Lipids and the Critically Ill Patient

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Lipid Metabolism in the Critically Ill Patient

Lipid metabolism is altered in the critically ill patient as a result of changes in the status of hormones and other mediators [for reviews see, 1–3]. Enhanced mobilization of adipose tissue triacylglycerol stores is characteristic of the metabolic response to severe stress. This process is promoted by catecholamines and inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1, and is exaggerated by the decreased insulin sensitivity of adipose tissue. The release of fatty acids from adipose tissue is frequently in excess of energy requirements. Those fatty acids not oxidized may be re-esterified into triacylglycerols in the liver and packaged into very low-density lipoproteins (VLDLs). Hepatic triacylglycerol production is increased in critical illness and this can lead to lipid deposition (steatosis) in the liver. Nevertheless, hepatic triacylglycerol output (as VLDLs) is also increased in critical illness. In some conditions (e.g. trauma or after surgery) triacylglycerol clearance is not impaired (or may even be increased) and so plasma triacylglycerol concentrations remain normal (or may even be decreased). However, in some conditions (e.g. sepsis), the activity of adipose tissue lipoprotein lipase is suppressed by inflammatory cytokines (e.g. TNFα and IL-1) and insulin resistance, and so triacylglycerols are not efficiently cleared from the circulation. Thus, hypertriacylglycerolemia occurs in such patients. VLDLs can bind endotoxin and target it for degradation in liver parenchymal cells. Thus, the increase in VLDL concentration may be, in part, a protective mechanism. The plasma cholesterol concentration is decreased in stress conditions, with the concentrations of both low- (LDLs) and high-density lipoproteins (HDLs) being decreased. This decrease occurs despite increased hepatic cholesterol production. The decreased HDL concentration
A Role for Lipids in Nutritional Support of the Critically Ill Patient

In the meta-analysis of total parenteral nutrition [4], there was a trend towards less complications if lipids were not included in the regimen (p = 0.09 vs. lipids), although inclusion of lipids did not affect mortality. Whether exogenously supplied lipids are, in fact, detrimental to the critically ill patient remains a controversial point, and they are frequently included in nutritional support regimens. Lipids provided enterally undergo normal intestinal metabolism with the fatty acids appearing in circulating chylomicrons. Infused lipid emulsions acquire apolipoproteins from circulating lipoproteins and follow the pathway of chylomicron metabolism. It is important that the lipids used in critically ill patients provide essential fatty acids and fat-soluble vitamins and that the component polyunsaturated fatty acids (PUFAs) be adequately protected against peroxidation by including sufficient α-tocopherol. The lipids contained in emulsions used in nutritional support have traditionally been based on soybean oil, which is rich in the n-6 fatty acid linoleic acid (18:2 n-6). Nutritional support has traditionally been aimed at supplying substrates to meet energy demands and providing building blocks for wound healing and tissue repair, and in the process helping to prevent body wasting. Critically ill patients may be at risk of compromised immunity, resulting in decreased resistance to infection. Furthermore, it is now realized that some patients show an early hyperinflammation than might be damaging to the host. Thus, nutritional support is now aimed at providing substrates to support the immune system and nutrients (and other factors) that can modulate the inflammatory state. It is in these two areas that fatty acids are thought to offer great opportunity for improvement in patient outcome.

Polyunsaturated Fatty Acids, Inflammation and Immunity

Biosynthesis of Polyunsaturated Fatty Acids

There are two main families of PUFAs, the n-6 (or omega-6) and the n-3 (or omega-3) families. Mammalian cells cannot synthesize n-6 or n-3 PUFAs de novo, because they lack the δ-12 and δ-15 desaturase enzymes (found in most plants) for insertion of a double bond at the n-6 or n-3 position (fig. 1). The n-6 and n-3 fatty acids are essential substrates for many of the major
regulatory lipids in the body and as they cannot be synthesized in the body, they must be obtained from the diet. The commonly consumed PUFAs are linoleic acid (18:2 n-6) and \(-\text{linolenic acid} (18:3 \text{ n-3}). Once consumed these fatty acids can be converted to the longer chain, more unsaturated derivatives (fig. 1). Thus linoleic acid is converted to arachidonic acid (ARA; 20:4 n-6) and \(-\text{linolenic acid} is converted to eicosapentaenoic acid (EPA; 20:5 \text{ n-3}) and docosapentaenoic acid (22:5 n-3; fig. 1). There is some controversy about the extent to which docosahexaenoic acid (DHA; 22:6 n-3) can be synthesized from EPA in humans. EPA, docosapentaenoic acid and DHA are termed long-chain n-3 PUFAs. These fatty acids are found in oily fish and in the preparations known as fish oil.

Arachidonic Acid as a Substrate for Synthesis of Bioactive Mediators

The principal functional role for 20-carbon PUFAs is as substrates for synthesis of the family of bioactive mediators known as eicosanoids, which include prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs), lipoxins, and hydroxyeicosatetraenoic acids (fig. 2). Although several 20-carbon PUFAs are able to serve as precursors of eicosanoids, ARA is usually
the principal substrate for their synthesis. This is because the membranes of most cells contain large amounts of ARA, compared with other potential eicosanoid precursors (including EPA). ARA in cell membranes can be mobilized by various phospholipase enzymes, most notably phospholipase A2, and the free ARA can subsequently act as a substrate for the enzymes that synthesize eicosanoids (fig. 2). Metabolism of ARA by cyclooxygenase (COX) enzymes gives rise to the 2-series PG and TX (fig. 2). There are two isoforms of COX: COX-1 is a constitutive enzyme and COX-2 is induced in inflammatory cells as a result of stimulation and is responsible for the markedly elevated production of PG which occurs upon cellular activation. Metabolism of ARA by the 5-lipoxygenase (5-LOX) pathway gives rise to hydroxy and hydroperoxy derivatives and the 4-series LT, LTA4, B4, C4, D4 and E4 (fig. 2).

