for the changes in the physiologic or pathologic process are needed. In fact, many in vitro studies using cell cultures are generally performed using pure individual fatty acids, whereas animal studies are conducted by supplementing fish and vegetable oils that are a mixture of various fatty acids. Thus, there seems to be a sort of dichotomy in the way experiments are designed while performing in vitro and in vivo studies. This naturally results in misinterpretation and difficulties in extrapolating in vitro results to an in vivo situation and in the application of animal studies to the clinic. This may explain why the results obtained from in vitro and animal studies could not be replicated in humans. Two examples may be cited to explain this paradoxical situation.

Fatty acid composition of fish and vegetable oils and their effect on experimental results

It is well known that elevated plasma triacylglycerol (TG) levels are a risk factor for ischemic events (e.g., cardiovascular disease [CVD], stroke, peripheral vascular disease). Hence, efforts are being made to reduce elevated plasma TG levels. A recent multicenter, randomized, double-blind placebo-controlled trial involved patients with established CVD or with diabetes mellitus and other risk factors who are already on statins and had a fasting plasma TG level of 135 to 499 mg/dL and a low-density lipoprotein cholesterol level of 40 to 100 mg/dL when administered 2 g of icosapent ethyl (contains highly purified and stable EPA ethyl ester) twice a day, the patients showed a significant reduction in cardiovascular deaths compared with those in the placebo arm [9,10]. In contrast to this, another randomized placebo-controlled trial in which men $\geq$50 y of age and women $\geq$55 y were administered vitamin D_3 (at a dose of 2000 IU/d) and marine ω-3 fatty acids at a dose of 1 g/d showed no reduction in incidence of major cardiovascular events or cancer compared with the placebo group, suggesting essentially a negative result [11,12]. These results, however, contrast each other [9,11]; in one trial EPA was found to be beneficial [9] and in the other EPA/DHA supplementation in the form of fish oil capsules (1 g/d as a fish oil capsule containing 460 mg of ω-3 fatty acids including 460 mg of EPA and 380 mg of DHA) was found to not be beneficial [11]. However, one needs to take into consideration the dose and composition of ω-3 fatty acids administered. It is pertinent to note that in the trial that gave positive results [9], pure EPA was administered, whereas in the study with negative results fish oil was administered as a fish oil supplement that contained not only EPA and DHA but also other components of fish oil such as SFAs and OA, LA, and ALA. Although the exact fatty acid composition of fish oil supplementation was not mentioned, it is apparent that it was not a pure preparation of just EPA and DHA but contained several other fatty acids (including SFAs to the extent of $\geq$160 mg). Based on these apparently paradoxical results, I suggest that the differences in the results could be due to simultaneous administration of SFAs along with EPA and DHA in the form of fish oil. It is likely that the SFAs present in the fish oil supplement probably interfered with the beneficial action on EPA/DHA that are otherwise known to possess antiinflammatory, antioxidative, plaque-stabilizing, and membrane-stabilizing properties [13–16].

Our studies revealed that oral supplementation of oils rich in EPA/DHA and γ-lineolic acid/AA can prevent the development of alloxan to induced type 1 diabetes mellitus (T1DM) in experimental animals [7]. Because these oils contain a variety of fatty acids, we next evaluated the effect of individual pure fatty acids (including unsaturated, poyunsaturated and saturated fatty acids) on alloxan-induced T1DM and noted that of all the fatty acids tested, surprisingly AA was the best [17–19]. These results clearly established that although several oils rich in a variety of fatty acids are capable of preventing alloxan-induced T1DM in experimental animals (evening primrose oil, fish oil, and AA single-cell oil ARASCO, a rich source of AA, all prevented T1DM), when the same study was repeated using individual fatty acids, only AA and to a limited extent EPA and DHA showed potent antiinflammatory and antidiabetic actions [17–19]. This emphasizes the fact that the fatty acid composition of the oils employed can influence the final outcome of the studies. In this context, it is noteworthy that palmitic acid, an SFA that is present in significant amounts in various oils, especially fish oil, can cause impairment of insulin action and β-cell dysfunction and apoptosis [20–23], whereas EPA, DHA, and AA (AA > EPA $\geq$ DHA) may actually protect β cells from endogenous and exogenous toxins such as alloxan, streptozotocin (STZ), doxorubicin and benzo(a)pyrene (BP) [17–19]. We observed that alloxan, STZ, doxorubicin, and BP inhibit the activities of desaturases so that formation of AA and EPA and DHA from their respective dietary LA and ALA would not occur in adequate amounts. As a result, alloxan- and STZ-treated animals showed lower plasma, hepatic, and renal content of AA, EPA, and DHA; whereas that of PA was increased [7,17–19; and UN Das, MD, DSc, 2019, unpublished data]. This deficiency of AA, EPA, and DHA is expected to lead to decreased formation of their antiinflammatory lipoxin (LX)A4, resolvins, protectins, and maresins that have antidiabetic actions [17–19; and UN Das, MD, DSc, 2019, unpublished data]. Putting these results together, it is proposed that oils that are a mixture of various fatty acids that have significant PA content (and possibly other SFAs as well), may negate the beneficial actions of EPA/DHA/AA. Thus, it is likely that in the study that reported no beneficial action(s) of fish oil supplementation in the prevention of CVDs and cancer, [11,12] the negative results could be attributed to the imbalance between PA and other SFAs versus EPA/DHA/AA. Such an assumption may explain the beneficial results seen with pure EPA ethyl ester [9].

