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Angaben zur Veröffentlichung / Publication details:

Heller, Axel R., Thomas Rössel, Birgit Gottschlich, Oliver Tiebel, Mario Menschikowski, R. J. Litz, Thomas Zimmermann, and Thea Koch. 2004. "Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients: omega-3 fatty acid after cancer surgery." *International Journal of Cancer* 111 (4): 611–16. https://doi.org/10.1002/ijc.20291.

OMEGA-3 FATTY ACIDS IMPROVE LIVER AND PANCREAS FUNCTION IN POSTOPERATIVE CANCER PATIENTS

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Epidemiologic studies have indicated that high intake of saturated fat and/or animal fat increases the risk of colon and breast cancer. Omega-3 PUFAs in fish oil (FO) can inhibit the growth of human cancer cells *in vitro* and *in vivo*. These effects are related to the uptake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) into the cellular substrate pool and their competitive metabolism with arachidonic acid (AA) at the cyclooxygenase and 5-lipoxygenase levels. The metabolites of EPA and DHA have less inflammatory and immunosuppressant potency than the substances derived from AA. Based on previous experimental data, we hypothesized that FO supplementation after major abdominal cancer surgery would improve hepatic and pancreatic function. Ours was a prospective, randomized, double-blinded clinical trial on 44 patients undergoing elective major abdominal surgery, randomly assigned to receive total parenteral nutrition (TPN) supplemented with either soybean oil (SO 1.0 g/kg body weight daily, $n = 20$) for 5 days or a combination of FO and SO (FO 0.2 + SO 0.8 g/kg body weight daily, $n = 24$). Compared to pure SO supplementation in the postoperative period, FO significantly reduced ASAT [0.8 ± 0.1 *vs.* 0.5 ± 0.1 mmol/(l · sec)], ALAT [0.9 ± 0.1 *vs.* 0.6 ± 0.1 mmol/(l · sec)], bilirubin (16.1 ± 5.3 *vs.* 6.9 ± 0.6 mmol/l), LDH (7.7 ± 0.4 *vs.* 6.7 ± 0.4 mmol/(l · sec) and lipase (0.6 ± 0.1 *vs.* 0.4 ± 0.1 μmol/(l · sec) in the postoperative course. Moreover, patients with increased risk of sepsis (IL-6/IL-10 ratio >8) showed a tendency to shorter ICU stay (18 hr) under omega-3 PUFA treatment. Weight loss as encountered after the SO emulsion of 1.1 ± 2.2 kg was absent in the FO group. After major abdominal tumor surgery, FO supplementation improved liver and pancreas function, which might have contributed to the faster recovery of patients.

Key words: *omega-3 fatty acid; fish oil; soybean oil; immunonutrition; inflammation; acute-phase response; parenteral nutrition*

Epidemiologic studies have indicated that high intake of saturated fat and/or animal fat increases the risk of colon and breast cancers.[1] Further laboratory experiments showed reduced risk of colon carcinogenesis after omega-3 PUFA supplementation. In a phase II clinical trial of patients with colonic polyps, dietary FO supplements inhibited cell proliferation. Mechanisms accounting for the antitumour effects in animal models are reduced levels of PGE_2 and inducible NO synthase as well as increased lipid peroxidation or translation inhibition and subsequent cell-cycle arrest.[2]

In patients with advanced cancer, weight loss is a major cause of morbidity and mortality. While it is possible to increase energy and protein intake on the enteral or parenteral route, this appears to have little impact on patients' progressive weight loss.[3] Clinical studies in the last few years have provided evidence for beneficial effects of FO administration in cancer cachexia[4] and during radio- and chemotherapy.[5] Omega-3 EPA is capable of downregulating the production and action of a number of mediators of cachexia, *e.g.,* IL-1, IL-6, TNF-α and proteolysis-inducing factor.[6,7] However, SO (omega-6) emulsions appear to impede tumoricidal activity compared to EPA.[8]