Eicosanoids act as mediators in their own right (e.g. PGE2 causes pain), modify the responses to other mediators (e.g. PGE2 potentiates the pain caused by bradykinin) and act as regulators of other processes, such as platelet aggregation, blood clotting, smooth muscle contraction, leukocyte chemotaxis, inflammatory cytokine production, and immune function. The effects of eicosanoids on inflammation and immunity have attracted much attention in recent years [5]. The effects of PGE2 and LTB4 have been studied most widely. PGE2 has a number of proinflammatory effects including inducing fever, increasing vascular permeability and vasodilation and enhancing pain and edema caused by other agents such as bradykinin and histamine. PGE2 suppresses production of TNFα and IL-1 and so in these respects is anti-inflammatory. PGE2 suppresses lymphocyte proliferation and natural killer cell activity and inhibits production of IL-2 and interferon.
(IFN)-γ, and so in these respects PGE₂ is immunosuppressive. PGE₂ also promotes immunoglobulin (Ig) E production by B lymphocytes; IgE is a mediator of allergic inflammation. TXA₂ promotes platelet aggregation, leukocyte adhesion, and smooth muscle contraction. LTB₄ increases vascular permeability, enhances local blood flow, is a potent chemotactic agent for leukocytes, induces release of lysosomal enzymes, enhances generation of reactive oxygen species, and enhances production of TNFα, IL-1, and IL-6. In all of these respects LTB₄ is proinflammatory. In inflammatory conditions increased rates of production of ARA-derived eicosanoids are found and elevated levels of certain eicosanoids are found in blood and tissues from patients with inflammatory disorders, burns and critical illness. Interestingly, recent studies have shown that PGE₂ inhibits 5-LOX, so preventing the generation of the inflammatory 4-series LTs [6]. Furthermore, PGE₂ was found to induce generation of the 15-LOX product lipoxin A₄, a known inflammation ‘stop signal’ [6]. Thus, although PGE₂ does possess distinct proinflammatory actions, it is involved in mediating the resolution of inflammation through effects on the generation of other eicosanoids.

Alternatives to n-6 Polyunsaturated Fatty Acids for Use in Critically Ill Patients

Although most standard lipid emulsions for use in critically ill patients are based upon soybean oil, there is a view that an excess of n-6 PUFAs should be avoided since this could contribute a state where physiological processes become dysregulated. However, while there are some studies that indicate that provision of emulsions rich in n-6 PUFAs is detrimental to the host (e.g. impairing immune function), there are other, similar studies showing no such impairment [for references see, 7]. Nevertheless, nutritional support regimens containing alternative types of fatty acids are being sought. One alternative is to reduce the amount of n-6 PUFA-containing oil by partly replacing it with medium-chain triglycerides (MCTs; i.e. triacylglycerols containing fatty acids of carbon chain length 6–12). This approach will not be further discussed here. A second approach is to replace part of n-6 PUFA-rich oil in emulsions designed for parenteral use with olive oil, which is rich in the n-9 monounsaturated fatty acid oleic acid (18:1 n-9). This approach is currently under investigation and will not be discussed further here. The third approach is to replace part of n-6 PUFA-rich oil with fish oil, which contains long-chain n-3 PUFAs.

Eicosapentaenoic Acid as an Arachidonic Acid Antagonist

When fish oil is provided, EPA is incorporated into cell membrane phospholipids, partly at the expense of ARA. Thus, there is less ARA available for eicosanoid synthesis. In addition, EPA inhibits the oxidation of ARA by COX. Hence, fish oil decreases production of PGs like PGE₂, of thromboxanes like TXA₂ and of LTs like LTB₄. This has been demonstrated many times in cell culture, animal feeding and healthy volunteer studies. Thus, n-3 PUFAs
can potentially reduce platelet aggregation, blood clotting, smooth muscle contraction, and leukocyte chemotaxis, and can modulate inflammatory cytokine production and immune function (fig. 2).

In addition to inhibiting metabolism of ARA, EPA is able to act as a substrate for both COX and 5-LOX (fig. 2), giving rise to derivatives which have a different structure to those produced from ARA (i.e. 3-series PGs and TXs and 5-series LTs). Thus, the EPA-induced suppression in the production of ARA-derived eicosanoids is accompanied by an elevation in the production of EPA-derived eicosanoids. The eicosanoids produced from EPA are considered to be less biologically potent than the analogues synthesized from ARA, although the full range of biological activities of these compounds has not been investigated. The reduction in generation of ARA-derived mediators which accompanies fish oil consumption has lead to the idea that fish oil is anti-inflammatory (fig. 2). Additionally, recent studies suggest that metabolism of EPA by COX gives rise to a novel series of eicosanoids that are anti-inflammatory in nature [8].

The isolated, perfused rabbit lung has been used as a model to study the pathophysiological effects of ARA- and EPA-derived eicosanoids. Infusion with *Escherichia coli* hemolysin was shown to induce vasoconstriction/hypertension, mediated by TXB2, and vascular permeability/leakage, mediated by 4-series LTs [9, 10]. Inclusion of free ARA in the perfusate increased TXB2 and 4-series LT generation, arterial pressure and vascular leakage. In contrast, inclusion of EPA decreased TXB2 and 4-series LT generation, arterial pressure and vascular leakage and increased generation of TXB3 and 5-series LTs [9, 10]. Perfusion of isolated rabbit lungs with a fish oil-containing emulsion markedly attenuated the vascular inflammatory reaction (hypertension) induced by calcium ionophore [11]. Compared with perfusion with a soybean oil-rich emulsion, fish oil decreased the concentration of LTC4 in the perfusate by >50% and increased the concentration of LTC5 from barely detectable (<10 pg/ml) to a concentration very similar to that of LTC4 (approximately 150 pg/ml) [11]. These observations indicate that n-3 PUFAs can significantly inhibit the acute inflammatory responses induced, or at least marked, by production of ARA-derived eicosanoids.

### n-3 Polyunsaturated Fatty Acids and Inflammatory Cytokines

Although the action in antagonizing ARA metabolism is a key anti-inflammatory effect of n-3 PUFAs, these fatty acids have other effects that might occur downstream of altered eicosanoid production or might be independent of this [12]. Cell culture, animal feeding and healthy human volunteer studies have demonstrated that n-3 PUFAs can decrease the production of TNFα, IL-1β, IL-6 and tissue factor by stimulated monocytes, macrophages, osteoblasts, chondrocytes and/or endothelial cells [for review see, 16]. Endotoxin was used most often as the cell stimulus in these studies.
**Fish Oil and Animal Models of Endotoxemia and Sepsis**

The importance of a hyperinflammatory response, characterized by overproduction of TNFα, IL-1β, IL-6 and IL-8, in the progression of trauma patients towards sepsis is now recognized. Enhanced production of ARA-derived eicosanoids, such as PGE₂, is also associated with trauma and burns. The inflammatory effects of infection can be mimicked by administration of endotoxin, which causes an elevation in circulating concentrations of inflammatory cytokines. The ability of n-3 PUFAs to decrease production of inflammatory cytokines and eicosanoids suggests that fish oil might be a useful agent to aid the control of endotoxemia and the so-called systemic inflammatory response syndrome (SIRS).

