Pharmaconutrition with Omega-3 Fatty Acids: Status Quo and Further Perspectives

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Abstract: Beneficial rapid onset effects of omega-3 fatty acids from fish oil on host defense compensatory fit into the comprehensive pathophysiology of critical illness. Because of balanced pro- and anti-inflammatory effects on a variety of host defense subsystems even septic patients had earlier recovery and improved survival.

This review focuses in a compressed view on the beneficial aspects of omega-3 fatty acid supplementation on diverse organ functions, host defense and on balanced pro - and anti-inflammatory effects. Clinical impact of fish oil based pharmaconutrition during critical inflammation processes and immune response in humans is thoroughly discussed.

Key Words: Nutrition, fish oil, immunity, acute phase response, omega-3 fatty acids, intensive care medicine, critical illness, lung injury.

INTRODUCTION

Cellular lipid membranes represent a dynamic high turnover barrier system, which separate the intracellular from the extracellular space and easily adapt to respective demands. In addition to this barrier function membrane lipids can be oxygenized to biologically active lipid mediators (eicosanoids). These function as "local mediators" [1] due to their short half life and can quickly reach considerable concentrations in intercellular microenvironments.

Two omega-3 polyunsaturated fatty acids (omega-3 FA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are mainly found in maritime sources. Omega-6 polyunsaturated fatty acids on the opposite derive from terrestrial sources (the typical western diet). EPA (C20:5) and DHA (C22:6) can be found in a concentration of 0.1-1.2 % in deep-sea fish and therefore are the main omega-3 FA nutritional reservoir for humans (Fig. (**1**)). Biochemical pathways for omega-3 desaturation exist only in chloroplasts, so only algae and plankton are capable of forming those essential fatty acids. This is due to the inability of mammalian cells of introducing double bonds in positions prior to carbon 9 counting from the omega terminus. Direct consumption of deep-sea fish is a simple method of including omega-3 FA in a daily diet. The amount of omega-3 FA per 100g of fish varies between different fish species. Mackerels have the highest content of omega-3 FA with 2.2 g / 100 g body weight. In a normal diet and under physiological conditions the minimal requirement of omega-3 FA can be achieved by eating two meals of deep sea fish (each including 100-200g of fish) per week.

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CLINICAL IMPACT OF OMEGA 3 FATTY ACIDS

Epidemiological studies on omega-3 FA of the early seventies of the last century demonstrated cardiovascular beneficial effects among Inuit populations still consuming a traditional diet high in polyunsaturated omega-3 FA [2].

Diets enriched with omega-3 FA result in a change of the omega-3-/ omega-6- ratio in the membrane composition of multiple cells. In the field of clinical nutrition, however, one further step to improve outcome is including omega-3 FA in a concept of immunonutrition in critically ill patients [3, 4].

In contrast to numerous studies investigating the effects of long term (weeks to months) supplementation with omega-3 FA, more recent interest was focused on the question of whether or not omega-3 FA are integrated into the membrane lipid pool even after short-term intravenous infusion. Following major abdominal surgery we found that intravenous fish oil rapidly improved liver function [5] without untoward effects on platelet function and coagulation [6]. Moreover, omega-3 FA helped to maintain the balance between pro- and anti-inflammatory cytokines and, thus, prevented hyper-inflammatory complications. This was confirmed in 661 Patients who received a fish oil infusion [3]. Fish oil significantly lowered the occurrence of comorbid infection and improved survival. Similar observations were made in patients with sepsis [7] and acute respiratory distress [8, 9].

LIPID MEDIATORS AND THE PHYSIOLOGICAL INFLAMMATION PROCESS

Eicosanoids are "local mediators"[1]. They are generated in various tissues and cells e.g. lung, liver, kidney or neutrophils, and usually develop their effects at the site of production because of their short half-life due to quick enzymatic inactivation. Arachidonic acid (AA) is the mother substance of the pro-inflammatory eicosanoids. It is released from

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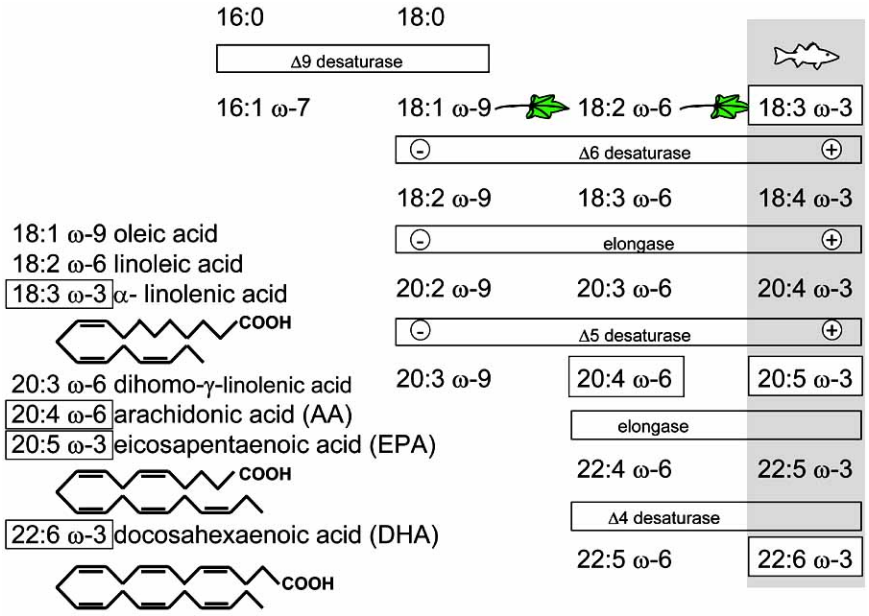