Beyond the beneficial effects of long-term intake of omega-3 PUFA in cancer patients, we likewise observed rapid-onset effects in previous experimental studies. Compared to SO emulsion, we found decreased inflammatory pulmonary vascular response in isolated rabbit lungs after omega-3 PUFA infusion.[9] Lung edema formation was blunted because proinflammatory 4-series leukotrienes were shifted to less inflammatory 5-series leukotrienes and, consequently, pulmonary vascular resistance and permeability were reduced.[9] These rapid effects of omega-3 PUFA were confirmed in patients with acute respiratory distress syndrome, showing improved pulmonary function within a few days on an omega-3 fatty acid–enriched diet.[10] The background of these beneficial effects was reduced release of proinflammatory AA derivatives.[11]

Following major abdominal nonliver surgery, increases in ALAT were observed and correlated with ultrastructural damage of the liver.[12] 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 providing several humoral factors, which induce, support and ultimately terminate regenerative mechanisms. This APR of the liver sets off immediately after the (surgical) trauma and upregulates coagulation factors and proteinase inhibitors for wound healing and complement components and opsonins (e.g., CRP) for early bactericidal activity at the site of trauma.[13] If properly regulated, APR is self-terminating upon completion of reparatory activity of the organism.[14] Under certain circumstances, such as SIRS or sepsis, the APR may

Abbreviations: AA, arachidonic acid; ALAT, alanine aminotransferase; APR, acute-phase response; ASA, American Society of Anesthesiologists; ASAT, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; DHA, docosahexaenoic acid; EN, enteral nutrition; EPA, eicosapentaenoic acid; FO, fish oil; GLM, general linear model; ICU, intensive care unit; LDH, lactate dehydrogenase; PGE_2, prostaglandin E_2; PUFA, polyunsaturated fatty acid; SAPS, simplified acute physiology score; SIRS, systemic inflammatory response syndrome; SO, soybean oil; TNF, tumor necrosis factor; TPN, total parenteral nutrition.

Grant sponsor: Fresenius-Kabi.

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get out of control and consequently damage host tissue by overwhelming activation.[9,14,15]

Poeze *et al.*[16] demonstrated that increased transaminases and bilirubin precede the development of organ dysfunction after elective high-risk surgery, and hyperbilirubinemia has been associated with a 2-fold longer ICU stay[17] and increased incidence of complications after esophageal resection.[18] Moreover, inadequate hyperactivation of the APR in patients with unresectable pancreatic cancer was associated with shorter time of survival.[19]

After omega-3 fatty acid introduction, Pscheidl *et al.*[20] found improved splanchnic perfusion and increased lactate clearance in the liver. In addition, this group provided evidence for enhanced hepatic immune competence in terms of bactericidal capacity after FO supplementation during endotoxemia.[21] Furthermore, preliminary data of our group from 661 patients demonstrated the value of omega-3 fatty acids, particularly in postoperative patients, in terms of shorter hospital stay and lower infection and complication rates.[22]

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 FO emulsion might improve liver function in patients undergoing surgical procedures for treatment of upper gastrointestinal cancer. Secondary end points were the organ dysfunction score SAPS II[23] and the length of stay in the ICU and in hospital, as well as the body weight development of patients after surgery. Patients at risk for the development of SIRS in the postoperative course[24] were identified by calculation of the IL-6/IL-10 ratio on postoperative day 1.

MATERIAL AND METHODS

Patients

With institutional review board approval and the written, informed consent of patients, 44 patients suffering from carcinoma of the gastrointestinal tract or the pancreas were prospectively enrolled. Elective surgery (Table I) was performed between May 1999 and February 2000. Postoperatively, patients were observed for 5 days either in the 13-bed ICU of the Department of Anesthesiology or in the 16-bed ICU of the Department of Surgery. All patients received TPN for 5 days in a double-blinded manner. After inclusion in the study, patients were randomly assigned to receive TPN supplementation with either SO or SO + FO emulsion (Table II).