Fish oil feeding to rats resulted in a markedly altered profile of post-endotoxin circulating eicosanoids (e.g. less PGE₂, TXB₂ and 6-keto-PGF₁α) and of eicosanoid generation by isolated alveolar macrophages (40% less LTB₄ and over 10 times more LTB₅) [13, 14]. Mice fed fish oil and then injected with endotoxin had significantly lower plasma TNFα, IL-1β and IL-6 concentrations than mice fed safflower oil [15]. Fish oil-containing parenteral nutrition significantly decreased serum TNFα, IL-6 and IL-8 concentrations in burned rats [16]. Fish oil feeding in guinea pigs or rats or fish oil infusion in guinea pigs enhanced survival following endotoxin challenge [for references see, 15]. Fish oil feeding decreased endotoxin-induced metabolic perturbations (fever, acidosis, hypotension, anorexia, weight loss) in guinea pigs and/or rats [for references see, 15]. Fish oil (or EPA) improved heart and lung function and decreased lung edema in endotoxic rats [14, 17, 18] and pigs [19].

Total parenteral nutrition using fish oil as the lipid source was found to prevent the endotoxin-induced reduction in blood flow to the gut and to reduce the number of viable bacteria in mesenteric lymph nodes and liver following exposure to live bacteria [20]. Fish oil did not, however, decrease bacterial translocation across the gut and the authors concluded that fish oil must have improved bacterial killing. Fish oil administration prior to exposure to live pathogens decreased mortality of rats compared with vegetable oil [21]. More recently, fish oil infusion after induction of sepsis by cecal ligation and puncture in rats was shown to decrease mortality (and PGE₂ production) compared with vegetable oil [22]. Intragastric administration of fish oil into chow-fed rats prior to cecal ligation and puncture improved survival compared with vegetable oil or saline infusion [23].

**Studies of Fish Oil-Containing Parenteral Nutrition in Patients**

Parenteral nutrition supplemented with fish oil has been shown to affect circulating inflammatory mediator concentrations and/or the capacity of leukocytes to produce inflammatory mediators in various patient groups. For example, infusion of a fish oil-containing lipid emulsion into postoperative
patients resulted in an increased capacity of stimulated blood leukocytes to generate LTC$_4$ 6 days after operation [24]. Fish oil infusion was also found to decrease the production of TXB$_2$ and to increase the production of TXA$_3$ by platelets from patients after surgery [25]. In another study, patients received either a MCT-long-chain triacylglycerol mix or this mix also containing fish oil for 5 days following surgery [26]. Patients in the fish oil group received 3 g (days 1 and 2) and 6 g (days 3, 4 and 5) n-3 PUFAs/day. Neutrophils from patients infused with fish oil produced less LTB$_4$ and significantly more LTB$_5$ at postoperative days 6 and 10. Plasma TNF$_\alpha$ (days 6 and 10) and IL-6 (day 10) concentrations were lower in patients receiving fish oil [26]. This study did not report clinical outcomes. Recently the results of three further studies with parenteral fish oil administration have become available [27–29]. In the first of these, patients received total parenteral nutrition that included an 8% soybean oil plus 2% fish oil emulsion (controls received a 10% soybean oil emulsion) for 5 days following surgery [27]. Patients in the fish oil group received 0.2 g fish oil/kg body weight/day; it is not clear from the fatty acid compositions of the emulsions provided exactly how much n-3 PUFAs this would equate to. There were no differences between groups with respect to the concentrations and/or activities of a range of coagulation factors, the function of platelets, and complications. Another study compared the effects of lipid emulsions on lymphocyte functions in patients following large bowel surgery [28]. Patients received lipid-free total parenteral nutrition or parenteral nutrition including 10% soybean oil or 8.3% soybean oil plus 1.7% fish oil for 5 days postoperatively. The amount of fish oil provided was 0.1 g/kg body weight for the first day and 0.2 g/kg body weight for days 2–5; this equated to about 3 g long-chain n-3 PUFAs/day based on a 70-kg body weight. Blood lymphocyte numbers and functions were measured before surgery and at days 3 and 6 after surgery. Although surgery affected blood lymphocyte numbers, there were no differences between the groups with respect to the numbers of total lymphocytes, T cells, B cells, CD4+ lymphocytes, CD8+ lymphocytes or natural killer cells in the circulation at any of the time points. Furthermore, there were no differences between the groups with respect to lymphocyte proliferation stimulated by a mitogen. In contrast, ex vivo IL-2 production was increased in the fish oil group, and the decline in ex vivo IFN-γ production after surgery was prevented by fish oil [28]. Thus, this study indicates that, in these patients, parenteral fish oil does not impair cell-mediated immune responses, and may even preserve or improve them. Weiss et al. [29] infused 10% fish oil on the day before surgery and on days 1–5 after surgery into patients undergoing abdominal surgery. On postoperative days 4 and 5 the patients also received standard total parenteral nutrition, which included 50 g fat/day. Control patients received the same regimen apart from the fish oil infusions. White cell count, the serum concentrations of C-reactive protein and TNF$_\alpha$, and neutrophil respiratory burst activity were not different between groups, although they were affected by surgery. TNF$_\alpha$ production by
endotoxin-stimulated whole blood tended to be lower at postoperative day 5 in the fish oil group, but the difference did not reach significance. The serum IL-6 concentration was significantly lower in the fish oil group at days 0, 1 and 3 after surgery. In contrast, monocyte expression of human leukocyte antigen-DR, which is involved in antigen presentation, was preserved in the fish oil group but declined at days 3 and 5 after surgery in the control group [29]. No differences in infection rates or mortality between the groups were observed. Postoperative stay in the intensive care unit tended to be shorter in the fish oil group (4.1 vs. 9.1 days) as did total hospital stay (17.8 vs. 23.5 days). Postoperative stay on the medical wards was significantly shorter in the fish oil group [29]. These studies indicate the potential for significant modification of the inflammatory and immune changes induced by surgery by infusion of n-3 PUFAs in the form of fish oil. However, larger studies are needed to evaluate the effects on complication rates, hospital stay and mortality.