Metabolites of PUFAs and their role in various diseases

An additional factor that needs active consideration is the metabolites formed from AA, EPA, and DHA and their potential roles in the pathobiology of various diseases. For instance, the beneficial action of AA in the prevention of alloxan- and streptozotocin-induced T1 and T2DM, respectively, could be due to formation of its antiinflammatory metabolite LXA4 [24–26]. This lends support to the concept that the beneficial actions of AA, EPA, and DHA could be due to the formation of their antiinflammatory metabolites such as LXA4 from AA; resolvins from EPA; and resolvins, protectins and maresins from DHA [27,28]. This implies that failure to derive the expected beneficial actions of AA, EPA, and DHA in a given study could be due to the presence of unwanted and potentially harmful SFAs such as PA in the oil and lack of or decreased formation of antiinflammatory LXA4, resolvins, protectins, and maresins owing to the absence or deficiency of cofactors needed

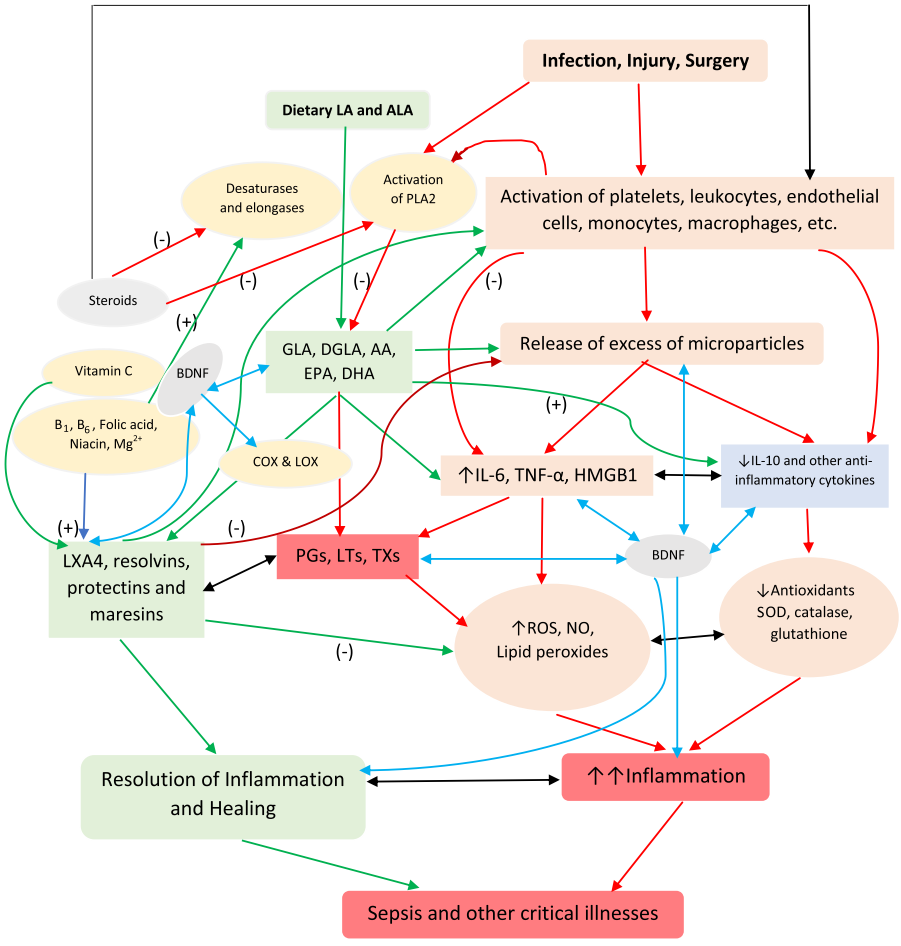

Fig. 1. Role of pro- and antiinflammatory cytokines, bioactive lipids, ROS, lipid peroxides, BDNF, and metabolism of dietary EFAs and factors or cofactors that modify their metabolism and their role in sepsis and other critical illnesses. The possible roles of vitamin C, steroids vitamins B_1, B_6, folic acid, and BDNF in the metabolism of EFAs are also shown. Interaction(s) among PUFAs and their metabolites, cytokines, microparticles, and inflammation and their role in sepsis are also depicted.

It is likely that BDNF may serve as a cofactor for normal activity of desaturases. BDNF may also enhance the formation of LXA4/resolvins and protectins/maresins that are antiinflammatory metabolites of AA/EPA/DHA. BDNF may have both pro- and antiinflammatory actions depending on the context and its local concentrations. It is not known, but it is possible that BDNF may act on COX and LOX enzymes to regulate the formation of LXA4/resolvins/protectins/maresins from AA/EPA/DHA.