Fig. (1). Formation of polyunsaturated fatty acids in fish and plants. +/- represents substrate affinity of respective enzyme systems. Mammalians are unable to elongate ad desaturate higher degree unsaturated fatty acids to a relevant extent.

membrane phospholipids in the course of inflammation by phospholipases and is metabolized to prostaglandins, leukotrienes, lipoxins and resolvins (Fig. (**2**)).

Lipid mediators are a fundamental part of the complex processes leading to the main signs of inflammation. The inflammatory reaction is characterized by the stimulation of humoral and cellular mediator systems, which alter microvascular tone and permeability. Lipid mediators are essentially involved in the regulation of these complex actions. Prostaglandins such as PGE_2 and PGI_2 support the formation of an inflammatory edema, by their vasodilative properties, and produce pain at the site of inflammation. Fatty acid peroxides and leukotrienes additionally increase the local permeability of vessels and are potent chemoattractants for neutrophil granulocytes resulting in a further accumulation of phagocytes in the microcirculation at the site of action. Platelet activating factor is another important lipid mediator, which maintains inflammatory activity by stimulation of neutrophils [1] and, likewise, influences the vascular tone and permeability.

THE EICANOSOID PATHWAY

In case of inflammation membrane-linked phospholipase A_2 (PLA_2) mobilizes fatty acids, particularly AA from the lipid membrane. Omega-6 FA, such as linoleic acid (C18:2) and AA (C20:4) are found in plant oils and fatty tissues of mammalians, which represent the major part of FAs in the diet of industrial population. In individuals without relevant dietary intake of omega-3 FA, AA is predominantly released from the phospholipid pool of cellular membranes, which is metabolized by two major pathways to pro-inflammatory mediators [10].

The vaso- and bronchoconstrictive metabolites thromboxane A_2 (TXA_2) and prostaglandin (PG) $F_{2\alpha}$ are produced *via* the cyclooxygenase (COX) -pathway. The TXA_2 induced vaso- and bronchospasm predominates the relaxing effects of simultaneously generated prostacyclin (PGI_2) and PGE_2 on smooth muscle cells of vessels and bronchioli. The pattern of eicosanoids formed depends on the enzyme content of the particular cells [1]. While TXA_2 is produced mainly in platelets and macrophages, PGI_2 is derived from endothelial cells.

Besides the described COX- pathway, AA is also metabolized *via* the lipoxygenase (LOX)-pathway forming the leukotrienes (LTB_4, LTC_4, LTD_4, LTE_4) and other eicosanoids, which increase capillary permeability and attract neutrophils *via* chemotactic properties. LTB_4 is produced in neutrophils and macrophages, while eosinophils and mast cells form LTC_4, LTD_4 and LTE_4 [11].

EFFECTS OF OMEGA-3 FATTY ACIDS ON THE EICOSANOID PATHWAY

When cell membranes are loaded with omega-3 FA after fish oil diet or infusion, in case of inflammation EPA competes with AA for metabolisation *via* the COX- and LOX-pathway. The EPA- derived metabolites have lower biological activity [12], compared to the analogous AA-derivatives. While AA is metabolized by COX to diene prostanoids (prostaglandins and thromboxane) and by LOX to 4 series-leukotrienes (tetraenoic leukotrienes) and hydroxyeicosatetraenoic acids (HETE), EPA is converted to triene-prostanoids by COX (Fig. (**2**)). In comparison with the AA-derived TXA_2, the EPA-derived COX-product of the 3-series TXA_3 has considerably reduced pro-aggregatory and vasoconstrictive properties, while PGI_3 possesses similar antiaggregatory and vasodilative effects to PGI_2. Moreover, EPA represents a preferred substrate for the 5-LOX. After the enzymatic conversion of EPA, the 5-series leukotrienes (LTB_5, C_5, D_5, E_5) are generated, which have partially antagonistic biologic effects, compared to AA-derivatives. The vasoconstrictive and chemotactic potency of LTB_5 is two orders of magnitude lower than the activity of LTB_4 [13].

