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Invited critical review

Omega-3 fatty acid effects on biochemical indices following cancer surgery

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Contents

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1. Introduction

1.1. Omega-3 and omega-6 fatty acids

Maritime food sources include two omega-3 polyunsaturated fatty acids (omega-3 FA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as opposed to omega-6 polyunsaturated fatty acids (omega-6 FA) found in terrestrial sources (the typical Western diet). Deep-sea fish contain 0.1–1.2% omega-3 FA such as EPA (C20:5) and DHA (C22:5) [1] and therefore are the main omega-3 FA nutritional reservoir for humans. Historically, the intake of saturated FA and unsaturated omega-3 and omega-6 FA was approximately equal. Modern nutritional habits that emphasize industrially produced vegetable oils and animal fats have disturbed this balance, resulting in a proportional decrease of omega-3 FA intake [1]. Intensive research in recent years has broadened our understanding of omega-3 FA effects, uncovering for instance an omega-3 FA dependant formation of eicosanoids with immuno-modulatory characteristics.

When available, EPA is released from membrane sources in states of inflammation and competes with arachidonic acid (AA) for enzymatic metabolism resulting in a reduction of inflammatory and chemotactic derivatives. On the subcellular level, omega-3 FA modulate nuclear factor kappa-B derived upregulation of the acute phase response and, thus, prevent overshooting immune response. As a result, improved outcome after supplementation with omega-3 FA was observed in a broad range of diseases ranging from chronic disorders to cancer and critical patient conditions.

In contrast to numerous studies investigating the effects of long-term (weeks to months) supplementation with omega-3 FA, more recent interest has focused on the question of whether or not omega-3 FA are integrated into the membrane lipid pool even after short-term intravenous application. In a study of patients undergoing major abdominal surgery, incorporation of omega-3 FA was shown in liver and gut mucosa tissue as well as in tumor tissue after a five days of preoperative administration [2].

Following major abdominal surgery we found that short-term intravenous administration of omega-3 FA improved liver function without untoward effects on platelet function and coagulation. Moreover, omega-3 FA helped to maintain the balance of pro- and anti-inflammatory cytokines and thus prevented hyper-inflammatory complications. This was confirmed in 661 patients who received a fish oil infusion during peri-operative intensive care therapy. Fish oil significantly decreased the incidence of co-morbid infections. If at least 5% fish oil was included in daily alimentary intake, patients needed substantially less antibiotics and had shorter length of hospital stay. The two main factors contributing to the length of stay in a multifactor-regression model were the amount of omega-6 FA (+1.6 d/100 g) and the delay of nutrition onset (+1.42 d/day of delay) [3]. Subsequent in-depth diagnosis-related analysis of the same database showed that fish oil had the most favorable effects on survival, infection rates, and length of stay when administered in doses between 0.1 and 0.2 g/kg/day. Multiple quasi-linear regression models revealed that a fish oil dose of 0.23 g/kg/day reduced intensive care unit stay and showed that an inverse linear relationship exists between dosage and intensive care unit stay after major abdominal surgery [4].

In view of clinical consequences, these findings with FA supplementation show prophylactic benefit as well as mitigation of acute effects and were readily achieved by a simple rearrangement of nutritional components.

1.2. Lipid mediators

Lipid mediators are a fundamental part of the complex process leading to inflammation. The inflammatory reaction is characterized by the stimulation of humoral and cellular mediator systems and the release of a wide variety of inflammatory mediators that 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 inflammatory edema (tumor) by their vasodilative properties (rubor) and contribute to the development of hyperalgesia at the site of inflammation (dolor). FA peroxides and leukotrienes additionally increase local permeability and are potent chemoattractants for neutrophil granulocytes resulting in a further accumulation of phagocytes in the microcirculation at the site of action.

The precursors for all lipid mediators are FA as a part of cellular lipid membranes. It should be noted that a fundamental component of membrane lipids is AA, a four-fold polyunsaturated FA consisting of twenty carbon atoms.