Studies of Fish Oil-Containing Enteral Nutrition in Patients

A large number of studies incorporating fish oil into enteral formulae have been conducted in intensive care and surgical patients. The majority of these trials have used the commercially available product IMPACT® which contains arginine, nucleotides and n-3 PUFAs. n-3 PUFAs make up about 10% of the fatty acids in IMPACT, and it contains about 3 g n-3 PUFAs/l. A comprehensive meta-analysis of 15 randomized, controlled studies using IMPACT or Immun-Aid® (also rich in arginine, RNA and n-3 PUFAs) has been performed [30]. This analysis confirmed significant reductions in infection rate, number of ventilator days and length of hospital stay, but not in overall mortality. Table 1 lists the studies of enteral nutrition involving n-3 PUFAs that have reported immune and/or inflammatory outcomes. A number of studies have reported circulating lymphocyte numbers and subsets and circulating immunoglobulin concentrations and most report little difference in these compared with the control group. Some studies have reported aspects of immune function such as phagocytosis, respiratory burst, lymphocyte proliferation, human leukocyte antigen-DR expression on monocytes and cytokine production; several of these studies report some significant improvements in the these functions in patients given IMPACT compared with the control group. The most frequently reported outcomes of these types are those related to inflammatory cytokines, which is perhaps not surprising given their role in progression to SIRS. One study has reported lower spontaneous production of TNFα and IL-6 by diluted whole blood after several days of IMPACT administration [36]. Several studies report lower circulating concentrations of IL-6 in the IMPACT group, while there are also reports of lower circulating TNFα concentrations (for references see table 1).
<table>
<thead>
<tr>
<th>Ref No.</th>
<th>Type</th>
<th>Formula studied</th>
<th>Immune/inflammatory outcomes</th>
<th>Effects of formula with fish oil on immune/inflammatory outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>Burns (av. 40% BSA)</td>
<td>50:50 Fish oil:safflower oil vs. 50:40:10 MCT:corn oil:soybean oil vs. 70:30 soybean oil:MCT</td>
<td>Lymphocyte count Bacterial killing by neutrophils</td>
<td>None None</td>
<td>↓ Wound infections, infectious episodes and length of hospital stay (expressed as percent of original BSA burn) in fish oil group No effect on mortality</td>
</tr>
<tr>
<td>32</td>
<td>ICU (trauma, surgery, sepsis)</td>
<td>IMPACT vs. Standard</td>
<td>Lymphocyte proliferation</td>
<td>↑ At days 3 and 7</td>
<td>No effect on length of hospital stay or mortality</td>
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<tr>
<td>33</td>
<td>Cancer surgery</td>
<td>IMPACT vs. Standard</td>
<td>Complement C3 Circulating lymphocyte and subset numbers HLA-DR expression on monocytes Lymphocyte proliferation</td>
<td>None None</td>
<td>↓ Number of patients with infectious/healing complications in IMPACT group No effect on mortality</td>
</tr>
<tr>
<td>34</td>
<td>Cancer surgery</td>
<td>IMPACT vs. Standard</td>
<td>Circulating IgG and IgM Circulating lymphocyte subsets IFN-γ production by stimulated lymphocytes</td>
<td>IgG ↑ at day 16; IgM ↑ at days 7 and 10</td>
<td>Number of T cells, helper T cells and B cells ↑ at days 7, 10 and 16 ↑ At day 16</td>
</tr>
<tr>
<td>Page</td>
<td>Cancer surgery</td>
<td>IMPACT vs. Standard</td>
<td>PGE₂ production by endotoxin stimulated cells</td>
<td>Time-dependent ↓ by up to 60%</td>
<td>↓ Infections and length of hospital stay</td>
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<td>35</td>
<td>Cancer surgery</td>
<td>IMPACT vs. Standard</td>
<td>Spontaneous or mitogen-stimulated production of: IL-1α, IL-1β, IL-2</td>
<td>None</td>
<td>IL-1α ↑ At day 16 (+mitogen)</td>
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<td></td>
<td></td>
<td></td>
<td>IL-2R ↑ At days 7 and 10 (+mitogen)</td>
<td>IL-6 ↓ At days 3 and 7 (spontaneous)</td>
<td>IL-6 ↓ At days 3 and 7 (spontaneous)</td>
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<td></td>
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<td>TNFα ↓ At day 7 (spontaneous)</td>
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<td>36</td>
<td>Cancer surgery</td>
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<td>Circulating IgA, IgG, IgM</td>
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<td>Circulating IgA, IgG, IgM None</td>
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<td>Circulating TNFα</td>
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<td>IL-1, IL-6, sIL-2R</td>
<td>Some</td>
<td>Phagocytosis by monocytes and neutrophils ↑ At days 8–10 for monocytes</td>
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<td></td>
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<td></td>
<td>Leukocyte counts and subset numbers</td>
<td></td>
<td></td>
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<td>37</td>
<td>Cancer surgery</td>
<td>IMPACT vs. Standard vs. low-fat TPN</td>
<td>Circulating IgA, IgG, IgM</td>
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<td>Circulating IgA, IgG, IgM None</td>
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<td>Circulating complement C3</td>
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<td></td>
<td>Circulating TNFα</td>
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<td></td>
<td></td>
<td></td>
<td>IL-1, IL-6, sIL-2R</td>
<td>Some</td>
<td>Phagocytosis by monocytes and neutrophils ↑ At days 8–10 for monocytes</td>
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<td>Leukocyte counts and subset numbers</td>
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<td></td>
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<tr>
<td>38</td>
<td>Cancer surgery</td>
<td>IMPACT vs. Standard vs. TPN</td>
<td>Circulating IgA, IgG, IgM</td>
<td>None</td>
<td>Circulating IgA, IgG, IgM None</td>
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<td>Circulating complement C3</td>
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<td>Circulating TNFα</td>
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<td>TNFα</td>
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<td>Phagocytosis by monocytes and neutrophils ↑ At day 8 for monocytes</td>
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<th>Ref No.</th>
<th>Type</th>
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<th>Immune/inflammatory outcomes</th>
<th>Effects of formula with fish oil on immune/inflammatory outcomes</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>39</td>
<td>Trauma</td>
<td>IMPACT vs. Standard</td>
<td>Circulating IL-6, Circulating lymphocytes and subset numbers, Phagocytosis by monocytes, DTH response</td>
<td>↓ At day 8, ↑ At days 4 and 8</td>
<td>None</td>
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<td>40</td>
<td>Cancer surgery</td>
<td>IMPACT vs. Standard</td>
<td>Circulating C-reactive protein, Circulating lymphocytes and subset numbers, IL-2R expression on lymphocytes, HLA-DR expression on monocytes</td>
<td>↓ At day 4, ↑ At day 7</td>
<td>None</td>
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<td>41</td>
<td>Cancer surgery</td>
<td>IMPACT vs. Standard</td>
<td>Circulating IgA, IgG, IgM, Circulating complement C3, Circulating sIL-2R</td>
<td>None</td>
<td>↑ At days 1, 4 and 8</td>
</tr>
</tbody>
</table>