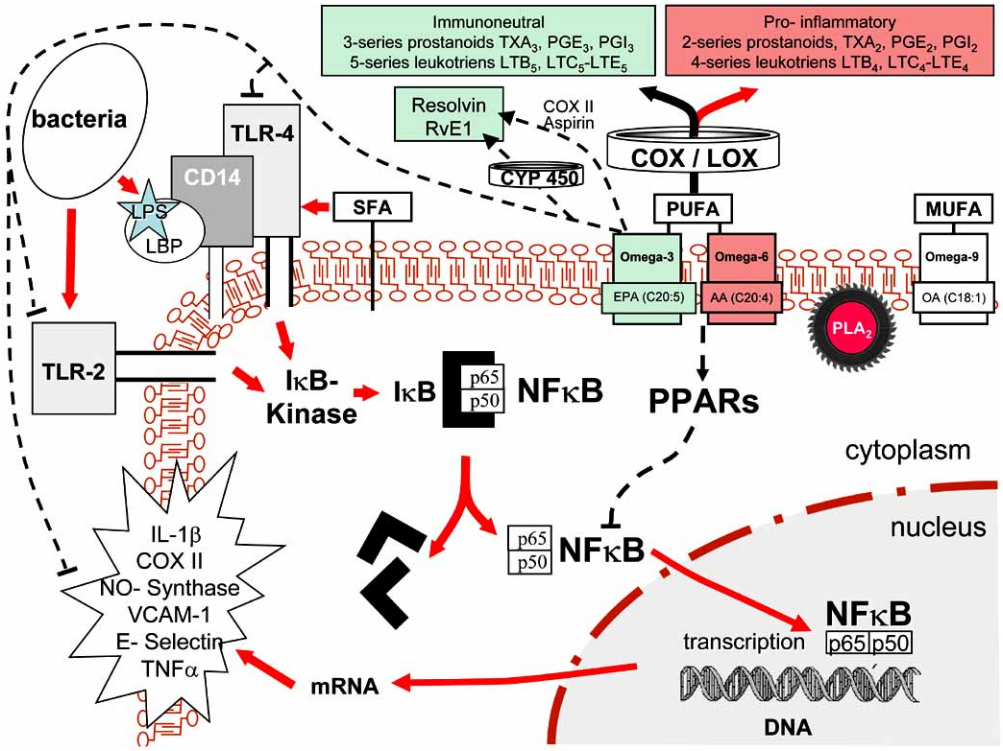

Fig. (2). Eicosanoid pathways and effects of omega 3 fatty acids on the toll like receptor (TLR)- nuclear factor kappa B (NFκB)- axis.

Depending on the fatty acid content of cellular membranes lipid mediators are generated from omega-3- or omega-6-polyunsatureated fatty acids (PUFA) *via* the cyclo- or lipoxygenase pathway. The arachidonic acid- (AA) metabolites leukotrienes (LT) and thromboxane (TX) A_2 with pro-inflammatory and eicosapentaenoic acid- (EPA) derivatives with reduced inflammatory properties. The mono unsaturated fatty acid (MUFA) oleic acid (OA) and saturated fatty acids (SFA) without relevant inflammatory mediator generation.

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; Omega-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).

More recently a class of lipid mediators derived from EPA has been described with anti- inflammatory activity [14] termed resolvins (resolution phase interaction products). These mediators have been detected in inflammatory models during the resolution phase of inflammation. Two pathways of resolvin generation were found so far. The first one is aspirin dependent. The presence of aspirin blocks COX I and to a slightly lesser extent COX II. Consequently, prostaglandin synthesis is inhibited and lipid mediatior synthesis is redirected to HETEs and lipoxin formation. Under additional neutrophil LOX-5 activity bioactive RvE_1 and 15-epi-LXA_5 are generated from EPA. Besides the aspirin COX II pathway RvE_1 can be generated independent from aspirin *via* a cytochrome P450 monooxygenase. RvE_1 has shown anti-inflammatory properties in various models of inflammation in a nanomolar range [15].

SIGNAL TRANSDUCTION EFFECTS OF OMEGA-3 FATTY ACIDS

While the impact of omega-3 FA on lipid mediator generation has been greatly clarified, up to now the understanding of subcellular effects, is limited. Omega-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 improvements of blood rheology after fish-oil intake. Furthermore, omega-3 FA modify receptor functions [16] membrane linked enzyme systems (Fig. (**2**)) as well as signal transduction [17] to the level of NFκB and beyond [18]. Recent work of Lee and coworkers demonstrated that activation of general pro-inflammatory pathways, such as NFκB and COX II expression by saturated fatty acids and inhibition of this induction by polyunsaturated fatty are mediated through a common signaling pathway derived from toll-like receptor (TLR)-4 [19]. 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 fatty acids. In addition, TLR-2 is activated by cell surface components by gram-positive bacteria.