1.3. Nomenclature

Unsaturated FA are divided into mono- and poly-unsaturated FA. Depending on the location of the first double bond (as determined from the methyl end of the polyunsaturated FA), these molecules are further classified as omega-3, omega-6 and omega-9 FA. Oleic acid (C18:1) is a mono-unsaturated FA which can be synthesized by mammalians, whereas omega-3 and omega-6 FA are essential for humans [5]. Omega-6 FA, such as linoleic acid (C18:2) and AA (C20:4), are found in plant oils and fatty tissues of mammalians and represent the

major part of FA in the diet of industrialized populations. 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 [6,7].

1.3.1. Pathways

The vaso- and broncho-constrictive metabolites thromboxane A_2 (TXA_2) and prostaglandin (PG) $F_{2\alpha}$ are produced via the cyclooxygenase-pathway. 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 that are produced depends on the enzyme content of the particular cells [6]. While TXA_2 is produced mainly in platelets and macrophages, PGI_2 is derived from endothelial cells. PGE_2 is chiefly synthesized in the renal medulla. Mast cells are the main source for PGD_2.

In addition, AA is also metabolized via the lipoxygenase-pathway resulting in leukotrienes (LTB_4, LTC_4, LTD_4, LTE_4) and other eicosanoids, which increase capillary permeability and attract neutrophils via chemotactic properties [6]. LTB_4 is produced in neutrophils and macrophages, while eosinophils and mast cells form LTC_4, LTD_4 and LTE_4 [8].

2. Omega-3 fatty acid effects

2.1. Effects on lipid mediators

If a cell membrane's lipid content of omega-3 FA is significant, EPA competes with AA for metabolization via the cyclo- and lipoxygenase pathway [9]. The EPA-derived metabolites have lower biological activity [10], compared to the analogous AA-derivatives. While AA is metabolized by cyclooxygenase to diene prostanoids (prostaglandins and thromboxane) and by lipoxygenase to 4 series-leukotrienes (tetraenoic leukotrienes) and hydroxyeicosatetraenoic acids (HETE), EPA is converted to triene-prostanoids by cyclooxygenase. In comparison with the AA-derived TXA_2, the EPA-derived cyclooxygenase product of the 3-series TXA_3 has considerably reduced pro-aggregatory and vasoconstrictive properties, while PGI_3 possesses similar anti-aggregatory and vasodilative effects as PGI_2. Moreover, EPA represents a preferred substrate for 5-lipoxygenase [11]. After enzymatic conversion of EPA, 5-series leukotrienes (LTB_5, C_5, D_5, E_5) are generated, which have partially antagonistic biologic effects, compared to AA-derivatives [12]. The vasoconstrictive and chemotactic potency of LTB_5 is two orders of magnitude lower than the activity of LTB_4 [13].

Depending on the enzyme pattern of the respective cell (e.g. thrombocytes, endothelial cells, leucocytes, etc.) these FA are turned into endoperoxides through the enzyme cyclooxygenase, from which prostaglandins, prostacyclins and thromboxanes are formed. The enzyme lipoxygenase creates hydroperoxides as a first step, which finally produce leukotrienes. The derivatives formed from EPA are different from the analogous AA derivatives in structure and biological activity [6].

2.2. Systemic effects

Besides affecting the lipid mediator formation, omega-3 FA are capable of altering cellular functions determined by physical characteristics of biomembranes, such as composition of phospholipids and cholesterol content [14]. Omega-3 FA modify the function of membrane-linked enzyme systems, signal transduction [15] and receptor function [16]. For humans it has been postulated that the release of interleukin 1 and TNF influenced by omega-3 FA could alter the virus replication rate of HIV [17]. Moreover it has been reported that the expression of certain oncogenes is modulated by omega-3 FA [18]. The anti-arteriosclerosis effects of omega-3 FA have been investigated intensively. Doses of 2–6 g/d omega-3 FA appear capable of lowering plasma triglyceride levels and increasing HDL in contrast to LDL and cholesterol that remain constant or even decrease slightly [19].