Exclusion criteria

Exclusion criteria were age <18 or >80 years, ASA status >3, BMI <16 or >30, hypertriglyceridemia, pregnancy, hyperthyroidism, chronic liver disease, pancreatitis, HIV infection, hepatitis, severe cardiac or renal disease or medication with insulin, corticoids, cytostatics or cyclooxygenase inhibitors.

Interventions

All patients received TPN for 5 days postoperatively, as shown in Table II, by an indwelling central venous 3 lumen catheter. Glucose (Glucosteril 40%; Fresenius-Kabi, Bad Homburg, Germany), amino acids (Aminosteril 10%, Fresenius-Kabi) and SO emulsion (Lipovenoes 10% PLR, Fresenius-Kabi) were provided to both groups by infusion pumps (Volumed μVP5000, Fresenius-Kabi). In the FO group, the omega-6 lipid content of TPN was partially replaced by omega-3 PUFAs (Omegaven, Fresenius-Kabi) up to 0.2 g/kg body weight daily, which is the maximum recommended daily dosage. Thus, in the FO group, the omega-3/omega-6 ratio was 1:4. Moreover, all patients daily received fat- (Vitalipid; Pharmacia, Erlangen, Germany) and water- (Soluvit, Pharmacia) soluble vitamins as well as trace elements (Addel N, Pharmacia). Calculated on body mass, the nutrition in both groups was isonitrogen, isocaloric.

Patients were assigned to the respective groups by computer-derived block randomization. The pharmacist was the only person aware of the randomization list. Accordingly, she prepared the solutions in the Central Pharmacy of the University Hospital for each individual patient. TPN was then delivered blinded (with patient identification) to the ICUs and further handled by a nurse who was unaware of the study protocol. The investigators were, thus, blinded to the infused drug. On postoperative day 1, baseline values were obtained before TPN was started (8:00 A.M.).

TABLE I – DEMOGRAPHIC CHARACTERISTICS (MEAN ± SD)

Group	SO (n = 20)	SO + FO (n = 24)	p
Age (years)	60.8 ± 10.9	61.0 ± 12.6	0.96
Gender (male/female)	14/6	18/6	1.00
SAPS II at entry	12.0 ± 5.2	12.4 ± 5.2	0.80
BMI	24.5 ± 4.1	25.2 ± 4.4	0.56
Surgery (min)	346 ± 77	349 ± 76	0.91
Surgical procedure			0.74
Esophagectomy	3	4	
Gastrectomy	8	10	
Whipple procedure	8	10	
Total colectomy	1	0	

Blood samples

For laboratory measurements, 15 ml of whole blood (10 ml serum, 3 ml EDTA, 2 ml citrated) were withdrawn from an arterial line daily at 8:00 A.M. Analysis of liver and pancreatic enzymes was immediately performed. Serum vials for analysis of cytokines were separated and kept deep-frozen at −80°C until measurement.

Routine laboratory parameters and reference values

The parameters ALAT [<0.67 mmol/(l · sec)], ASAT [<0.62 mmol/(l · sec)], bilirubin (<17 mmol/l), LDH [3.87.7 mmol/(l · sec)], α-amylase (<100 U/l), lipase [0.1–1.0 μmol/(l · sec)], CRP (<5 mg/l), procalcitonin (<0.5 ng/ml) and fibrinogen (1.5–4.5 g/l) were quantified in the Department of Clinical Chemistry, University Hospital of Dresden (Dresden, Germany) according to standard procedures.

Enzyme immunoassays

For quantitative detection of IL-6 and IL-10, enzyme immunoassays were performed with the double-sandwich technique according to the manufacturer's instructions by the hormone laboratory of the Department of Clinical Chemistry. Sample concentrations were measured with a microplate reader (MR5000; Dynatech, Denkendorf, Germany) at wavelengths between 405 and 490 nm. Sensitivity of the tests (R&D Systems, Wiesbaden, Germany) were IL-6 <0.7 pg/ml and IL-10 <3.9 pg/ml.