As a result of down regulation of nuclear transcription factors formation of cytokines such as TNFα and IL-1 [20] in monocytes was reduced after fish-oil. Thus, omega-3-FA interfere with early inflammatory signal transduction and

prevent hyperinflammatory states. A large body of experimental data confirms that omega-3 FA attenuate overwhelming inflammatory reaction [21], ameliorate host defense [22], improve intestinal blood flow and gut barrier function [23] in septic states. These different biologic properties of omega-3 FA offer promising therapeutic potential in different diseases by supplementation nutrition with omega-3 FA even after short term administration [24].

IMMUNOLOGICAL ASPECTS OF OMEGA-3 FATTY ACIDS

The reaction of an immunologically active cell is not dependent on the concentration of a single mediator; rather a multitude of mediators and receptors as well as the interaction between cells determines the individual cellular reaction. Thus, therapeutic strategies aiming purely towards immune- augmentation bear the risk of additional tissue damage [25]. Anti-inflammatory interventions on the opposite depress host defense and pose the patient to immune compromise. Moreover, monocausal therapeutic interventions regardless of the direction (immunostimulating- or depressing) remain without effect [26, 27], considering the immunologic network transmitting inflammatory signals simultaneously and redundantly. Further, up-regulation of receptors enables signal transduction despite low concentration of stimulating mediators.

Through positive feed back loops inflammatory activation in host defense can induce hyperinflammatory states with subsequent severe tissue injury, culminating in multiple organ failure, in particular, when parallel anti- inflammatory control mechanisms are depressed. Omega-3 FA are capable of dampening early hyperinflammatory processes, by changing cell to cell signal transduction (Figs. (**2, 3**)). For ease of understanding Fig. **3** only differentiates the immunomodulatory effects of omega 3 FA on the pro- inflammatory side.

Other features of host defense, however, are enhanced by omega-3 fatty acids without inducing hyperinflammatory states. Moreover, the post- traumatic metabolism was improved [5], which may in part be explained by RvE_1 activity [15]. This complex regulation is conferred by reduced release of pro-inflammatory arachidonic acid- derivatives and PAF, on the other hand by the amplification of anti-inflammatory EPA-derivatives, which lower the formation of cytokines such as TNF and IL-1 [20], without inhibiting phagocytosis, burst activity or bactericidal activity [28]. The observed modulation by omega-3 FA -effects cannot unequivocally be assigned to the pro- or anti-inflammatory side. While pro- inflammatory eiccosanoids are down- regulated, cellular host defense mechanisms are augmented (Fig. (**3**)). In this context the dynamic time course of the inflammatory reaction has to be taken into account: the early phase (0-72 h) is characterized by the predominance of pro-inflammatory eicosanoids, cytokines TNFα, IL-1, IL-6, IL-8 and the in parts overlapping later phase by the predominance of anti-inflammatory cytokines IL-4, IL-10, IL-13 and TGFβ. This time course of cytokine production can differ in patients with recurrent septic episodes.

In this complex inflammatory environment success of future therapeutic strategies will depend on the prompt determination of the individual immune status and individual genetic disposition [29]. These factors will then determine the adequate interpretation of serum cytokine levels and goal directed inhibition or augmentation of cytokine cascades.

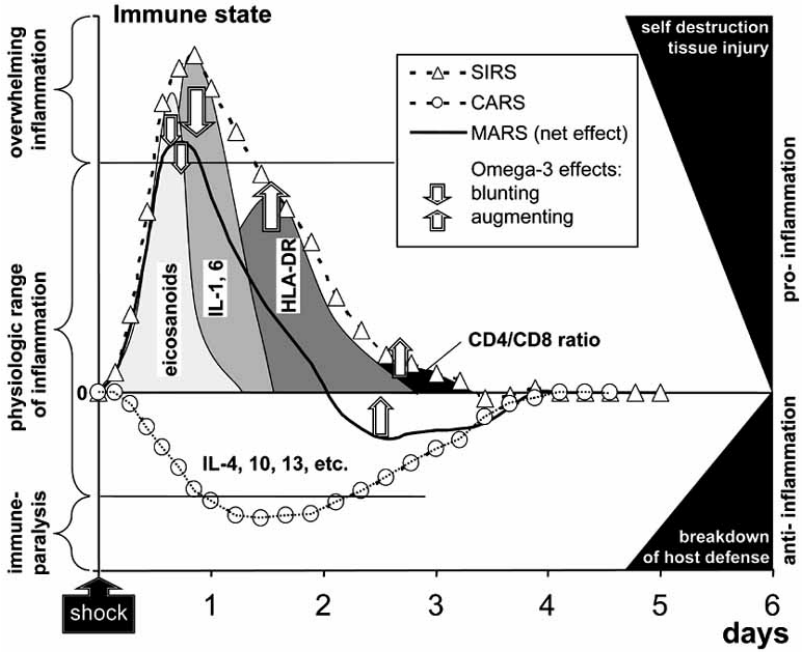

Fig. (3). Clinical targets of immunomodulation by omega-3 FA.