No effects on infection rate, length of hospital or ICU stay or mortality

↓ Number of antibiotic days, percent infected patients and length of hospital stay
**Cardiac bypass surgery** (IMPACT vs. Standard)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cardiac bypass IMPACT vs. Standard</th>
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<tbody>
<tr>
<td>Circulating IL-6</td>
<td>↓ At days 1, 4 and 8</td>
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<tr>
<td>Circulating sIL-1R</td>
<td>↓ At days 4 and 8</td>
</tr>
<tr>
<td>DTH response</td>
<td>↑ At days 1, 4 and 8</td>
</tr>
<tr>
<td>Monocyte HLA-DR expression</td>
<td>None</td>
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<tr>
<td>DTH response</td>
<td>↑ At admission</td>
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**Cancer surgery** (Nutrison vs. Standard)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cancer surgery Nutrison vs. Standard</th>
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<tbody>
<tr>
<td>Circulating C-reactive protein</td>
<td>↓ At day 8</td>
</tr>
<tr>
<td>Circulating lymphocytes and subset numbers</td>
<td>↑ Total lymphocytes and percent T cells, T helper cells, NK cells at day 8 ↓ Cytotoxic T cells at day 8</td>
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<tr>
<td>Circulating IL-1, IL-2</td>
<td>None</td>
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<tr>
<td>Circulating TNFα, IL-6</td>
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<tr>
<td>Circulating PGE₂</td>
<td>None</td>
</tr>
<tr>
<td>Neutrophil phagocytosis</td>
<td>↑</td>
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<td>Neutrophil respiratory burst</td>
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BSA = Body surface area; DTH = delayed-type hypersensitivity; HLA = human leukocyte antigen; ICU = intensive care unit; IFN = interferon; Ig = immunoglobulin; IL = interleukin; MCT = medium-chain triglyceride; NK = natural killer; PG = prostaglandin; R = receptor; TNF = tumor necrosis factor; TPN = total parenteral nutrition.
Although many of these observations fit with the effects of n-3 PUFAs that might be predicted based upon studies in cell culture, animals and healthy humans, and could be used as evidence of the efficacy of n-3 PUFAs in the trauma and postoperative settings, the complex nature of the formulae prevents such a clear interpretation. The effects could be due to any one of the specified nutrients (i.e. arginine, RNA, n-3 PUFAs) or to the combination of these nutrients. Indeed, the positive outcomes from the use of IMPACT and Immun-Aid have often been used as evidence for the benefit of arginine in these settings.

One other recent trial performed in patients with moderate and severe acute respiratory distress syndrome has used an enteral preparation apparently differing only in lipid source from the control (32% canola oil + 25% MCT + 20% borage oil + 20% fish oil + 3% soy lecithin vs. 97% corn oil + 3% soy lecithin) [44]. However, as well as the difference in fatty acid composition between the formulae, the n-3 PUFA-rich formula contained more vitamin C and E than the control and contained β-carotene, taurine and carnitine, which the control did not. Patients received about 7 g EPA, 3 g DHA, 6 g γ-linolenic acid, 1.1 g vitamin C, 400 IU vitamin E and 6.6 mg β-carotene per day for up to 7 days. By 4 days the numbers of leukocytes and neutrophils in the alveolar fluid had significantly declined in the fish oil/γ-linolenic acid group and were lower than in the control group. Furthermore, arterial oxygenation and gas exchange were improved in the treatment group. Patients in the treatment group had a decreased requirement for supplemental oxygen, reduced time on ventilation support, and shorter length of intensive care unit stay (12.8 ± 1.1 vs. 17.5 ± 1.7 days). Total length of hospital stay also tended to be shorter (29.4 ± 2.6 vs. 34.6 ± 3.3 days). Fewer patients in the treatment group developed new organ failure (4/51 vs. 13/47). Mortality was 19% in the control group and 12% in the treatment group, but this was not a significant difference. Nevertheless, this study suggests the efficacy of n-3 PUFAs (in combination with γ-linolenic acid, MCT, antioxidant vitamins, taurine and carnitine) in this group of patients.

Concluding Statement

Inflammation is a normal part of host defense. However, excessive or inappropriate inflammation is a component of a range of acute and chronic human diseases, including the systemic inflammatory response to trauma, injury and infection. Inflammation is characterized by the production of inflammatory cytokines, ARA-derived eicosanoids, other inflammatory mediators (e.g. platelet-activating factor) and adhesion molecules. n-3 PUFAs decrease the production of inflammatory cytokines and eicosanoids. They act both directly (e.g. by replacing ARA as an eicosanoid substrate and inhibiting ARA metabolism) and indirectly (e.g. by altering the expression of
inflammatory genes through effects on transcription factor activation [12]). Thus, n-3 PUFAs are potentially potent anti-inflammatory agents. As such, they may be of therapeutic use in a variety of acute and chronic inflammatory settings. Evidence of their clinical efficacy is strong in some settings (e.g. in rheumatoid arthritis) but generally weak in others (e.g. in asthma). An emerging application is in critically ill patients. At the levels that have been used parenterally or enterally they do not appear to exert any adverse effects. Parenteral nutrition including n-3 PUFAs appears to preserve immune function better than standard total parenteral nutrition and appears to partly prevent some aspects of the inflammatory response. There may be some clinical benefit from these effects. n-3 PUFAs are a component of enteral formulae (e.g. IMPACT, Immun-Aid) that have been examined in a number of clinical trials. There is a lack of consistency in many of the immune and inflammatory outcomes from these studies. However, several studies do report maintenance of immune function and a decreased capacity for production of some inflammatory cytokines. Unlike the studies using parenteral nutrition, it is not possible to ascribe these effects to n-3 PUFAs, since the formulae contain several other ‘immunonutrients’. Nevertheless, these studies support the inclusion of n-3 PUFAs in such formulae.

