

Review Article

Controversies in clinical nutrition: omega-3 fatty acids in parenteral nutrition

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ABSTRACT: *Theoretical considerations suggest that an excessive or imbalanced supply of n-6 fatty acids may play a role in creating an inflammatory and immunosuppressed state, so approaches to decreasing the amount of linoleic acid used in parenteral lipid emulsions are being sought. One approach is to partly replace soybean oil with fish oil. Long-chain n-3 fatty acids from fish oil decrease the production of inflammatory eicosanoids and cytokines. They act both directly, by replacing arachidonic acid as an eicosanoid substrate and by inhibiting arachidonic acid metabolism, and indirectly by altering the expression of inflammatory genes through effects on transcription factor activation. An emerging application of n-3 fatty acids is in postsurgical or critically ill patients where they may be added to parenteral formulas. Parenteral nutrition including n-3 fatty acids appears to preserve immune function better than standard formulas and appears to partly prevent some aspects of the inflammatory response. Studies to date are suggestive of clinical benefits from this approach, especially in postsurgical patients, but evidence of clinical benefit in patients with sepsis is very limited. (Nutritional Therapy & Metabolism 2008; 26: 15-22)*

KEY WORDS: *Cytokine, Eicosanoid, Fatty acid, Fish oil, Immune function, Inflammation, Parenteral nutrition, Sepsis, Surgery*

OMEGA-3 (N-3) FATTY ACIDS

All fatty acids are hydrocarbon chains with a carboxyl group at one end and a methyl group at the other. The carboxyl group is reactive and readily forms ester links with alcohol groups: for example, those on glycerol or cholesterol, in turn forming acylglycerols (e.g., triacylglycerols and phospholipids), and cholesterol esters. The most abundant fatty acids have straight chains of an even number of carbon atoms. Fatty acid chain lengths vary from 2 to 30 or more, and the chain may contain double bonds. Fatty acids containing double bonds in the acyl chain are referred to as unsaturated fatty acids; a fatty acid containing 2 or more double bonds is called a polyunsaturated fatty acid (PUFA). Saturated fatty acids do not contain double bonds in the acyl chain. Although fatty acids have systematic names, a shorthand notation for fatty acids has come into frequent use (Tab. I). This relies on identifying the number of carbon atoms in the chain and the number of double bonds and their position. Unsaturated fatty acids are named simply by identifying the number of double bonds and the position of the first double bond counted from the methyl terminus (with the methyl, or ω , carbon

as number 1) of the acyl chain. The way the first double bond is identified is as ω -x (or n-x), where x is the carbon number on which the double bond occurs. Thus, linoleic acid, the simplest member of the omega-6 (or n-6) PUFA family is denoted as 18:2n-6, indicating a total of 18 carbons in the acyl chain and the presence of 2 double bonds with the first of these on carbon number 6 counting from the methyl end. Likewise, α -linolenic acid the simplest member of the n-3 PUFA family is denoted as 18:3n-3. Linoleic and α -linolenic acids cannot be synthesized by mammals, but are found in significant, but varying, quantities in many vegetable oils, including corn, sunflower, and soybean oils, and in products made from such oils, such as margarines (1). Between them, linoleic and α -linolenic acids contribute over 95%, and perhaps as much as 98% of dietary PUFA intake in most Western diets (1), with intake of the former exceeding that of the latter by 5- to 20-fold (1, 2).

Although linoleic and α -linolenic acids cannot be synthesized by humans they can be metabolized to other fatty acids. This is achieved by the insertion of additional double bonds into the acyl chain (i.e., unsaturation) and by elongation of the acyl chain. Thus, linoleic acid can be converted via γ -linolenic acid (18:3n-6) and di-