The correlation between high plasma lipid concentrations and development of arteriosclerosis is well known. It has been shown that fish-oil diets reduced intima hyperplasia [20] and coronary sclerosis [21]. In other patient studies, diets supplemented with omega-3 FA resulted in reduced rates of restenosis after percutanous transluminal coronary angioplasty (PTCA) [22]. Within the scope of diabetic vascular occlusive disease [23] and neuropathies [24], omega-3 FA showed protective vessel wall effects and an improvement of rheology [25]. These findings could be based on a reduced formation of platelet-derived growth factor (PDGF) from vascular endothelium after a diet with omega-3 FA [26], or increased release of "endothelium derived relaxing factor" nitric oxide (NO) [27]. NO in combination with vasodilative prostaglandins [28] supports the artery and resistance vessel smooth muscle relaxation.

3. Omega-3 fatty acids and cancer

3.1. Omega-3 fatty acid effects on cancer development

Epidemiological studies have indicated that a high intake of saturated fat and/or animal fat increases the risk of colon and breast cancer [29,30]. Certain polyunsaturated FA found in fish oil can inhibit the in vitro growth of a variety of human cancer cell lines [31]. Diets rich in omega-3 FA reduced the cancer risk of prostate, colorectal and breast cancer [29]. However, a meta-analysis over 38 prospective high quality cancer incidence studies found a large heterogeneity in reported outcome [32]. The authors of the meta-analysis concluded that little evidence exists to support omega-3 FA intake in reduced risk of cancer incidence [32]. While it is difficult to demonstrate prophylactic effects in large populations, therapeutic effects have been reported by different groups [29,33–35]. The mechanisms discussed for the prevention of tumor growth may also apply for metastatic or residual cancer cells. Thus, consumption of omega-3 FA offers a non-toxic way to augment cancer therapy, support chemotherapy and significantly increase life span.

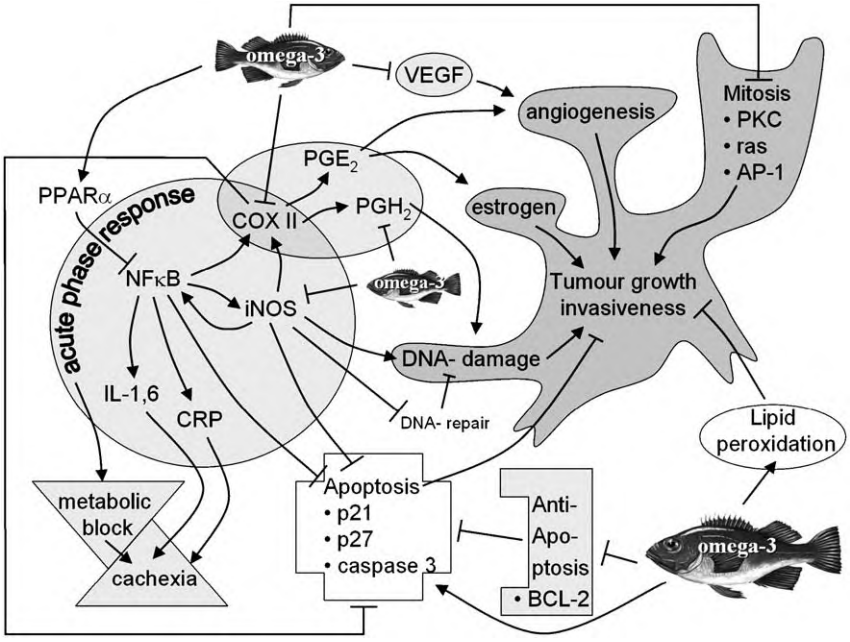

Fig. 1. Mechanisms of omega-3 FA action in tumor growth. Cyclooxygenase (COX) II and inducible NO synthase (iNOS) are key propagators of tumor development and inhibitors of tumoricidal activity. → favors activity; ⊥ blocks activity [1].

