Benefits of ω-3 fatty acids in parenteral nutrition

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Introduction

Since the epidemiological studies of Dyerberg et al.[1] in the early 1970s, demonstrated that the Greenland Inuit, eating diets high in fish oil, have lower incidences of thrombosis, coronary heart disease and myocardial infarction, interest has been focused on ω-3 polyunsaturated fatty acids (FA). Since then, numerous studies have been

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carried out in vitro as well as in vivo that showed that ω-3 FA exhibited fewer inflammatory properties when compared to ω-6 FA.[2] Besides the beneficial effects of long-term intake of ω-3 FA on the development of cancer and cardiovascular diseases, encouraging results were obtained also in critically ill patients after short-term supplementation with long-chain ω-3 FA.[3] Compared to the delayed bioavailability of enterally administered ω-3 FA, the intravenous route allows for a fast onset of the beneficial effects in acute diseases.

Consequently, in recent years increased research activities in clinical nutrition of the critically ill were concentrated on ω-3 FA as a supplement for optimized parenteral nutrition with adjunctive therapeutic effects. With the introduction of fish oil into parenteral nutrition the evolution of lipid emulsions resulted in a mixture of oils with a reduced ω-6 FA share and an optimized ω-6 to ω-3 FA ratio of about 3:1–2:1.[4–6]

The mechanisms of action of this fascinating immunomodulatory concept in the critically ill patient will be outlined and the current experimental and clinical data will be presented.

Metabolism and biologic effects of ω-3 FA

Apart from energy supply, polyunsaturated ω-3 FA exert immune modulating and organ protective effects.[2,7] Depending on nutritional intake, ω-3 FA are incorporated in the phospholipid pool of cellular membranes and replace the ω-6 FA thereby increasing membrane fluidity and influencing lipid mediator and cytokine production.[9,10] The concept that nutritional supplementation with ω-3 FA exerts immunomodulatory and organ protective effects that are based on the multiple interactions of ω-3 FA is summarized in Fig. 1.

While the impact of ω-3 FA on lipid mediator generation has been greatly clarified, up to now the understanding of subcellular effects is limited. ω-3 FA affect biophysical characteristics of cellular membranes by alteration of the membrane phospholipid composition and the content of cholesterol, which improves membrane fluidity. The associated increase in the deformability of blood cells might account for improvement of blood rheology after fish oil intake. Furthermore, ω-3 FA modify the function of membrane-linked enzyme systems, signal transduction and receptor functions (Fig. 2). Recent work of Lee et al.[11] demonstrated that activation of general proinflammatory pathways, such as NFκB and cyclooxygenase-2 expression by saturated FA and the inhibition of this induction by polyunsaturated FA are mediated through a common signaling pathway derived from toll-like receptor (TLR)-4. TLR-4 conveys signals as a part of innate immunity from the endotoxin receptor (CD14) on the surface of macrophages to the inner cell and may, likewise, be activated by saturated FA. In addition, TLR-2 is activated by bacterial cell surface components. Activated TLR-4 and TLR-2, respectively, activate the enzyme IκB-kinase resulting in a diminished blockade-function of inhibitory factor kappa B (IκB). Thus, NFκB may translocate into the nucleus to setup transcription activity of inflammatory DNA-gene loci. Consequently, inflammatory receptors, enzymes and cytokines are expressed.

ω-3 FA modify cellular receptor functions[12] and downstream signal transduction features[13] until the level of NFκB and beyond.[14,15] As a result of down regulation of nuclear transcription factors, formation of cytokines such as TNFα and IL-1[16] in monocytes was reduced after fish oil administration. Taken together, ω-3 FA seem to interfere with early inflammatory signal transduction processes and, thus, are capable of blunting hyperinflammation. A large body of experimental data confirms that ω-3 FA attenuate inflammatory reaction,[17] ameliorate host defense,[18,19] improve splanchnic blood flow and gut barrier function in septic states,[20] and prevent tumor growth.[21] These different biologic properties of ω-3 FA offer a promising prophylactic and therapeutic potential in different clinical settings which seems to be attainable by supplementation of parenteral nutrition with ω-3 FA even after short-term administration.[10]