TABLE I - FATTY ACID NOMENCLATURE

Systematic name	Trivial name	Shorthand notation
Octanoic	Caprylic	8:0
Decanoic	Capric	10:0
Dodecanoic	Lauric	12:0
Tetradecanoic	Myrsitic	14:0
Hexadecanoic	Palmitic	16:0
Octadecanoic	Stearic	18:0
<i>cis</i> -9-Hexadecenoic	Palmitoleic	16:1n-7
<i>cis</i> -9-Octadecenoic	Oleic	18:1n-9
<i>cis</i> -9, <i>cis</i> -12-Octadecadienoic	Linoleic	18:2n-6
All <i>cis</i> -9,12,15-Octadecatrienoic	α -Linolenic	18:3n-3
All <i>cis</i> -6,9,12-Octadecatrienoic	γ -Linolenic	18:3n-6
All <i>cis</i> -8,11,14-Eicosatrienoic	Dihomo- γ -linolenic	20:3n-6
All <i>cis</i> -5,8,11,14-Eicosatetraenoic	Arachidonic	20:4n-6
All <i>cis</i> -5,8,11,14,17-Eicosapentaenoic	Eicosapentaenoic	20:5n-3
All <i>cis</i> -7,10,13,16,19-Docosapentaenoic	Docosapentaenoic	22:5n-3
All <i>cis</i> -4,7,10,13,16,19-Docosahexaenoic	Docosahexaenoic	22:6n-3

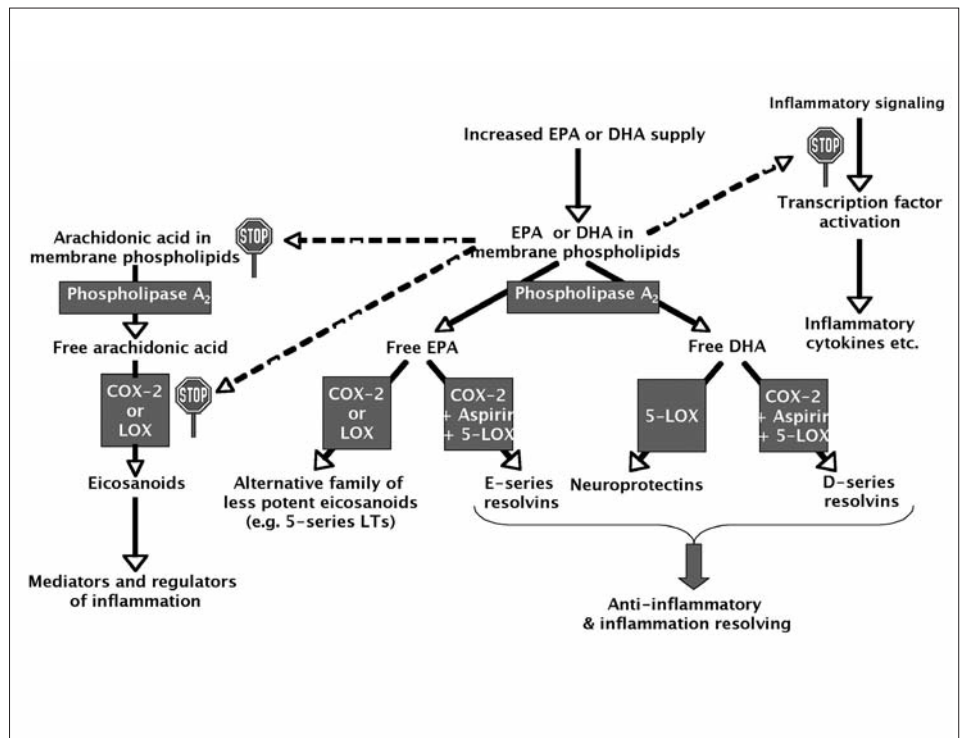
homo- γ -linolenic acid (20:3n-6) to arachidonic acid (20:4n-6). By an analogous set of reactions catalyzed by the same enzymes, α -linolenic acid can be converted to eicosapentaenoic acid (20:5n-3; EPA). Both arachidonic acid and EPA can be further metabolized, EPA giving rise to docosapentaenoic acid (22:5n-3) and docosahexaenoic acid (22:6n-3; DHA). Dietary intakes of the longer chain, more unsaturated PUFAs are much, much lower than of linoleic and α -linolenic acids (1). EPA, docosapentaenoic acid, and DHA are found in fish, especially so-called oily fish (tuna, salmon, mackerel, herring, and sardine) (3). The commercial products known as fish oils also contain these long-chain n-3 PUFAs, which typically will contribute about 30% of the fatty acids present (3).