3.1.1. COX II

Cyclooxygenase (COX) II is increased in a variety of human cancers, including colon, breast, esophagus, hepatocellular, cervical, bladder, and pancreatic cancer and may suppress apoptosis. Observations, that the inhibition of COX II by NSAIDs prevents tumor growth [36], also support the concept of omega-3 FA administration. Omega-3 FA down-regulate COX II expression, alter its metabolites, and consequently avoid PGE_2-induced increase of estrogen in breast cancer and PGH_2 induced DNA damage. Those pathways have comparable metabolic endpoints as COX II inhibition by NSAIDs. As in all growth processes, cancer growth is dependent on substrates and therefore angiogenesis. Vascular endothelial growth factors promoting tumor angiogenesis are favored by omega-6 FA metabolites such as PGE_2. Omega 3 derivatives do not support VEGF release by PGE_2 (Fig. 1).

3.1.2. NO synthase

Inducible NO synthase is another central source of pro-inflammatory and carcinogenic signals and may potentiate inflammation as well as tumor growth, due to its influence on other cascade systems such as COX and nuclear factor (NF) kappa b [37]. Excessive secondary activation of mediator systems can be controlled by avoiding iNOS up-regulation by omega-3 FA.

3.1.3. NF kappa B

EPA increases the activity of peroxisome proliferator activated receptors (PPAR), which inhibit the transcriptional activity of NF kappa B, and therefore regulate tumor promoting hyper-inflammatory activity. Moreover, it has been suggested that EPA may stabilize the cytoplasmic NF kappa B/I kappa B-complex and, consequently, may influence pro-inflammatory cytokine production and inflammatory response [31,38]. In addition, NF kappa B activation may block apoptotic pathways. By way of inhibition of NF kappa B or of anti-apoptotic genes, such as *BCL-2*, omega-3 FA may conserve host-tumor-destructing apoptotic mechanisms, improving tumor defense as a consequence [39,40].

3.1.4. Mitosis

Laboratory experiments showed a reduced risk of chemically induced colon carcinogenesis after omega-3 FA supplementation. In a phase II clinical trial of patients with colonic polyps, dietary fish oil supplements inhibited cell proliferation. Mechanisms accounting for anti-tumor effects in animal models are reduced levels of PGE_2, and inducible NO synthase as well as an increased lipid peroxidation, or translation inhibition and subsequent cell cycle arrest [31]. While AA omega-6 FA derivatives increase mitosis and therefore may promote tumor growth, omega-3 FA decrease mitosis-stimulating protein kinase C and decrease the activity of the *ras* and AP-1 oncogenes. Likewise, dietary fish oil decreased the concentration of secondary bile acids that act as colon tumor promoters. In addition, Eitsuka et al. have reported that omega-3 FA inhibit telomerase activity through direct inhibition of enzymatic activity and down regulation of one of the telomerase components [41].

3.1.5. Cachexia

Whitehouse et al. provide further molecular insights into the mechanisms of EPA-derived prevention of tumor growth [42]. Soleus muscles from mice bearing a cachexia-inducing tumor (MAC16) showed increased in vitro protein degradation. EPA suppressed catabolism through inhibition of an ATP-dependent proteolytic pathway. Proteasome activity was

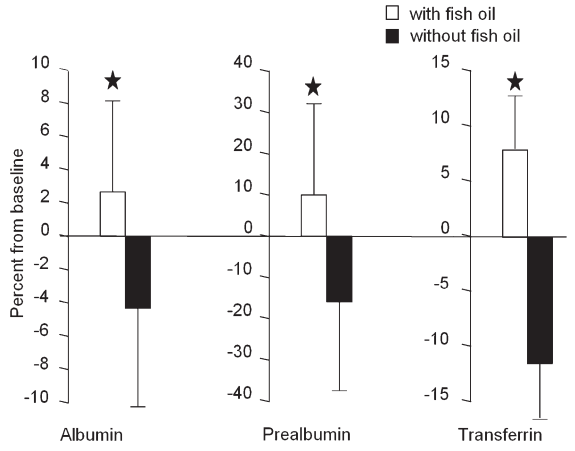

Fig. 2. Percentage changes in concentrations of acute phase proteins in patients with advanced pancreatic cancer and weight loss either with nutritional supplementation with enriched with fish oil or full supportive care [median and interquartile range]. The fish oil group received a daily dose of 2.18 g EPA and 0.92 g DHA for 24 d (*$p<0.05$ Mann–Whitney U test) [33].

completely suppressed, together with attenuation of the expression of 20S proteasome alpha-subunits and the p42 regulator, suggesting that EPA induces an attenuation of the proteasome expression up-regulation in cachectic mice, and this correlated with an increase in skeletal muscle protein expression (i.e. myosin).