Effects of short-term infusion of ω-3 FA

In view of the clinical consequences in acutely ill patients, more recent interest was focused on the question of whether or not ω-3 FA are integrated into the phospholipid pool even after short-term intravenous application, and whether they induce organ protective effects by means of their metabolites after inflammatory stimulation. Recent studies in humans by Mayer et al.[22] have shown that several hours of parenteral nutrition with ω-3 FA significantly decreases the ω-6/ω-3 FA ratio in the plasma-free FA fraction and in the monocyte membrane lipid pool which was associated with a suppression of monocyte generation of proinflammatory cytokines (TNFα, Interleukin-1, -6, -8) in response to endotoxin. Additionally, adhesive

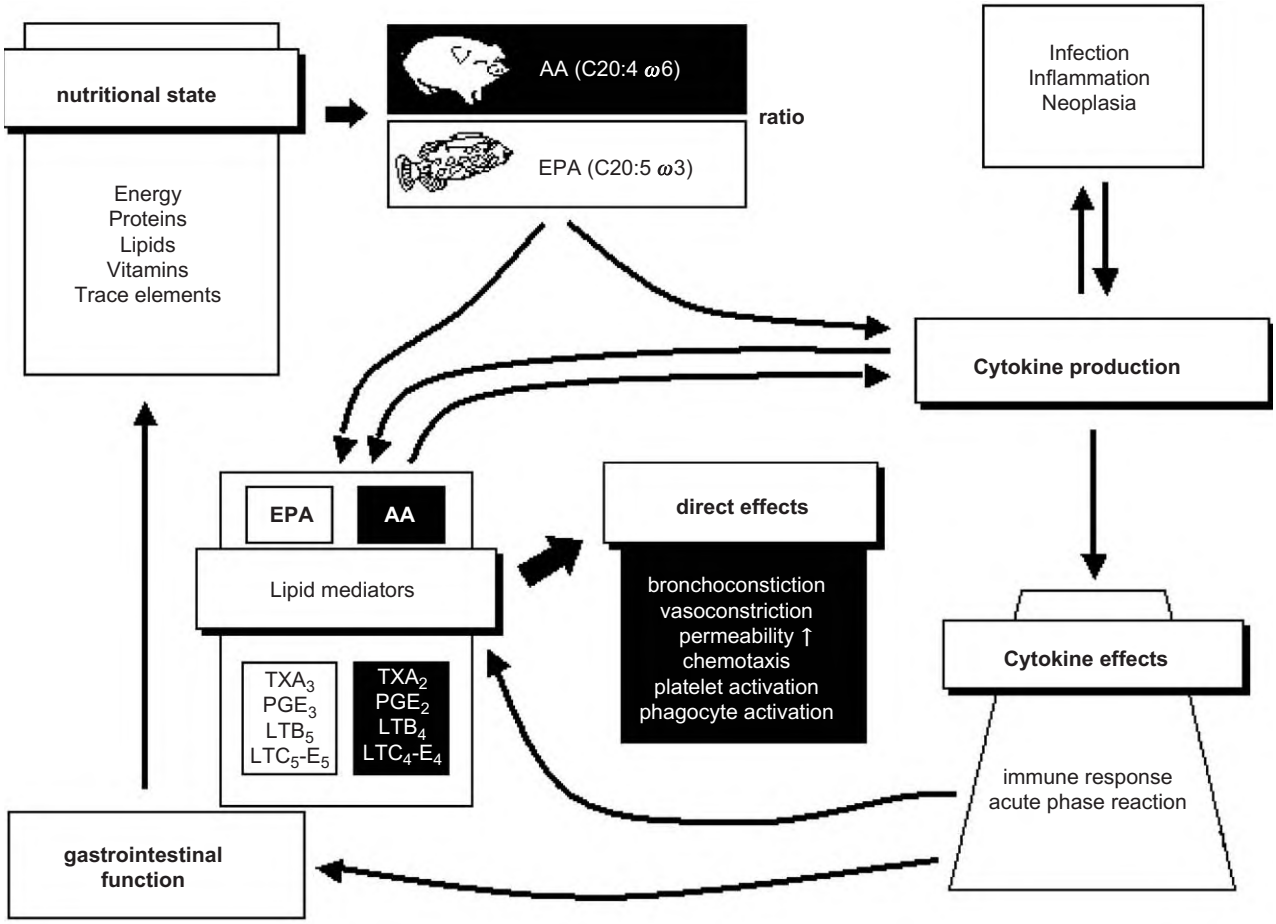

Figure 1 Effects of the ω-6 (black)/ω-3 (white) FA ratio on the regulation of inflammation. The human nutritional condition is determined by the constituents of nutrition. Concerning lipids, the ratio between ω-3 and ω-6 FA determines the type and intensity of the inflammatory reaction, in terms of lipid mediators and cytokine production. While arachidonic acid (AA)-metabolites (black boxes) may induce hyperinflammation, eicosapentaenoic acid (EPA)-derived mediators are more immunoneutral. Cytokine production itself as part of the acute phase response is closely coupled to lipid mediator generation via positive feed back loops, for example, by triggering the expression of COX II or iNOS. These complex interactions apply for infection and inflammation to the same degree as they do for tumor cell defense. As a result of over activated immune responses, gastrointestinal function may be impaired and therefore, worsen nutritional state.