Overwhelming partial reactions are blunted (pro- inflammatory eicosanoids, interleukins), weak defense mechanisms are augmented (HLA-DR, CD4/ CD8-ratio). Systemic inflammatory reaction syndrome (SIRS), compensatory anti- inflammatory reaction (CARS), net immunreaction → mixed antagonistic reaction syndrome (MARS).

IMPACT OF OMEGA-3 FA ON CELLULAR IMMUNE RESPONSE IN HUMANS

Human clinical studies investigating the effects of lipid emulsions on leukocyte function are rare. In the last decade first studies describing beneficial effects of fish oil on the regulation of the cellular immune response were performed in chronic inflammatory diseases or autoimmune processes, such as ulcerative colitis [30], atopic dermatitis, or rheumatoid arthritis. Interestingly enough, these work focused on diseases in which the dysbalance of pro- and anti- inflammatory features is integral part of the respective pathomechanisms [31]. The observed clinical effects have been explained on mechanistic grounds of prostanoid and leukotriene antagonism. Clinical parameters such as morning stiffness or joint pain improved after doses of 2.6-8g omega-3-PUFAs per day. Doses of non steroidal antiphlogistics could be reduced or even abandoned [32]. Animal studies also revealed that fish oil has beneficial effects on nephritis, induced by lupus erythematosus. Proteinuria and histologic changes were markedly reduced, after omega-3-PUFA diet [33]. In acute, extended guttate psoriasis which is an inflammatory skin disease, characterized by an increased level of pro-inflammatory lipid mediators and cytokines, Grimminger and coworkers [34] showed a rapid improvement of clinical signs and changes in neutrophil leukotriene profile, as well as advances of the subjective patients assessment after intravenous application of 2.1g EPA and 21.0g DHA per day [35].

Further, the immuno- stimulating effect of omega-3 FA resulted in simultaneous increase of cytolytic T-lymphocytes, (CD56+3+), of antigen presenting T-lymphocytes (CD3+ HLADR+) and of B-lymphocytes after major abdominal surgery. Weiss and colleagues showed preservation of HLA-DR- positive cells [22] in postoperative patients receiving fish oil as opposed to soy bean oil. In the omega-6 group HLA-DR- positive cells significantly dropped. In this regard, omega-3 FA seem to preserve the cellular compensatory potential which is required to balance immune response.

Mayer and colleagues [24] observed a significant depression of bactericidal oxygen radical production in neutrophils after omega-6 FA as opposed to omega-3 FA in critical illness. Moreover, they presented data from monocytes of septic patients showing reduced levels of TNF alpha, IL-1, IL-6, and IL-8 due to fish oil administration, without effects on the anti-inflammatory IL-10 response [36]. Further, they demonstrated anti- inflammatory effects of fish oil, by showing endothelial monocyte rolling was induced by soy bean oil but not by fish oil, and omega-3 FA significantly reduced adherence and transmigration of monocytes [37]. These results are in line with preliminary data of clinical trials in which fish oil diets were shown to have restorative effects on the depressed cellular immunity and to improve the condition and survival of patients on intensive care units [38] in particular in progressed disease states.

Altogether the phagocytic response is one of the most complexly regulated systems within the mammalian organism. Multitudes of back coupling mechanisms are responsible for up-regulating the immune response and for subsequent shut down of hostile responses during recovery. Multiple anti- inflammatory strategies to cure sepsis of recent decades have failed. Lessons learned from those studies are that the complexly regulated host defense cannot be modulated by one simple anti- inflammatory approach, which on one hand may save the organism from self-destruction but on the other hand leads to further septic complications. Within this framework omega-3 FA seem to fulfill the role of modulators rather than the part of any pro- or anti- inflammatory player. It is just this fine balance of avoiding both, overwhelming inflammation and immuno-paralysis, which must be re-established to enable restoration of homeostasis and recovery. Through modulating effects on both the pro- and the anti- inflammatory players, omega-3 FA might serve to offset imbalances of the cellular immune response and, thus, enable rapid restoration of homeostasis and recovery.

INFLAMMATORY REACTIONS IN THE LUNG

The lung is subject to multiple threads during its physiological function, but in particular during infection an inflammation. The critical pulmonary air- blood interface must deal with a number of challenges. Firstly this interface must be kept tight towards both sides allowing diffusible gas exchange, but preventing air bubbles from entering the blood stream and vice versa preventing blood from entering the alveolar space. Further, the lung is the only organ receiving the complete cardiac output resulting in large blood volume flows per gram of tissue depending on the degree of body activity. Because of the limitations of lymph drainage transcapillary plasma leakage can critically increase, followed by lung edema. So, on account of its large alveolar and vascular surfaces a fine balance in vascular tone and mediator generation is required to preserve pulmonary (micro-) structure and function, in particular in critical illness.