Next to invasive or non-invasive tumor growth, weight loss is a major cause of morbidity and mortality in patients with advanced cancer. While it is possible to increase energy and protein intake via the enteral or parenteral route, this seems to have little impact on patients' progressive weight loss. This has led to the suggestion of a partial metabolic block to the accretion of lean tissue in patients with cancer [43], which may be due to pro-inflammatory cytokines, alterations in the balance of neuroendocrine hormones, and specific tumor-derived proteolytic and lipid-mobilizing factors. In recent years, several clinical studies have provided evidence for beneficial effects of fish oil administration in cancer cachexia and during radio- and chemotherapy. It has been suggested that EPA is capable of down-regulating the production and action of a number of mediators of cachexia, such as IL-1, IL-6, TNFα and proteolysis-inducing factor [38,44]. On the other hand soybean oil emulsions seem to impede tumoricidal activity as compared to EPA [45]. In a study comparing EPA and megestrol acetate supplementation in 412 patients with incurable malignancies (other than brain, breast, ovarian, prostate, or endometrial cancer) Jatoi et al. found no advantage of EPA versus

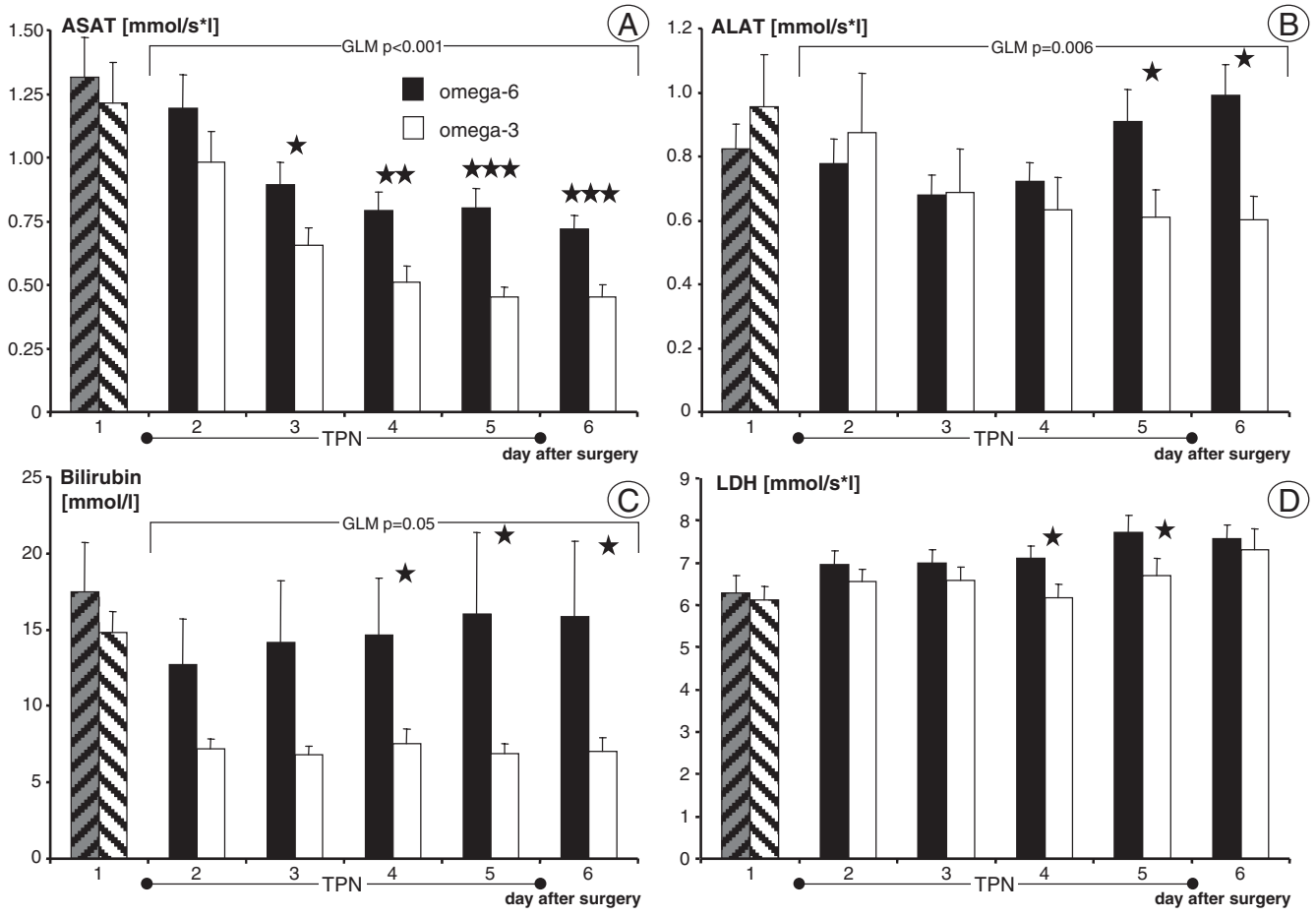

Fig. 3. (A) Aspartate aminotransferase (ASAT), (B) Alanine aminotransferase (ALAT) (C) Bilirubin (D) Lactate dehydrogenase (LDH) (means±SEM) after major abdominal cancer surgery followed by total parenteral nutrition (TPN) supplemented with soybean oil (omega-6, black columns) or with fish oil (omega-3, white columns) emulsions. *Post hoc* Bonferroni adjusted daily comparison: *$p<0.05$; **$p<0.01$; ***$p<0.001$; hatched columns baseline before TPN [66].

megestrol acetate [46]. EPA was less effective than megestrol acetate in causing a 10% weight gain above baseline, but was relatively comparable to MA with respect to appetite stimulation, survival, and quality of life [46]. Barber and co-workers have shown that a fish-oil-enriched nutritional supplement reverses weight