THE RATIONALE FOR USING N-3 PUFAS (AS FISH OIL) IN PARENTERAL NUTRITION

Lipids were introduced into parenteral nutrition formulas in the 1960s to provide a more balanced supply of calories, along with glucose. The lipid typically used in parenteral nutrition is soybean oil or a combination of soybean oil and medium-chain triglycerides. In the former, linoleic acid will comprise about 50% of fatty acids present, while in the latter it will be about 25%. Such emulsions do not contain the long-chain n-3 PUFAs typical of fish oil but they do contain some α -linolenic acid (about 14% of the amount of linoleic acid). It is considered that this may represent a situation of excessive supply of n-6 PUFAs, especially relative to

the fish oil-type n-3 PUFAs. The perceived problem of an excessive or imbalanced supply of n-6 PUFAs is that the elongation product of linoleic acid, arachidonic acid, is a precursor to bioactive eicosanoid mediators such as prostaglandin E₂ (PGE₂), which has many proinflammatory properties (4) and is also immunosuppressive (5), and leukotriene B₄ (LTB₄) which is proinflammatory (6). Thus, it is considered possible that an excessive supply of n-6 PUFAs could act to promote or at least exacerbate states of inflammation and of immunosuppression. Indeed, a meta-analysis of lipids might be detrimental with respect to complications, especially in very ill patients ($p = 0.09$, for lipids vs. no lipids) (7); most of the studies included in the meta-analysis used soybean oil-based lipid emulsions. Furthermore, a recent study in patients following major gastrointestinal surgery identified that the amount of n-6 PUFAs infused was 1 of 2 predictors of the length of hospital stay (increased by 1.6 days/100 g of n-6 PUFA infused), the other being the delay in the onset of initiating nutritional support (8). A number of in vitro experiments have shown that soybean oil-based lipid emulsions can exert immunosuppressive effects (see (9) for references), which would clearly be detrimental in patients at risk of infection and sepsis. Clinical trials with soybean oil-based lipid emulsions provide conflicting evidence, some showing selective immunosuppressive effects (10-12), perhaps linked to poorer patient outcomes (11). However, others studies do not show such effects on the immune system (13-15) or on clinical outcomes (16). Nevertheless, there is a view developing that the use of lipid

Fig. 1 - Mechanisms by which long-chain *n*-3 PUFAs exert antiinflammatory effects. Increased dietary supply of eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) results in their incorporation into inflammatory cell membranes partly at the expense of arachidonic acid. EPA and DHA also inhibit arachidonic acid metabolism by cyclooxygenase (COX) and lipoxygenase (LOX) enzymes. Thus EPA and DHA decrease the production of arachidonic acid-derived eicosanoids. EPA metabolism by COX-2 and 5-LOX enzymes gives rise to eicosanoids that are typically less potent than those formed from arachidonic acid. DHA metabolism by 5-LOX gives rise to antiinflammatory neuroprotectins. Metabolism of EPA or DHA by COX-2 and 5-LOX in the presence of aspirin gives rise to antiinflammatory resolvins. EPA and DHA also inhibit the signaling pathway leading to activation of nuclear factor kappa B (NFκB), a transcription factor that induces expression of a number of inflammatory genes including those encoding inflammatory cytokines, adhesion molecules, and COX-2.



emulsions based solely upon soybean oil in parenteral nutrition may not be optimal and that emulsions should have a lower ratio of n-6 to n-3 PUFAs than is found in soybean oil or soybean oil–medium-chain triglyceride emulsions (17-20). One approach to decreasing the amount of linoleic acid present in emulsions and to decreasing the n-6 to n-3 PUFA ratio has been to partly replace soybean oil with fish oil.