In pulmonary circulation in particular, inflammatory activation of neutrophils induces interactions with the endothelium (selectins and β2-integrins) and release of pro-inflammatory arachidonic acid derivatives, which result in capillary damage, and consequently in increased leakage. These mechanisms are crucial pathogenic factors for the development of acute lung injury. The mortality of acute respiratory distress syndrome (ARDS) still remains high. In the last years numerous experimental and clinical studies were conducted to evaluate new therapeutic strategies in the treatment of ARDS. Adjuvant approaches such as monoclonal antibodies against pro-inflammatory cytokines and endotoxin have been tested succesfully in experimental studies yet did not show significant effects on patient outcome in clinical studies.

Administration of fish oil represents a promising adjuvant strategy because of its anti-inflammatory effects combined with a lower impairment of cellular immune function such as bacterial clearance and killing as compared to long chain omega-6 FA [23, 39]. Improvement of the critically ill was encouraging after replacing arachidonic acid in cellular membranes with long chain omega-3 FA such as eicosapentaenoic acid and docosahexaenoic acid contained in fish oil [40].

We used isolated perfused and ventilated rabbit lungs to assess short term inclusion into and rapid availability from the cellular phospholipid pool. In the first step we investi-

gated the lipid membrane composition by gas chromatography after short term infusion of omega-3 fatty acids [41]. Therefore, we induced a low level inflammatory reaction in isolated and perfused rabbit lungs stimulated by A_{23187} calciumionophore. A significant uptake of the omega-3 fatty acids EPA and DHA was observed after only three hours of lung perfusion with fish oil containing fatty acid emulsion compared to controls. Moreover, the pulmonary arterial pressure after inflammatory stimulation was considerably blunted during perfusion with omega-3 FA, and was associated with a 50% reduction of extravascular lung water [42].

These data correlated with the synthesis of EPA- derived cysteinyl-leukotrienes, while the AA- derived leukotrienes and thromboxanes were only detectable in small quantities. Compared to controls, treatment with omega-3 FA did not influence release of vasodilatory prostacyclin. These results suggest a relevant uptake of EPA into lung tissue after 3 hours of perfusion and metabolisation of EPA due to inflammatory activation.

The clinical impact of these findings [41, 42] were very well demonstrated in patients with lung failure by Gadek [8] and Singer [9]. Due to the improvement of pulmonary gas exchange lower inspiratory oxygen concentrations and lower levels of positive endexspiratory pressure were sufficient to assure adequate oxygen delivery to the tissues compared to controls. Mechanical ventilation and ICU stay was significantly shortened by fish oil application. Re- evaluation of the patients serum from the Gadek study [8] revealed reduced humoral host response in terms of IL-6, IL-8, TNFα, and LTB_4 and gave the biochemical and pathophysiological rationale for the clinical observed improvement of pulmonary condition [43] as postulated by our group from experimental studies earlier [41, 44].

In view of clinical consequences, these findings point toward prophylactic and therapeutic effects in inflammatory diseases and acute lung injury [45], which seem to be attainable by simple rearrangement of nutritional components. Finally, recent recommendations of the Canadian society for nutrition recognized the evidence based therapeutic value of omega-3 FA in acute respiratory distress [46].

OMEGA 3 FA AND LIVER FUNCTION

Following major abdominal surgery increases in liver transaminases were observed and correlated with ultrastructural damage of the liver [47]. In the postoperative course intact liver function is crucial not only for energy balance (glucose and lactate metabolism) but also for providing factors, which 1. induce, 2. support, and 3. ultimately terminate regenerative mechanisms. This acute-phase response (APR) of the liver sets off immediately after the (surgical) trauma and in first line, up-regulates coagulation factors and proteinase inhibitors for wound healing, and complement components and opsonins (C-reactive protein) for early bactericidal activity at the site of trauma. If properly regulated, APR is self-terminating upon completion of reparatory activity of the organism [48]. Under certain circumstances such as the systemic inflammatory response syndrome (SIRS) or sepsis APR may get out of control and may consequently damage host tissue by overwhelming activation [49, 50].

Poeze and colleagues demonstrated that increased transaminases and bilirubin precede the development of organ dysfunction after elective high-risk surgery [51] and hyperbilirubinaemia was associated with a two-fold duration of ICU-stay [52] and an increased incidence of complications after esophageal resection. Moreover, inadequate hyperactivation of the APR in patients with unresectable pancreatic cancer was associated with shorter time of survival.

In rats Pscheidl found improved perfusion and increased lactate clearance in the liver after omega-3 fatty acids [53]. In addition, this group provided evidence for enhanced hepatic immune competence in terms of bactericidal capacity after fish oil during endotoxemia [23]. Further, they demonstrated improved perfusion and fewer translocation of viable bacteria from the gut into mesenteric lymph nodes and the liver after omega-3 fatty acids [54]. Based on these data and on the notion that rapid effects of omega-3 fatty acids can be achieved within a few days, we hypothesized, that administration of a fish oil emulsion might improve liver function in patients undergoing surgical procedures for treatment of intestinal cancer. Fish oil administration resulted in a significantly better recovery of the liver enzymes ASAT and ALAT as well as of bilirubin and, thus, exhibited liver protective effects [5].