interactions of monocytes with the endothelium were reduced while surface expression of adhesive molecules (CD11b, CD18, CD49) essential for the cellular defense, were unaltered. In a further trial,[10] the same research group demonstrated that infusion of fish oil emulsion (Omegaven®, Fresenius Kabi) compared to soybean oil emulsion (Lipovenoes®, Fresenius Kabi) in patients with septic shock results in a rapid switch in plasma-free FA fraction to predominance of ω-3 FA, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and a suppression of proinflammatory cytokine production and respiratory burst.

Rapid incorporation of ω-3 FA in cellular membranes has been shown for human circulating blood cells: leukocytes,[10,24,25] platelets,[25,26] red blood cells, monocytes, macrophages[22] and also for organ tissue.[9]

In isolated and cell-free perfused rabbit lungs we were able to show a relevant uptake of the ω-3 FA EPA and DHA into the tissue as early as 3 h after lung perfusion with 1% of fish oil emulsion (Omegaven®, Fresenius Kabi) in the perfusion buffer. During inflammatory stimulation of the lungs, induced by calciumionophore, which triggers arachidonic acid (AA) metabolism via transmembraneous Ca^{2+}- influx, the rise of pulmonary arterial pressure was considerably blunted. Compared to controls receiving either saline or soybean oil emulsion (Lipovenoes®, Fresenius Kabi) the lung weight increase was reduced by 50% in the Omegaven® treated lungs, indicating reduced edema formation.[27] The