References


Discussion

Dr. Planas Vila: It is now a reality that fish oil lipid emulsion is superior to long-chain triacylglycerol (LCT) or medium-chain triglyceride (MCT) LCT because, in MCT LCT, the amount of n-6 fatty acid is lower than in LCT alone but the ratio of n-3 to n-6 fatty acid is the same. My question is should we be concerned about the auto-oxidation of n-3 fatty acids of fish oil in very ill patients?

Dr. Calder: By oxidation you presumably mean peroxidation, the damaging oxidation that occurs because of the larger number of double bonds in n-3 fatty acids. Yes, I think that is a worry and it is a worry if one is recommending fish oil for oral administration or for parenteral administration. I think we have therefore to ensure that there is appropriate antioxidant protection and monitoring of both the products and the individual. I think that is perhaps the one concern about n-3 fatty acids.
Dr. Planas Vila: Because another possibility is a lipid emulsion with a mix of fish oil and also with olive oil.

Dr. Calder: One of the benefits of olive oil is that it is rich in oleic acid which only has a single double bond, and is therefore much more resistant to peroxidation than n-6 or n-3 fatty acids. In addition olive oil, as you would most certainly know, as a material naturally contains high levels of antioxidants, so I think there are two sides to the apparent benefit of olive oil.

Dr. De Bandt: To prolong the point on peroxidation, there was recently some controversy about the role of vitamin E supplementation and the importance of vitamin E with regard to the huge amount of fish oil supplied and the different responses to fish oil according to the presence or not of vitamin E.

Dr. Calder: I certainly think that in animal studies and in healthy human studies with very large amounts of fish oil being given, some of the effects reported are probably due to lipid peroxidation because of insufficient vitamin E. So I think the vitamin E n-3 polyunsaturated fatty acid balance is an important one, but we don't really know what that balance should be very precisely. Muggli [1] has calculated the vitamin E requirement according to the number of fatty acid double bonds and his equation seems to work alright in terms of inclusion of n-3 in foodstuffs, but I haven't seen anything about that in terms of clinical nutrition. But it is an important point for us to keep in mind.

Dr. Baracos: I have a question about dose. Could you comment, I wonder if dose is getting a patient to swallow a certain amount or dose is equal to achieving a certain level of n-3 fatty acids in phospholipids in a certain cell, and whether you can actually perfuse a concentrated priming dose to achieve such a level and then back off to a maintenance dose. I guess one of the reasons I think about this is I would like to know how much sushi I have to eat to keep it up, and also because I have tried to feed this as very big fish oil capsules to patients with advanced cancer and they find it hard to swallow. Then there are the enteral nutrition products, at least the ones I am experienced with come in attractive flavors like chocolate, hazelnut, soybean, and they also have the additional burden that the concentration of the n-3 fatty acid in the enteral formula comes along with a big piece of baggage which is the rest of the nutrients in that enteral formula, that is to say that those n-3 fatty acids are quite dilute as delivered in enteral formulae. So whatever the dose is, you have got to tell me which is the right one.

Dr. Calder: I am not going to tell you the right one. But you raise a number of important points. So far people have really worked, and I am talking about studies in healthy volunteers here, with the concept that more is better. But the curve that I showed suggested that it is not necessarily the case; there is probably a threshold. Many people, in fact most people, have not been concerned about the status of the cells that they are studying, merely about the amount of fish oil or n-3 fatty acids that the people they are studying are taking. But I personally think it is important to be clear about the status of the target cells that one is studying. So if you are interested in inflammation or immune function you have got to look in those cells and look at the n-3 fatty acid status or eicosapentaenoic acid (EPA) status. There is a linear dose-response relationship between the oral supply of EPA and the concentration of EPA in these cells, so you can sort of do a dose-response curve and see where you are. Now your second point is really related to how you get the amount that you might want to get into people. And it is true that in most fish oil capsules available only 30% of the fatty acids are long-chain n-3 fatty acids, so 70% of the fatty acids are not n-3. So this is a dilute form of supplementation. There are products available that are more highly enriched in n-3 fatty acids. But again if you want to supply a gram of long-chain n-3 fatty acids you have got to give people 3 of the typical capsules per day. If you want
to supply 10 g you have got to give them 30 of the typical capsules a day. People are not going to do that, and they can't afford to do it. In addition there is the problem of taste that you have highlighted and also the problem of nausea because above a certain level of consumption of this stuff people feel nauseous. If you are talking about public health nutrition, which you are not, there is really an alternative: eating oily fish a few times a week. In terms of clinical nutrition, obviously there is the problem with enteral nutrition of gastrointestinal upset and other sorts of things, and I don't know how people are going to get around that with the doses that are required.

_Dr. Berger:_ I would like to ask a bit more about this dose question. There was a nice trial carried out in Canada in burn patients. Garrel et al. [2] and his team studied major burns in 3 groups: standard enteral feed with 30% fat, and 2 low-fat groups both with 15% fat but 1 had fish oil. Those groups with reduced fat had the same reduction in infectious complications and so on. There was absolutely no difference between these 2 groups. What was interesting was the reduction in total fat, and here we are talking about actually increasing the amount of fat, which is against cardiovascular recommendations and so on.

_Dr. Calder:_ There is a major debate about the importance of the amount of fat versus the type of fat in public health nutrition, and some people actually don't think that the amount of fat is such a problem because the difficulty then is that people eat carbohydrates [3]. So the type of fat is important rather than the absolute amount. If for example people are eating 100 g fat/day and they are recommended to take 3 fish oil capsules/day, that isn't a major burden in terms of the amount of fat, but the recommendation in public health terms is not to take capsules but to eat fish instead of eating steak.

_Dr. Berger:_ But in the critically ill the amount is important.

_Dr. Calder:_ Yes I know that in clinical nutrition the amount of fat is a key issue and I think you have highlighted that when you are looking at extremes, which you can do in clinical nutrition but not so much in public health nutrition. Yes, the amount of fat is probably very important. Now one would imagine that against the background of lower fat, n-3 fatty acids would be more important but perhaps the effect of lowering fat is greater than the effect of n-3 fatty acids at the dose that was used in that study.

_Dr. Déchelotte:_ I would like to raise an issue about the kinetic effects of fish oil on the immune response and cytokine production. Most of the studies I am aware of were performed in peripheral blood cells after 5–7 days of supplementation of fish oil, and it seems also from clinical studies in patients that there is a need for at least 5 days either pre- or postoperatively to achieve any influence on leukotriene or prostaglandin production. Do you think that this time could be shorter in other tissues, maybe in the gut especially which is the route we use to provide fish oil, then we could achieve some earlier modulation in the gut before anything is to be seen.