Similar effects were reported by Hwang and co-workers in septic mice, who found reduced liver enzymes and mortality after fish oil administration, which was attributed to down-regulation of hepatocellular apoptosis [55].

IMMUNONUTRITION/ PHARMACONUTRITION

Nutrition solutions enriched with immune enhancing substances that are termed immunonutrition or recently even pharmaconutrition. The strict separation between nutritive and pharmacotherapy therefore is increasingly disappearing. While aliments are considered as substances, which maintain nutritive or metabolic processes of the organism, drugs are chemical substances, which can improve a pathophysiological condition. Immune or pharmaconutrition decrease the incidence and extent of septic complications (i.e. multiorgan failure) by means of their dual function [56]. By reducing length of hospital stay and antibiotic therapy a net costs saving is possible despite higher expenditures for the substances themselves [56]. At present mixes of nucleotides, arginine and omega-3 fatty acids are commonly used. Since pharmaconutritients are important as membrane components and modulators of biochemical processes, the goal of an optimized nutritional therapy should be to combine pharmacological, energetic and essential features of different substrates in an optimal way. To evaluate the multitude of work on immunonutrition in the last years with distinct outcome in various patient subgroups [57] meta-analyses have been performed [4, 58]. As a matter of fact, utilizing such mixes does not allow the identification of the effects of the single components, complicating improvement of such solutions.

Definite recommendations regarding nutrition therapy were formulated by a consensus conference in May 2001, in which existing evidence for beneficial effects of immunonutrition and respective target groups was documented [56]. Backbone of these recommendations was the meta-analysis

done by Heyland and others who examined 326 studies with 2419 patients [4]. This analysis showed a slight, but non-significant reduction of mortality by immunonutrition. The risk of post-operative infectious complications was significantly lower in the immunonutrition group (RR 0.53; CI 95%: 0.42-0.68). The length of hospital stay was significantly reduced both for post-operative and critically ill patients by an average of 3.3 days. On the basis of this differentiated evaluation recommendations for immunonutrition were given (Gade A recommendations with level I evidence). Patients that definitely profit from immunonutrition therapy are therefore patients with elective gastro-intestinal, particularly with preexisting malnutrition (albumin < 35 g/l) and patients with multiple trauma and / or blunt or penetrating torso trauma (Injury severity score ≥ 18).

PERITONITIS AND ABDOMINAL SEPSIS

Despite data on ex vivo stimulated cells from septic patients receiving fish oil have been reported by Mayer and Grimminger [24, 36, 40] little information exist in literature regarding the effect of omega 3 FA in peritonitis and abdominal sepsis on clinical outcome. First randomized preliminary reports demonstrate favorable effects of omega-3 FA fish oil supplementation on survival in critically ill patients. Fish oil supplementation over 5 days in 54 patients with abdominal sepsis [59] reduced CRP-levels as indicator of the inflammatory reaction. Moreover, a lower re-operation rate was found and ICU- as well as hospital stay was significantly reduced in the fish oil group. Higher grade of evidence most recently was given by Pontes-Arruda in a prospective randomized clinical trial [7]. Significantly lower ventilatory support, lower ICU-stay and improved survival were found in septic patients after enteral omega-3 FA.

In addition, Tsekos retrospectively analyzed the effects of routine peri- and postoperative parenteral application of fish oil supplements on 249 ICU patients [60]. The results indicate that in particular the preoperative start of parenteral fish oil (10g/day) beneficially influences patient outcome in terms of decreased hospital mortality, requirement of post-operative mechanical ventilation and hospital stay. In a prospective, open label, multicenter trial in 661 patients receiving parenteral fish oil we evaluated survival, length of ICU-stay, hospital stay and use of antibiotics, with respect to the primary diagnosis and extent of organ dysfunction [3]. Compared to the subgroup receiving less than 0.05g/kg/d of fish oil significantly more patients survived when 0.1-0.2 g/kg/d were administered. This observation may be attributed to the lower requirement of antibiotic treatment, when fish oil was given in daily doses between 0.15 and 0.2 g/kg. Fig. (**4**) shows the relationship of fish oil dose and ICU stay in the subgroup of septic patients. The predicted mortality by the SAPS II- score was 21.7% The true mortality in this group, however, was substantially reduced in the dose-independent analysis (mean fish oil-dose 0.10 g/kg/d) by 7.4 % (CI_{95} 3.1-11.8). Optimized dosage was furthermore sufficient to reduce mortality by 16.0% (CI_{95} 5.8-26.2) in those patients. As