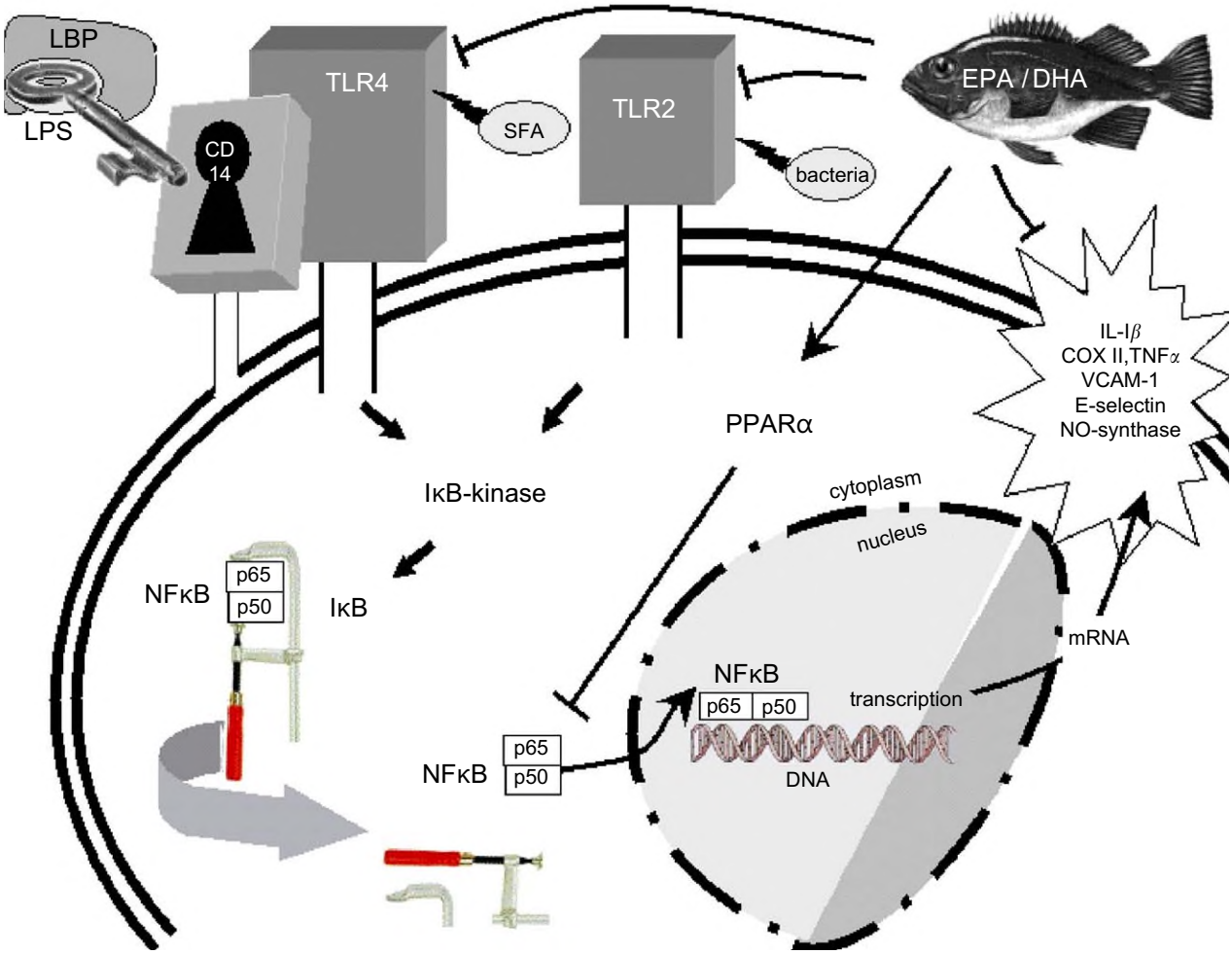

Figure 2 Effects of ω-3 FA on the toll like receptor (TLR)-nuclear factor kappa B (NFκB)-axis. While TLR-4 confers the presence of a gram-negative infection to the inner cell, TLR-2 reports the presence of gram-positive bacteria. Saturated fatty acids (SFA) may, likewise, activate the TLR-4 cascade. Via IκB-kinase the blockade- function of inhibitory factor kappa B (IκB) is postponed and NFκB may translocate into the nucleus to setup transcription activity of inflammatory DNA-gene loci. Consequently inflammatory receptors, enzymes and cytokines are expressed; ω-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may competitively interfere into the activating sequence on various levels of the cascade. Lipoid binding protein (LBP); lipopolysaccharide (LPS); peroxisome proliferator-activated receptor (PPAR).

latter observations after ω-3 FA were paralleled with a considerable reduction of the capillary filtration coefficient as an indicator of vascular permeability.[27] These data correlated with an increased synthesis of EPA-derived cysteinyl-leukotrienes, while the AA-derived leukotrienes and thromboxane A_2 were only detectable in small quantities. Compared to controls, treatment with ω-3 FA did not influence release of vasodilatory prostacyclin.