_Dr. Calder:_ In studies on healthy volunteers you are right that rather prolonged periods of supplementation have actually been looked at. The shorter studies are 3 weeks in duration, and probably the maximal change in fatty acid composition has occurred at 3 weeks, but it probably takes 2–3 weeks with oral supplementation. People haven't looked at the functional effects during that sort of loading period. So time is important and of course in the clinical arena one can't play so much with time. However, studies using infusion of fish oil-containing parenteral nutrition show effects or differences between groups that are apparent reasonably early on, within a matter of a few days [4]. Recent data from some groups [5] are suggesting that the incorporation of fatty acids provided intravenously can be very quick into some targets, for example into the endothelium. So it may be that there is very quick incorporation into some pools, and by looking at circulating white blood cells we are just not picking that up.
Dr. Déchelotte: But what about enterocytes?

Dr. Calder: I think one of the advantages with something like enterocytes is the rapid rate of turnover. So when there is increased availability of particular fatty acid substrates there is the possibility of their incorporation.

Dr. McClain: Do you think that fish oils are equally protective for all cell types and organs? The reason I am asking this is that if you want to induce experimental liver injury, you give fish oils along with some other toxin such as ethanol.

Dr. Calder: There is a problem: I think that some particular situations and processes where there is liver damage are particularly sensitive to n-3 fatty acids, and you know you can kill animals with liver disease by giving them fish oil. So I think that is a problem.

Dr. McClain: It is a worry in intensive care unit (ICU) patients, where the liver is one of the first organs damaged during multiple organ failure.

Dr. Calder: Obviously it is a worry, one hopes that people who are involved in this research in the clinical arena are looking at that and are concerned about it. I haven't seen anything from enteral or parenteral studies that has indicated a problem there. But you are right that there may be differences between tissues, certainly there are differences between people.

Dr. Neu: Is there a difference between the inflammatory response that you see between preformed docosahexaenoic acid (DHA) and fish oils?

Dr. Calder: I think you are asking what is the active ingredient in fish oil, which is a mix of fatty acids? That is not absolutely clear; people have tried to differentiate between EPA and DHA and there are several papers reporting that each of those is the active fatty acid, so that is unclear. If they work through antagonism of arachidonic acid metabolism then I would put my money on EPA because DHA is not a good substrate for cyclooxygenase and lipoxygenase.

Dr. Neu: This is of major interest right now in pediatrics because many of the formula companies in Europe and Japan have actually started to add DHA to the formulas, and now in the United States we are seeing thousands of babies that have been treated with DHA-containing formulas, and I don't think we really know the mechanism of potential beneficial effects here and it is a preformed fatty acid that they are adding.

Dr. Calder: The idea there is that the DHA is important for brain and eye development and therefore preterm and perhaps term infants have a requirement for DHA to be supplied. You are right that people who have been looking at brain and visual development have not been looking at any other physiological system, so they don't know the potential difficulties or problems within that area.

Dr. Herndon: I would like to come back to a question from Dr. Berger. I don't quibble that fish oils are better than linoleic acid but the question that I would pose to each individual performing a clinical trial is that they do kinetic studies in the body to demonstrate what contribution these exogenously delivered oils have towards total fat economy. Endogenous lipolysis occurs to such a huge extent throughout the hospital course that the primary fat source is from endogenous fat. That amount of endogenous fat can't be handled by the liver as it is, and so no excess fat should be given to the liver except perhaps minimal essential fatty acids for neurological development in neonates.

Dr. Calder: I can't comment. I think n-3 fatty acids have been included in a range of enteral formulae that have been used for a long period of time now in trials and in normal application. I am not aware of reports of adverse effects related to the n-3 content of those products.

Dr. Herndon: I think specifically those studies looked at whole body fat kinetics and they have not looked at the liver. They have had naïve outcomes and naïve results.
Dr. Calder: The authors are somewhere in the room.

Dr. Herndon: I will be happy to discuss it with them.

Dr. Déchelotte: Going with protein metabolism and fish oil we have rather little data in comparison to the immunological and inflammatory parameters in this field. Barber et al. [6] presented very nice studies in pancreatic cancer patients with high doses of n-3 fatty acids showing a reduction in cachexia and an improvement in some protein levels and even perhaps some reduction in the proteasome activity. Do you think we could expect something of this kind in ICU patients?

Dr. Calder: I think you are right that the studies of Barber et al. have used very high doses and I think these are probably the studies that Dr. Baracos was referring to earlier on. The mechanism of action that they identified is a downregulation of proinflammatory cytokine production thereby decreasing the drive on muscle proteolysis, liver acute phase protein synthesis, and so on. So it fits within the context of what I have been talking about, but you are right that they used very high doses although from the top of my head I can't remember what the doses were.

Dr. Déchelotte: Would you expect fish oil to have any direct effect on muscle proteasomes, for instance, regardless of its being mediated by less cytokine response?

Dr. Calder: A lot of recent studies have shown in experimental systems the effects of n-3 fatty acids on many cell-signaling systems including kinases and so on, and that perhaps relates to the work on NFκB and other transcription factors. Certainly they may be active on signaling pathways that lead to activation of many intracellular events including protein degradation, but I haven't seen anything specific on proteasomes.

Dr. McClave: Not all the immune formulas have fish oil, some have MCT oil, and my question is, my understanding of the n-6 contents in the membrane is that they represent long-term ingestion and they don't change very dynamically, very quickly. Are we doing anything by switching out the amount of fat with MCT or is there any immune modulation that is not going to displace the n-6.

Dr. Calder: Immunologically not very much has been shown with MCTs. I think they were seen as an alternative for a simple way of decreasing the amount of n-6 fatty acids available without really increasing the total fat burden because of their ready oxidation. You are right that it is quite difficult to change the n-6 fatty acid content of cell membranes and there are actually only 2 ways to change the arachidonic acid content, and that is to either give arachidonic acid or to give long-chain n-3 fatty acids and they have opposing action. In fact you can change the linoleic acid content of the diet over quite a wide range but you won't change the arachidonic acid content. I think the very first slide I showed of mouse macrophages taken from animals that were fed for 10 weeks on lots of things, coconut oil, olive oil, vegetable oil, the arachidonic acid content was exactly the same.