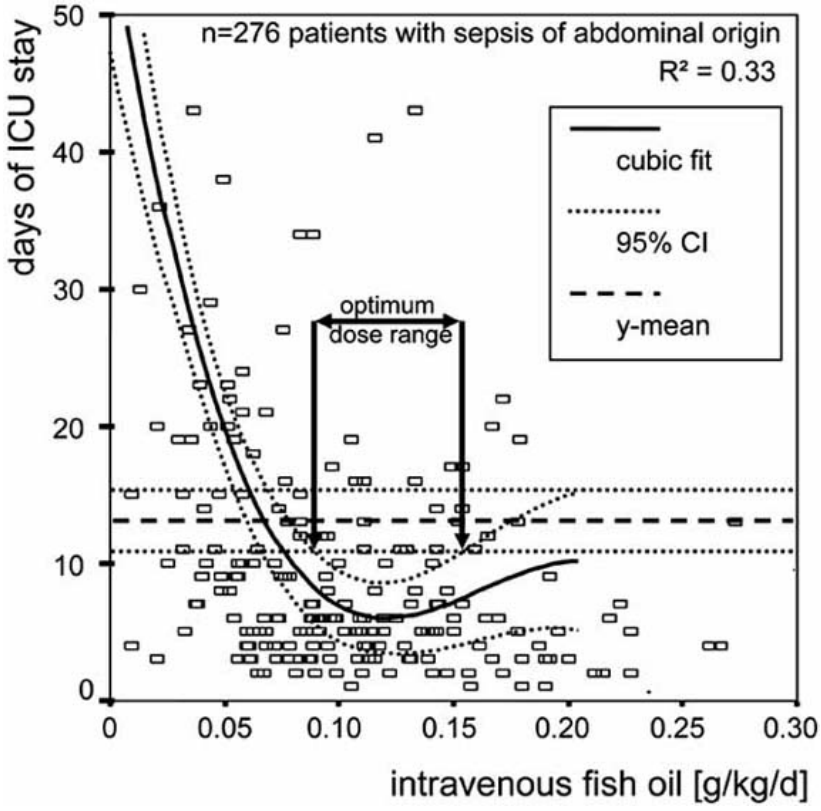

Fig. (4). Effects of fish oil dose variation on length of ICU stay in surviving patients with abdominal sepsis (bivariate analysis corrected for disease severity) [3]. Optimum dose range given for minimizing length of ICU stay in a cubic polynomial fit. Non survivors are not included due to their bias on length of stay. Dotted lines 95% confidence intervals.

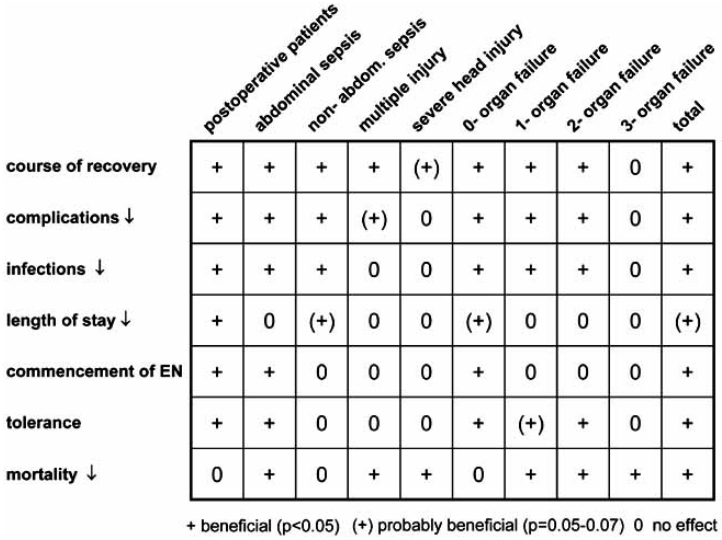

Fig. (5). Clinical effects of pharmaconutition with fish oil in different patients as assessed by attending physicians. + beneficial, (+) probably beneficial; 0 no effect. [3].

previously discussed, these observations are in accordance with recent published results [59, 60] and stand in line with experimental data by Kelbel [39] and Pscheidl [23] who found improved bactericidal activity in animals treated with omega-3 FA. The latter results were confirmed by Weiss in a randomized trial in postoperative patients [22]. After perioperative administration of 10g/d 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 stay was observed in the fish oil group.

OUTLOOK

Supplementation with omega-3 FA improves survival and accelerates recovery of the patients with diverse chronical and acute diseases states (Fig. (**5**)). These substantial effects were shown in different diseases to a variable extent. According to most recent recommendations [29, 46] we found omega-3 FA to be a valuable nutritional additive to improve outcome in patients with peritonitis, trauma, abdominal SIRS and sepsis, but also to reduce infections and complication rates in postoperative patients. Regarding the poor body of literature with respect to outcome data of single substrates such as omega-3 FA, further prospective randomized double-blinded trials are required to delineate the definite value of adjunctive therapy with omega-3 FA.

CONFLICTS OF INTEREST

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