The potential clinical impact of these findings[9,27] was meanwhile assessed in a cohort of patients with ARDS by Gadek and the 'Enteral Nutrition in ARDS Study Group' in 1999.[3,14] Due to the improvement of pulmonary gas exchange lower inspiratory oxygen concentrations and lower levels of positive endexspiratory pressure were able to assure adequate oxygen delivery in comparison with controls.[3] As a result, the number of respirator-free days after ω-3 FA application increased and the length of hospital stay was shortened.

Effects of ω-3 FA on clinical outcome in patients with major abdominal surgery

It has been shown that even short-term parenteral nutrition with fish oil increased EPA and DHA in

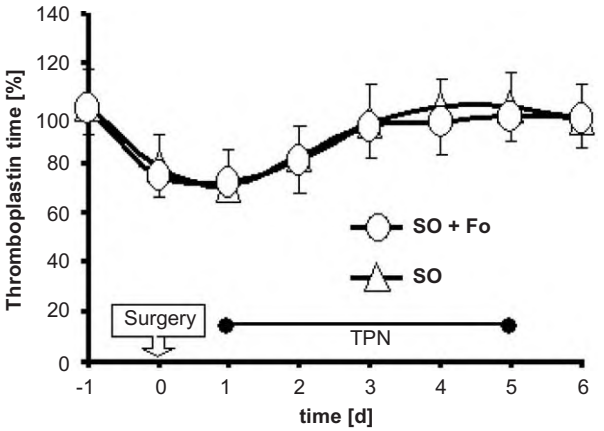

Figure 3 Thromboplastin time after major abdominal surgery followed by total parenteral nutrition (TPN) over 5 days, including soybean oil (Δ) or SO+fish oil (O). No statistically significant difference between groups could be detected. Other coagulation factors like activated partial thromboplastin time, fibrinogen and antithrombin, as well as factors VIIa and XII were also measured and showed a similar pattern (data not shown).[31]

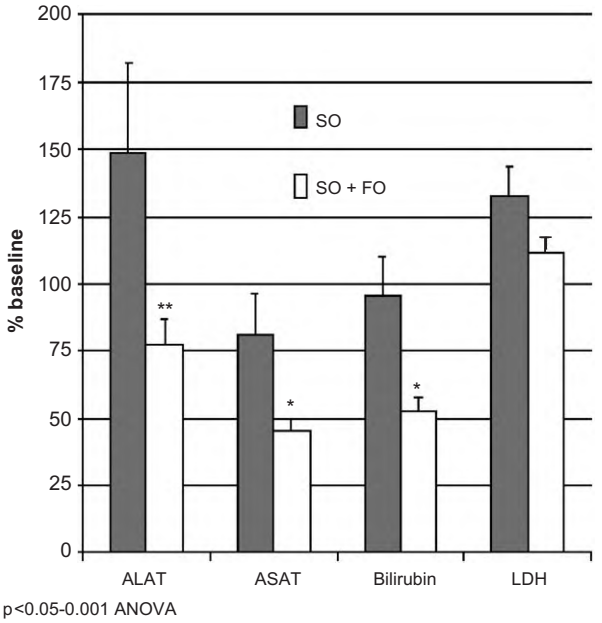

Figure 4 Compared to soybean oil (SO) treatment in the postoperative period, SO+fish oil (FO) significantly reduced ASAT, ALAT and bilirubin, at day 6 vs. baseline levels.*$P<0.05$ and **$P<0.001$.[32]