Corticosteroids influence metabolism of PUFAs. Corticosteroids are known to block the activity of desaturases and thus decrease formation of GLA, DGLA, AA, EPA, and DHA from LA and ALA; inhibit PLA2 activity and thus decrease the availability of DGLA. AA, EPA, and DHA for the formation of various eicosanoids; and suppress COX-2 activity and thus inhibit generation of proinflammatory PGs, LTs, and TXs. This may explain the controversial results obtained with corticosteroids in inflammation and sepsis. In the initial stages, when steroids are given, they suppress inflammation by decreasing the formation of proinflammatory PGs, LTs, and TXs by their action on COX-2 and by inhibiting the activity of PLA2 that results in decreases release of DGLA, AA, EPA, and DHA from the cell membrane lipid pool. Hence, continued use of corticosteroids results in deficiency of PUFAs (DGLA, AA, EPA, and DHA) owing to inhibition of desaturases that are needed for the conversion of dietary LA and ALA to AA/EPA/DHA and this, in turn, lead to decrease in the formation of LXA4, resolvins, protectins, and maresins, which are needed for resolution of inflammation and restoration of tissue homeostasis. Hence, continued use of steroids results in failure of resolution of inflammation and so inflammation and sepsis persists. In such a scenario, coadministration of PUFAs and vitamin C (as a cofactor needed for EFA metabolism and enhancer of PGE1, LXA4, resolvins, protectins, and maresins formation) along with corticosteroids will be of benefit in sepsis. It is likely that vitamins C, B_1, B_6, folic acid, niacin, Mg^{2+}, and BDNF may serve as cofactors of desaturases and enhance the formation of AA/EPA/DHA from LA and ALA and augment the formation of antiinflammatory LXA4, resolvins, protectins, and maresins. AA, arachidonic acid; ALA, α-linolenic acid; BDNF, brain-derived neurotrophic factor; COX, cyclooxygenase; DGLA, dihomo-γ-linolenic acid; DHA, docosahexaenoic acid; EFA, essential fatty acid; EPA, eicosapentaenoic acid; GLA, γ-linolenic acid; HMGB1, high-mobility group protein B1; IL, interleukin; LA, linoleic acid; LOX, lipoxygenase; LT, leukotriene; LXA4, lipoxin A4; Mg, magnesium; NO, nitric oxide; PG, prostaglandin; PLA2, phospholipase 2; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF, tumor necrosis factor; TX, thromboxane. (+) indicates increase in the synthesis, action and/or positive influence. (−) indicates decrease in the synthesis, action and/or negative influence.

for their formation or decreased activity of cyclooxygenase-2, 5-, 12-, and 15-lipoxygenase enzymes [24–26].