The use of fish oil in parenteral nutrition is theoretically an especially attractive option, because, as well as decreasing the supply of linoleic acid, the long-chain n-3 PUFAs in fish oil are themselves antiinflammatory (see (21-26) for reviews). The antiinflammatory actions of fish oil n-3 PUFAs (Fig. 1) include the following:

- decreased production of arachidonic acid-derived mediators such as PGE₂ and LTB₄ as a result of a reduction in arachidonic acid content of cell membranes and of inhibition of arachidonic acid metabolism (see (26) for references);
- increased production of eicosanoid mediators from EPA (e.g., LTB₅) – these mediators frequently having weak biological potency compared with the analogues produced from arachidonic acid (see (26) for references);
- increased production of resolvins and related compounds from EPA and DHA – these mediators being

potently antiinflammatory and inflammation resolving (27-29);

- decreased production of inflammatory cytokines, probably due to decreased activation of proinflammatory transcription factors such as nuclear factor kappa B and increased activation of antiinflammatory transcription factors such as peroxisome proliferator activated receptor gamma (see (24) for references).

The benefits of fish oil in animal models of experimental endotoxaemia have been clearly demonstrated. For example, fish oil (dietary or infused) enhanced survival of guinea pigs when exposed to intraperitoneal endotoxin, compared with safflower oil (30, 31), decreased endotoxin-induced metabolic perturbations in guinea pigs (32, 33), and improved heart and lung function, and decreased lung edema in endotoxic rats (34-36) and pigs (37-40). Infusion of fish oil into rats also receiving low-dose endotoxin decreased the number of viable bacteria in mesenteric lymph nodes and liver (41). Fish oil did not decrease bacterial translocation across the gut, and so the authors concluded that fish oil must have improved bacterial killing. Compared with linoleic acid-rich vegetable oils, fish oil fed to rats prior to exposure to live bacteria (either as a result of caecal ligation and puncture or intravenous administration of live Group B *Streptococcus*, respectively) resulted in

increased survival (42, 43). Infusion of fish oil after induction of sepsis by caecal ligation and puncture decreased mortality compared with vegetable oil (44). Intra-gastric administration of fish oil into chow-fed rats prior to caecal ligation and puncture improved survival compared with saline or vegetable oil infusion (45).

Thus, the picture that emerges from a range of experimental studies is that administration of long-chain n-3 PUFAs in the form of fish oil decreases inflammatory responses and increases survival upon exposure to endotoxin or to live pathogens.

USE OF FISH OIL IN PARENTERAL NUTRITION

Lipid emulsions that include fish oil have been used in clinical trials, and some have subsequently become commercially available at least in some countries. Omegaven, produced by Fresenius Kabi (Bad Homburg, Germany), is a lipid emulsion (lipid 100 g/L) using fish oil as the lipid source. Each 100 mL of Omegaven contains 2.7 to 5.9 g EPA plus DHA (information supplied by the manufacturers). It is recommended that Omegaven is used in combination with other emulsions (e.g., those based on soybean oil or mixtures of medium-chain triglycerides and soybean oil) so that Omegaven contributes 10% to 20% of infused emulsion. SMOFLipid is also produced by Fresenius Kabi. It is a lipid emulsion (lipid 200 g/L), with the lipid being a mix of 30% medium-chain triglycerides, 30% soybean oil, 25% olive oil, and 15% fish oil. Lipoplus, produced by B. Braun (Melsungen, Germany) is a lipid emulsion (lipid 200 g/L), with the lipid being a mix of 50% medium-chain triglycerides, 40% soybean oil, and 10% fish oil. Each 100 mL of Lipoplus contains 0.9 to 1.7 g EPA plus DHA (information supplied by the manufacturers). Lipoplus is known as Lipidem in some countries.

Studies in surgical patients

Intravenous infusion of a lipid emulsion containing fish oil into patients for 5 days following gastrointestinal surgery resulted in an altered fatty acid composition of leukocytes: EPA content was increased 2.5-fold (46). This would be expected to impact on the profile of eicosanoids produced from arachidonic acid and EPA. Indeed, several studies have demonstrated that intravenous infusion of lipid emulsions containing fish oil into patients who had undergone major gastrointestinal surgery results in lower production of arachidonic acid-derived LT (e.g., LTB₄, and LTC₄) and thromboxanes (e.g., thromboxane A₂), and higher production of