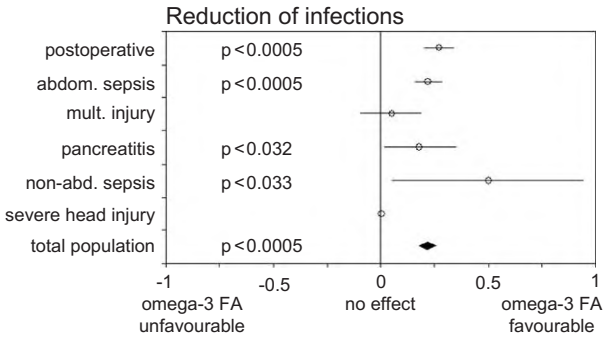

Figure 5 Effect of supplementation with ω-3 FA on the reduction of infections in subgroups with various diagnoses as judged by the attending physician. Mean and 95% confidence intervals.[33]

leukocyte[24] and platelet membrane phospholipids in postoperative patients[26] and during sepsis.[10] The decreased ratio of ω-6 to ω-3 FA in membrane phospholipids was associated with an altered lipid mediator and cytokine production. Fish oil-based parenteral nutrition in postoperative patients for 5 days reduced lipopolysaccharide (LPS) induced IL-1 release and thromboxane A_2 generation and was associated with a clinical reduction of sepsis incidence.[28] These results in surgical patients are in good agreement with those obtained from patients with active Crohn's disease[29] and cancer patients.[30]

In another study carried out by our group, including patients undergoing major surgery, cell-mediated immunity was less inhibited in the fish oil (Omegaven®, Fresenius Kabi)-treated group and importantly, coagulation and other platelet function were not negatively influenced by fish oil infusion[31] (Fig. 3). In addition, protective effects of ω-3 FA could be demonstrated by the recently published randomized controlled study in patients with gastrointestinal cancer undergoing major surgery which revealed an accelerated normalization of liver (Fig. 4) and pancreas enzymes after surgery in the group receiving parenteral fish oil (0.2 g/kg/day) and a trend toward shorter ICU stay in patients at risk for sepsis. In a subgroup of patients with risk for sepsis after gastrectomies and Whipple procedures, ICU stay was significantly reduced (fish oil group: 4.0 ± 0.3 vs. control: 5.3 ± 0.4 days).[32]

Further evidence of the protective effects of ω-3 FA was provided in a multivariable analysis of 661 patients receiving ω-3 FA in different amounts. Our group identified that the amount of infused ω-3 FA (Omegaven®, Fresenius Kabi) has a major impact on outcome. Depending on the dosage, the infection rate was significantly lower as expected (Fig. 5) which also applied for the subgroup of 233 postoperative surgical patients.[33] Patients who received at least 5% of the daily calorie intake as fish oil had a lower demand for antibiotics within the observation period. Postoperative patients were judged to have a shorter length of hospital

stay. Likewise, complications occurred rarer under fish oil supplementation as anticipated. Moreover, evaluation of the patient's clinical course was found more advantageous. Interestingly, the two mean factors contributing to the length of stay in a multifactor-regression model were the amount of ω-6 FA (+1.6 days /100 g of ω-6 FA) and the delay of nutrition (+1.42 days/day of delay). Further analysis of this cohort revealed distinct beneficial dose- and diagnosis-related effects of ω-3 FA on clinical outcome. ω-3 FA dose optimization around 0.15 g/kg/day significantly reduced ICU-stay from 8.7 to 5.3 days and hospital stay from 27.4 to 25.5 days, respectively. Based on these data parenteral nutrition with ω-3 FA can also be considered to be a cost-effective treatment. These results clearly demonstrate the clinically relevant beneficial effects of ω-3 FA on clinical outcome after major abdominal surgery.

Peritonitis and abdominal sepsis

Favorable effects of parenteral fish oil supplementation (Omegaven®, Fresenius Kabi) over 5 days have also been shown in a prospective randomized study including 54 patients with abdominal sepsis.[34] CRP-levels as an indicator of the inflammatory reaction were significantly lower, re-operation rates were found to be less and ICU, as well as hospital stay was significantly reduced in the fish oil group (Fig. 6).