loss in cachectic cancer patients [33]. Patients suffering from tumor cachexia in pancreatic cancer received a daily dose of 1.1 g EPA and weight loss of 2.9 kg per month was reversed by EPA. Not only that, but after seven weeks a weight gain of 2 kg was achieved. Moreover, improved activity of natural killer cells, lymphocyte proliferation and increases in CD4/CD8 ratio were observed after 1.8 g/d fish oil during radio-chemotherapy after esophagectomy [47]. Those effects were underscored by improvement of biochemical nutritional markers, as depicted in Fig. 2. In a randomized prospective double blind study Fearon et al. confirmed the positive effects of omega-3 FA on net gain of weight, lean tissue, and quality of life in patients with pancreatic cancer [48]. In a more recent study by the same group an 8-week oral application of protein dense oral supplement enriched with EPA in patients with pancreatic cancer led to an increase in physical activity and therefore possibly of quality of life [49].

3.2. Nutritional improvement of biochemical indices following cancer surgery

Following major abdominal non-liver surgery increases in ALAT were observed and correlated with ultra-structural damage of the liver [50]. In the postoperative course after major abdominal surgery, intact liver function is crucial not only for energy balance (glucose and lactate metabolism) but also for production of several humoral factors, which (a) induce, (b) support, and (c) ultimately terminate regenerative mechanisms. This acute-phase response (APR) of the liver begins immediately after (surgical) trauma and it primarily up-regulates coagulation factors and proteinase inhibitors for wound healing, complement components and opsonins (C-reactive protein) for early bactericidal activity at the site of trauma [51]. If properly regulated, APR is self-terminating upon completion of reparatory activity [52]. Under certain circumstances such as during systemic inflammatory response syndrome (SIRS) or sepsis APR may not terminate and consequently can damage host tissue by overwhelming activation [53].