Dr. Moore: I have had a long interest in acute lung injury and something that trauma surgeons see is fat embolism syndrome. In an early report Dr. Holman described that about 10% of the people with fat embolism syndrome did not have long bone fractures and he attributed this to the fact that they were administering exogenous Intralipid which was coming out of solution. Subsequently other people have correlated this ‘creaming effect’ with C-reactive protein levels, meaning that if a patient is stressed we should not infuse a lot of Intralipid. So the first question: do you think that happens? Second question: if it does come out of solution, two ways in which you could adversely affect somebody would be to clog up the reticuloendothelium system or the fat globules can cause a fat embolism syndrome in which nobody really knows what happens but it somehow causes acute bone injury. I wonder what your thoughts are.

Dr. Calder: There is only one aspect of your question that I can comment on which is that there is a very long history of studies with Intralipid showing this clogging up
of the reticular endothelium system in animals and humans administered Intralipid [7].
I think this was one of the earliest indications of the need for a modification of the
profile or the amount of lipid provided. So I think clearly historically it has been
documented that it happens, as you suggest, with Intralipid, and it may be that
modification of the lipid profile of emulsions can counter that because it can make the
particle more readily hydrolyzed at the endothelium wall in various places. Actually
MCTs, as you probably know, have the effect of increasing the ability of particles to be
hydrolyzed, so that would be an advantage for MCTs over n-6.

Dr. Rosenfeld: My question is about infantile respiratory distress syndrome (IRDS)
patients. Some of these patients are septic, and recent work recommending the
administration of fish oil to these patients improved the outcome. But I am worried
about septic patients who may have more harm than good with the fish oil with
immunosuppression and more peroxidation. I would like to hear your comment about
that.

Dr. Calder: In adult respiratory distress syndrome (ARDS), there is a particular
study which many of you may know by Gadek et al. [8]. I had two slides of that study
but I had to take those out along with about 30 other slides to keep to the time
allocated like every other speaker. In that study there was enteral provision of fish oil
along with some other active ingredients including γ-linolenic acid, taurine, and some
antioxidants like β-carotene. They quite clearly showed significant differences from
the standard enteral regimen in terms of many of the cellular and clinical markers they
were looking at, but not in mortality. I think that study seems to have quite an
important impact on people's view about the inclusion of fish oil in patients with ARDS.
There is the problem that we already highlighted of this sort of predisposition to lipid
peroxidation, and one of the things about the Gadek study was that it included
additional antioxidants which are very clearly specified in the article. So I think that
this is an important area which they have covered. You highlight the potential
for immunosuppression. Certainly if you give animals very high levels of fish oil you
get immunosuppression. There are studies in healthy humans that are suggestive of
immunosuppression with high levels of fish oil but with insufficient antioxidant
protection. The recent studies that I showed you on the parenteral administration of
fish oil, at least in the short-term, are in fact suggestive of the opposite: that n-3 fatty
acids maintain immune function in postsurgical patients. I think those studies are
quite clean and they were just looking at the inclusion of n-3 fatty acids. They did not
have all these other things like arginine and so on that are included in the enteral
formulae. So the parenteral studies suggest that in the short-term there is no
immunosuppression and there may be a protection of immune function.

Dr. Kudsk: There was a comment made before about the slow uptake of the oils
into membranes and that it may be quicker than you suspect. I remember a study by
Kenler et al. [9] that was published in the Annals of Surgery in which they gave fish
oil capsules daily preoperatively and within 5 days they found significant increases
incorporated in the red blood cell membranes.

Dr. Calder: Yes you are right, you can get them into membranes within days but
the maximum incorporation takes a matter of weeks and for red blood cells longer
because of the long half-life. But you are right, you can get them into cells reasonably
quickly.

Dr. Kudsk: I am curious about the potential mechanism of action. One purpose is
the suppression of the PG2 series, and it has been thought that it may be the primary
action. There have been studies in critically ill patients where prostaglandin synthesis
inhibitors and COX2 inhibitors have been ineffective generally in altering outcome in
critically ill patients. Couldn't that argue that there may be some other mechanism that
we haven't explored?
Dr. Calder: I agree with you completely. I personally don’t believe that these fatty acids work primarily as, let’s say, COX antagonists. I believe that they have effects on cell signaling in their own right, and I think that many of the studies I showed show direct actions of fatty acids in cell culture systems on gene expression. There are these studies on NFκB, on the IκB activation state and IκB phosphorylation, and so on. So I think they have effects on cell-signaling pathways that have nothing to do with eicosanoids. Nevertheless I think eicosanoids at the moment allow us to explain the potential but I think the reality is that they are working in a different way.

Dr. Nitenberg: I want to go back to the study by Gadek et al. [7], I think we have to be very cautious with this study because it was not an intent-to-treat study. 140 patients entered the study, but only 86 were analyzed, so I think the conclusions are not so clear. The second point is how to use these products in ICU patients. In septic patients because, as you have shown, the first part of the patient is probably in the first position and, maybe if we accord some value to the bone classification, it is then in the marked position which is the mixed inflammatory status. So according to the potential value of fish oil, do you think we have to give this type of oil only for the first 5 days, for 10 days, for 30 days, to stop for a while, to come back after? It is very difficult in clinical practice.

Dr. Calder: What I didn’t show on the slide, although it was redrawn from the original, is that these authors suggested a role for n-3 fatty acids throughout because of the potential to decrease the early inflammation and prevent the later immunosuppression. There is evidence for the first of these: I showed you data on tumor necrosis factor, IL-1 and IL-6. There is actually little evidence for the second. We and others have looked for increased IL-10 and TGF-β production and not seen it [10]. So I think the original idea of these authors that n-3 fatty acids should play a role throughout may not be entirely correct, but we have to do something to try to find the answer to your question. But it may be that there is a role for them early on and then we stop and move over to some other form of support.

Dr. McClave: Along the lines of this same comment I would be more worried about the arginine timing with these curves, that you hold back on the arginine in the first part and then start giving it in the second part.

Dr. Planas Vila: I am talking about lipid emulsions in critically ill patients, and in reality in general we find more hyperglycemia than hypertriglyceridemia in these patients, and when we find hypertriglyceridemia it is generally in patients who simultaneously receive another kind of lipid, such as glopophol, along with lipid emulsions. But if we administer lipid emulsions, we can safely administer 30–40% of nonprotein calories and control hypertriglyceridemia because I think for these patients it is worse to have hyperglycemia, and we have hyperglycemia every day in critically ill patients. It is a reality that in the lipid emulsions that have been used until now, LCT or MCT LCT, the amounts of n-6 fatty acids are too high, but really I am more afraid of hyperglycemia in this kind of patient.

References