These results agree well with data of the already mentioned trial with 661 patients including 268 patients with abdominal sepsis receiving parenteral fish oil (Omegaven®, Fresenius Kabi) who, likewise, had lower infection rates, and a reduced length of hospital stay.[35] Fish oil supplementation exerted dose-dependent beneficial effects on the observed outcome parameters. As compared to the subgroup receiving less than 0.05 g/kg/day of ω-3 FA significantly more patients survived, when 1.0–2.0 g/kg/day were administered. Further, doses exceeding 0.05 g/kg/day were sufficient to lower length of both, ICU and hospital stay (Fig. 7). The cause of such observations might be the lower requirement of antibiotic treatment, when ω-3 FA were given in daily doses between 0.15 and 0.2 g/kg.

As previously discussed, these observations are covered by recent literature[34,36] and agree with experimental data from Kelbel[18] and Pscheidl[20] who found improved bactericidal activity in ω-3-treated animals. The latter results were confirmed by Weiss et al.[19] in a double blind, controlled trial

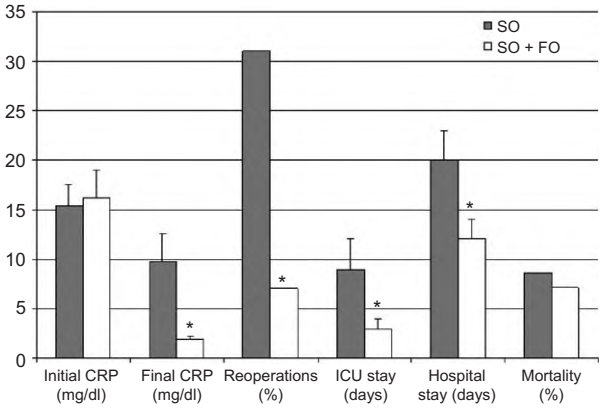

Figure 6 Fifty-four patients with sepsis from abdominal source (peritonitis, abscesses, postoperative fistulae) received for 5 postoperative days either a total parenteral nutrition with a soybean oil emulsion (SO) or a SO+fish oil emulsion (FO) up to a total of 1.4 g lipids/kg/day. No differences between groups were noticed in demographics, starting CRP and mortality. In the SO+FO group CRP levels on day 5 were significantly lower, patients needed less reoperations, had shorter ICU and hospital stay than in SO group. ($P<0.05$).[34]

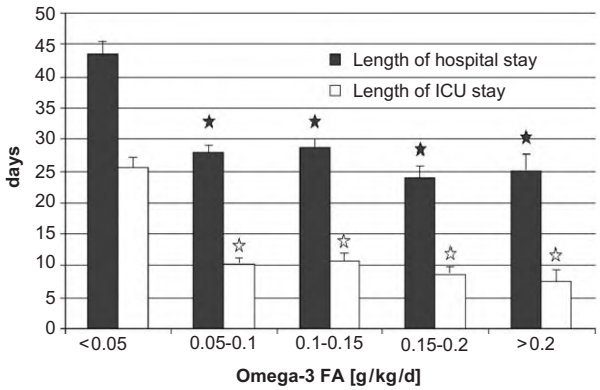

Figure 7 Dose related length of stay (mean and SD) in hospital (black columns), in ICU (white columns). Between-group comparisons are SAPS II and mortality adjusted in GLM-analysis ($P<0.001$). Post hoc Bonferroni adjusted: white asterisk ICU stay $P<0.001$ vs. dose lower than 0.05 g/kg/day; black asterisk hospital stay $P<0.001$ vs. dose lower than 0.05 g/kg/day.[33]

in postoperative patients. After perioperative administration of 10 g/kg/day of fish oil patients had less severe infections due to reduced immune suppression as evidenced by elevated HLA-DR-levels. In addition, a shorter ICU and hospital stays were observed in the fish oil group (17.8 vs. 23.5 days).