Poeze and colleagues demonstrated that increased transaminases and bilirubin precede the development of organ dysfunction after elective high-risk surgery [54] and hyperbilirubinemia was associated with a two-fold increase in ICU-stay [55] and an increased incidence of complications after esophageal resection [56]. Moreover, inadequate hyperactivation of APR in patients with unresectable pancreatic cancer was associated with decreased survival [35].

After omega-3 FA, Pscheidl et al. found improved splanchnic perfusion and increased liver lactate clearance [57]. In addition, this group provided evidence for enhanced hepatic immune competence in terms of bactericidal capacity after fish oil during endotoxemia [58]. Based on these data and on the notion that rapid effects of omega-3 FAs 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 upper gastrointestinal cancer [59]. Early convalescence of liver function boosts host defense, the coagulation system and protein synthesis required for wound healing. Patient recovery, in particular in those patents at risk of postoperative SIRS should therefore be expedited. Individuals at risk were identified by calculation of the IL-6/IL-10 ratio on postoperative day 1. This ratio, reported by Taniguchi et al., reflects pro- and anti-inflammatory balance and shows good correlation with the incidence of septic complications [60].

Compared to single parenteral supplementation with soy oil, additional fish oil application resulted in a significant decrease of the liver enzymes aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) as well as of bilirubin over the whole observation period. Moreover, lactate dehydrogenase (LDH) was reduced on days 4 and 5 in the omega-3 FA group and, thus, exhibited liver protective effects (Fig. 3).

The liver enzymes ASAT and ALAT as well as their ratio significantly increased after surgery. Serum levels of ASAT might, thus, be confounded by surgery-associated tissue injury and may, therefore, not exclusively reflect the hepatic condition. With respect to type and duration of surgical procedure, tissue trauma was distributed homogeneously over both groups.

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 [61]. Regarding splanchnic vasculature, Pscheidl demonstrated improved perfusion and decreased translocation of viable bacteria from the gut into mesenteric lymph nodes and the liver after omega-3 FA intake [27], which are the two parallel ways of spreading local intestinal inflammatory reaction to the liver and the lung. Control of these mechanisms could have contributed to the beneficial effects on pancreas and liver after total parenteral nutrition was supplemented with fish oil.

One of the immuno-stimulant fish oil effects was the amplification of the “positive hepatic acute-phase response” [28], as measured by CRP and fibrinogen. This immune-augmentation could in part be correlated to improved liver function, reflected by lower transaminases bilirubin and LDH levels The increased hepatic production of proteins of humoral host defense or of coagulation factors [62] correlates with higher serum-levels of opsonizing CRP or fibrinogen. Conversely, a weakened acute-phase reaction after burn injury was associated with elevated mortality rates [63]. However, the issue of the acute phase response seems to be two-edged. The APR is, on one hand, a *conditio sine qua non* for initiating repair mechanisms in properly regulated inflammatory response, as observed in postoperative patients. If on the other hand an inadequately prolonged or overwhelming APR is present as e.g. in advanced sepsis [64] or in patients with tumor cachexia [65] the APR turns from friend into foe. The APR itself then becomes a part of the pathomechanism and may induce unfavorable outcome.

4. Conclusion

In the past decade a growing number of links have been established between inflammation, cancer and routine signal transduction research. A multitude of common pathways have been described which are normally fine-tuned, but may fail during cancer and severe inflammation. Feedback mechanisms are responsible for up-regulation and cessation of the immune response. One lesson learned from immune-depressant approaches is that the regulatory complexity of host defense cannot be modulated by one simple anti-inflammatory approach, which on the one hand may save the organism from self-destruction but on the other hand may lead to further complications. Within this framework omega-3 FA seem to take on the role of a modulator rather than the part of any specific pro- or anti-inflammatory player. It is this fine balance of avoiding both overwhelming response and immunodeficiency, which must be re-established to enable restoration of homeostasis. In this regard, omega-3 FA might serve to offset cellular immune response imbalances and support anticancer therapy.

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