In this context, it is noteworthy that in vitro studies performed with rat insulinoma cells showed that alloxan-induced cytotoxicity can be prevented by various prostaglandins (PGs) and leukotrienes (LTs), whereas in vivo studies failed to prevent alloxan-induced T1DM [27,28]. These results once again emphasize the dichotomy between in vitro and in vivo results. This may in part be due to the complex interactions among various eicosanoids and differences in their actions. For instance, PGE1 and PGI2 are antiinflammatory in nature (although at times they may have proinflammatory actions depending on the context and local concentrations of the eicosanoid), whereas PGE2, PGF2α, LTs, and thromboxanes (TXs) have proinflammatory actions. But, paradoxically, it was observed that LTs and PGE2 may, in fact, protect against radiation-induced tissue damage [29]. This may, in part, be attributed to the effect of PGE2 to trigger the generation of LXA4, an antiinflammatory product from AA (PGE2, LTD4/LTE4, and LXA4 are derived from AA). This implies that when the inflammatory process attains its peak (owing to the presence of adequate amounts of PGE2 and LTs), it triggers and initiates the inflammation resolution process by directing the generation of LXA4 from AA, which hitherto has been

directed to form PGE2 and LTs [29,30]. Thus, the final action of the administered PGs/LTs/TXs from external sources depends on the sum of the differential actions of various eicosanoids at the site of administration/action [31,32].

Cytokines modulate PUFA metabolism

Yet another factor that needs to be considered in the pathobiology of inflammation and sepsis is the role of proinflammatory IL-6, TNF-α, and high-mobility group protein B1 (HMGB1), which suppress the activity of desaturases resulting in decreased formation of AA, EPA, and DHA and thus a reduction in the synthesis of LXA4, resolvins, protectins, and maresins. But paradoxically enhanced formation of PGs, LTs, and TXs ensues [32]. Supplementation of AA during the inflammatory process and when plasma PGs, LTs, and TXs were higher was found to increase the formation of LXA4 (and possibly, resolvins, protectins, and maresins) and thus suppress the inflammatory process. Previously, we showed that in sepsis and other inflammatory conditions, plasma concentrations of AA, EPA, and DHA are low. Hence, it is expected that infusion of AA/EPA/DHA may result in an increase in the production of LXA4, resolvins, protectins, and maresins and resolve inflammation. Furthermore, AA/EPA/DHA suppress IL-1, IL-6, TNF-α, and HMGB1 and reactive oxygen species (ROS) production [32]. Vitamin C, thiamine, folic acid, and vitamin B_6 are regarded as cofactors for normal activity of desaturases, and so their administration could enhance the formation of AA/EPA/DHA and consequently generation of LXA4, resolvins, protectins, and maresins, resulting in resolution of inflammation and recovery from sepsis (Fig. 1).

PUFAs in sepsis

Thus, based on the preceding discussion, it is interesting that Petronilho et al. [6] observed that fish oil supplementation diminishes the brain dysfunction after polymicrobial sepsis by reducing inflammatory and oxidative stress. It would have been more interesting had the authors measured the plasma and tissue levels of EPA/DHA, antiinflammatory metabolites resolvins, protectins, and maresins and correlated the same to the degree of neurologic benefit. It is noteworthy that the authors observed an increase in BDNF levels in hippocampus and prefrontal cortex and prevented cognitive impairment. We found that AA/EPA/DHA/LXA4 can enhance the formation and secretion of BDNF both by rat pancreatic β cells in vitro and in vivo and hypothalamus of experimental animals, implying a close interaction between PUFAs and BDNF [33]. This may explain the increase in brain BDNF levels observed by Petronilho et al. in their sepsis model. It would have been interesting had the authors measured plasma and tissue concentrations of various PUFAs and LXA4, resolvins, and protectins, which would have explained the beneficial action noted with the supplementation of fish oil.

It is noteworthy that several other studies did not show the benefits of EPA/DHA supplementation in patients with sepsis, although some did show some benefit [3,34–46]. Recent studies suggested that because vitamin C deficiency occurs, high-dose vitamin C may be of benefit in sepsis [32,47–49], which could be due to its antioxidant potential, effects on the immune system, reduction of inflammatory mediators, and probable bacteriostatic effect [32]. Yet another action of vitamin C could be its suppressive action on the production of microparticles similar to PUFAs and corticosteroids and is a cofactor for the normal activity of desaturases [33]. Hence, a combination of corticosteroids, vitamin C, and PUFAs can suppress the generation of microparticles, inhibit IL-1, IL-6, TNF-α, HMGB1, and ROS generation and enhance the synthesis and release of antiinflammatory cytokines, LXA4, resolvins, protectins, and maresins and restore antioxidant defenses, resulting in resolution of inflammation and suppression of sepsis [32,45–49] (Fig. 1). Hence, it is proposed that measurement of various cytokines, PUFAs, eicosanoids, and antioxidants, in addition to microparticles in sepsis, may aid in assessing the development, progression, and prognosis of sepsis.

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