Taken together a number of current trials suggest beneficial effects of ω-3 FA in parenteral nutrition

on recovery and outcome in patients with severe surgical interventions and in the critically ill by lowering the magnitude of inflammatory response and improving host defense.

Advantages of perioperative supplementation of ω-3 FA

The hypothesis that preoperative administration of fish oil modulates postoperative hyperinflammation by increasing the content of ω-3 FA in the substrate pools prior to inflammatory stimulation and postoperative stress was addressed in several studies. Weiss et al.[19] were the first group investigating the effects of preoperative and postoperative administration of ω-3 FA on the magnitude of postoperative immune and inflammatory responses. For this purpose, 24 patients with elective major abdominal surgery were randomized into two groups receiving either: (1) 10 g of fish oil (Omegaven®, Fresenius Kabi) 2 days before and for 5 days after surgery within a standard volume and nutrition therapy; or (2) the standard therapy alone for 5 postoperative days. The results showed a down regulation of the inflammatory response, and simultaneously, a smaller postoperative immune suppression associated with less severe infections in the ω-3 FA-group. In addition, a shorter ICU and hospital stay was observed after perioperative fish oil supplementation. Recently, a similar concept was studied by Tsekos et al.[36] They analyzed the effects of routine peri- and postoperative parenteral application of fish oil supplement (Omegaven®, Fresenius Kabi) on patient outcome in a retrospective 2 year survey of ICU patients ($n = 256$) scheduled for major abdominal surgery. The results again clearly indicate that the novel concept of perioperative provision of parenteral fish oil (10 g/kg/day) beneficially influences patient outcome in terms of decreased requirement of postoperative mechanical ventilation, readmission to ICU, length of hospital stay and hospital mortality (Fig. 8).

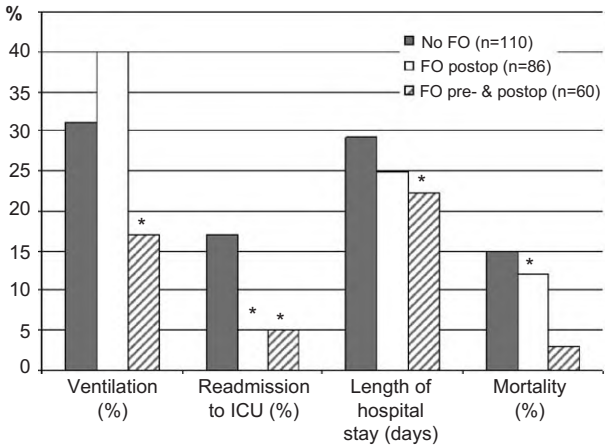

Figure 8 Retrospective evaluation of a 2-yr-longitudinal data base of ICU patients ($n = 256$) elected for major abdominal surgery. Group I ($n = 110$): postoperative standard parenteral nutrition (no FO); group II ($n = 86$): part of postoperative lipid emulsion replaced by fish oil (postop FO); group III ($n = 60$): in addition 2–3 days preoperative fish oil supplementation (pre-&postop FO). A decrease in the number of patients requiring mechanical ventilation, in readmission to ICU, length of hospital stay and mortality, was observed in group III compared to group I ($P < 0.05$).[36]

Conclusion

Increasing clinical data support the hypothesis that an optimal preoperative composition of cell membranes, before initiation of the inflammatory cascade, is more effective with respect to modulation of cytokine biology and patient recovery than mere postoperative nutrition therapy. Supplementation with ω-3 FA improves survival and accelerates recovery of the patients, even in critical illness. These effects were shown in different subpopulations to a variable extent. In accordance with most recent recommendations,[37,38] we found ω-3 FA to be a valuable nutritional additive for improved outcomes in patients with peritonitis, SIRS and sepsis.

In view of clinical consequences, the increasing body of literature on ω-3 FA points toward prophylactic and acute therapeutic effects in inflammatory diseases, which seem to be attainable by balanced arrangement of nutritional components including an increased share of ω-3 FA.

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