EPA-derived LT (e.g., LTB₅, LTB₅-isomers, and LTC₅) by blood leukocytes stimulated *ex vivo* (46-48). Plasma tumour necrosis factor alpha (TNF- α) concentrations were lower at day 6 postsurgery, while plasma interleukin 6 (IL-6) concentrations were lower at day 10 postsurgery in patients who had undergone major gastrointestinal surgery and then received a mix of medium-chain triglycerides, soybean oil, and fish oil (50:30:20 vol/vol/vol; this was a prototype version of Lipoplus) for 5 days postsurgery, compared with those who received a medium-chain triglycerides and soybean oil mix (50:50 vol/vol) (47). The study did not report clinical outcomes. A more recent study infused Omegaven, providing 10 g lipid (fish oil) per day, on the day before abdominal surgery and on days 1 to 5 following abdominal surgery (49). On days 4 and 5 the patients also received standard total parenteral nutrition, which included 50 g fat per day as soybean oil. TNF- α production by endotoxin-stimulated whole blood tended to be lower at postoperative day 5 in the fish oil group, but this was not significant. Serum IL-6 concentrations were significantly lower at days 0, 1, and 3 in the fish oil group than in controls. Monocyte expression of human leukocyte antigen-DR was preserved in the fish oil group, but declined at postsurgery days 3 and 5 in the control group. No differences in infection rates or mortality were observed. However, postoperative stay in intensive care tended to be shorter in the fish oil group (4.1 vs. 9.1 days in the control group) as did total hospital stay (17.8 vs. 23.5 days). Postoperative stay on medical wards was significantly shorter in the fish oil group ($p < 0.05$). Another study compared the effects of lipid-free total parenteral nutrition or parenteral nutrition including soybean oil or a mix of 83% soybean oil and 17% fish oil (Omegaven) (vol/vol) for 5 days after large bowel surgery (50). There were no differences between the groups with respect to the numbers of circulating lymphocytes, B lymphocytes, helper T lymphocytes, cytotoxic T lymphocytes, or natural killer cells before surgery or at days 3 and 6 postsurgery, although these were affected by surgery itself. There were no differences between groups with respect to T lymphocyte proliferation, but IL-2 production was increased in the fish oil group, and the postsurgery decline in interferon-gamma production was prevented by fish oil. Taken together, these studies indicate that inclusion of fish oil in parenteral nutrition regimens for gastrointestinal surgical patients modulates generation of inflammatory eicosanoids (46-48) and cytokines (47, 49) and may help to counter the surgery-induced decline in antigen-presenting cell activity (49) and T lymphocyte cytokine production (50). Importantly these studies do not reveal deleterious immunologic effects of fish oil infusion in

these patients. Furthermore, the only one of these fairly small studies to have examined hard end points like length of hospital stay suggests real clinical benefit from fish oil infusion in these patients (49). A more recent report from a larger cohort of patients receiving parenteral nutrition postsurgery does indicate a benefit for inclusion of fish oil in the regimen (51). There were no differences between the control group (50:50 medium-chain triglyceride–soybean oil) and the patients receiving fish oil (a mix of Omegaven with the 50:50 medium-chain triglyceride–soybean oil mix where a maximum of one third of the mix was fish oil) with respect to the proportion of patients who developed wound infections (6% in the fish oil group vs. 11% in the control group) or who died (12% vs. 15%), or in the length of hospital stay (25 vs. 29 days). However the proportion of patients in the fish oil group who were readmitted to intensive care (5%) was significantly lower ($p < 0.05$) than in the control group (17%). A group of patients also received the fish oil–containing emulsion for 2 days preoperatively. Here there were a number of very significant benefits. This group showed a significantly decreased need for mechanical ventilation (17% vs. 31% in the control group; $p < 0.05$), a significantly shorter length of hospital stay (22 vs. 29 days; $p < 0.05$), significantly less need for readmission to intensive care (5% vs. 17%; $p < 0.05$), and significantly lower mortality (3% vs. 15%; $p < 0.05$) (51). Another study revealed that intravenous infusion of a lipid emulsion containing soybean and fish oils (80:20 vol/vol) into patients for 5 days following major gastrointestinal surgery accelerated normalisation of liver and pancreatic function compared with soybean oil alone (52). Overall, there was no difference between the groups with respect to length of stay in the intensive care unit or in hospital. However, in a subgroup of patients at risk of sepsis, there was a reduced intensive care unit stay in the patients receiving fish oil (4.0 vs. 5.3 days in the control group; $p = 0.01$) (52). In a recently published study, a mixed group of over 650 patients including about 230 postsurgical patients received parenteral nutrition including fish oil (Omegaven) at 0.11 g/kg per day for at least 3 days (mean 8.7 days); there was a significantly lower rate of infections ($p < 0.0005$), fewer complications ($p < 0.005$), and shorter length of hospital stay ($p = 0.05$) in the postsurgery patients receiving fish oil compared with those receiving the control emulsion (8). These authors found that infusion of fish oil of about 0.15 g/kg per day decreased mean intensive care unit stay from 8.7 to 5.3 days and hospital stay from 27.4 to 25.5 days. Wichmann et al (53) reported length of hospital stay in post-gastrointestinal surgery patients receiving a control emulsion (soybean oil) or an emulsion

that included medium-chain triglycerides, soybean oil, and fish oil (50:40:10 vol/vol/vol; Lipoplus). Length of stay was significantly shorter ($p = 0.006$) in patients receiving fish oil (17.2 days) than in the control group (21.9 days). Thus, findings available from published studies in gastrointestinal surgical patients clearly demonstrate clinical benefit from the inclusion of long-chain n-3 PUFAs in parenteral nutrition regimens (8, 49, 51-53). However, the study of Tsekos et al (51) also demonstrates a much greater benefit if the fatty acids are additionally provided presurgery, which, of course, is only possible in elective surgery. The greater benefit of preoperative infusion of long-chain n-3 PUFAs may relate to better incorporation of the fatty acids into leukocytes and other tissues.

Studies in patients with established sepsis

Septic patients who were intolerant of enteral nutrition received a standard soybean oil–based emulsion or an emulsion containing fish oil (Omegaven) for 5 days (54) or 10 days (55). Blood leukocyte counts and serum C-reactive protein concentration tended to be lower, and production of LTB_5 by stimulated neutrophils was significantly higher in patients receiving fish oil (54). Production of $TNF-\alpha$, $IL-1\beta$, $IL-6$, $IL-8$, and $IL-10$ by endotoxin-stimulated mononuclear cells did not increase during infusion of the fish oil–containing emulsion, whereas production of the 4 proinflammatory cytokines was markedly elevated during the first 2 days of soybean oil infusion (55). These studies establish that infusion of long-chain n-3 PUFAs into patients with sepsis can modulate inflammatory mediator production and related inflammatory processes. This might be associated with clinical improvements: Heller et al (8) included 268 patients with abdominal sepsis in their study of parenteral n-3 PUFA infusion. They found a significantly lower rate of infection and shorter lengths of intensive care unit and hospital stay in those patients receiving fish oil more than 0.05 g/kg per day than in those receiving less than this. Mortality was significantly decreased in those patients who received fish oil more than 0.1 g/kg per day (8). Thus, these recent data are strongly suggestive of genuine clinical benefit from the inclusion of long-chain n-3 PUFAs in parenteral nutrition regimens given to patients with sepsis, although clearly more studies are needed in this patient group.

CONCLUSIONS

Theoretical considerations suggest that an excessive or imbalanced supply of n-6 PUFAs may play a role

in creating an inflammatory and immunosuppressed state, so approaches to decreasing the amount of linoleic acid used in parenteral lipid emulsions are being sought. One approach is to partly replace soybean oil with fish oil in such emulsions. Long-chain n-3 PUFAs from fish oil decrease the production of inflammatory eicosanoids and cytokines. They act both directly, by replacing arachidonic acid as an eicosanoid substrate and by inhibiting arachidonic acid metabolism, and indirectly by altering the expression of inflammatory genes through effects on transcription factor activation. An emerging application of n-3 PUFAs is in postsurgical or critically ill patients where they may be added to parenteral formulas. Parenteral nutrition including n-3 PUFAs appears to preserve immune function better than standard formulas and appears to partly prevent some aspects of the inflammatory response. Studies to date are suggestive of clinical benefits from this approach,

especially in postsurgical patients, but evidence of clinical benefit in patients with sepsis is very limited.

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