Monitoring of hemodynamics and fluid balance

During ICU stay, patients were continuously monitored by ECG, invasive blood pressure and pulse oximetry (M1165A/M1092A; Hewlett-Packard, Böblingen, Germany). Central venous pressure was measured intermittently by an indwelling central venous catheter. Total urine volume was collected daily for measurements of fluid and nitrogen balance as well as creatinine clearance.

Criteria for transfer from ICU to peripheral surgical ward

The necessity of ICU stay was defined by intensive care–experienced physicians (B.G., T.Z.). When the following criteria were fulfilled, patients were transferred to peripheral surgical wards: no evidence of anastomosis leakage or wound dehiscence, stable hemodynamics without catecholamines, no signs of SIRS or sepsis[25] spontaneous breathing and adequate gas exchange, no requirement of invasive monitoring, urine output >50 ml/hr, stable coagulatory and neurologic state, sufficient pain therapy.

Statistics

The impact of the type of fatty acids in parenteral nutrition on serum levels of liver aminotransferases was the primary end point of our study. Secondary end points were the organ dysfunction

TABLE II – REGIMEN OF DAILY TPN IN THE SO AND THE SO+FO GROUPS

Day	Both groups		SO lipids (Lipovenoes 10% PLR)	SO + FO lipids (Lipovenoes 10% PLR, Omegaven 10%)
	Glucose (Glucosteril 40%)	Amino acids (Aminosteril KE 10)		
1	2.0 g/kg	0.5 g/kg	0.8 g SO/kg	0.64 g SO/kg + 0.16 g FO/kg
2–5	3.0 g/kg	1.2 g/kg	1.0 g SO/kg	0.8 g SO/kg + 0.2 g FO/kg

score SAPS II[23] and the length of stay in the ICU and in hospital, as well as the lean body mass development of the patient after surgery. Patients at risk for the development of SIRS in the postoperative course[24] were identified by calculating the IL-6/IL-10 ratio on the first day after surgery.

Assuming a 2-sided type I error of 5% and a power of 80%, we calculated that a sample size of 20 patients in both groups was required to permit detection of a 25% reduction of ASAT.

Data are presented as arithmetic means ± SEM. Repeated-measurement analysis within and between groups was achieved with GLM according to 2-way ANOVA. Correction for *post hoc* multiple comparisons was performed according to Bonferroni. Baseline values obtained before onset of parenteral nutrition (day 1) were considered as individual covariates during statistical analysis. Analysis was performed using SPSS software (release 10.0.7; SPSS, Chicago, IL).

RESULTS

Clinical characteristics of patients

Data of all randomized patients were eligible for statistical analysis. Demographic characteristics of the patients concerning age, gender, SAPS II[23] at entry, BMI and surgical procedures are summarized in Table I. There were no significant differences between groups at entry.

General data

All patients were weaned from mechanical ventilation in the operating room and transferred to the ICU spontaneously breathing. The body mass–adjusted nutritional goal of TPN (according to Table II) was met in all cases. The surgical procedure temporarily worsened the acute physiologic status ($p < 0.001$) on the first postoperative day compared to the preoperative condition (SAPS II score preoperative 12 ± 5 points *vs.* postoperative 17 ± 6 points). During the 5 days of parenteral nutrition, no significant differences were observed between groups. After 5 days of supplementation, SAPS II was 15 ± 6 in the SO group and 14 ± 7 in the SO+FO group. Accordingly, there was no statistical difference in either length of ICU stay (Fig. 1) or length of hospital stay (SO 18.8 ± 8.4 days, SO+FO 19.1 ± 9.6 days). In the subgroup of patients at risk of sepsis (IL-6/IL-10 ratio ≥8), a tendency for a shorter ICU stay was observed ($p = 0.065$) after FO supplementation (Fig. 1), but length of hospital stay did not differ (SO 17.4 ± 2.2 days, SO+FO 19.3 ± 3.5 days). Exclusive analysis of patients at risk for sepsis after gastrectomies and Whipple procedures ($n = 19$) revealed a shorter ICU stay after FO (SO 5.3 ± 0.4 days, SO+FO 4.0 ± 0.3 days; $p = 0.01$). Administration of SO alone was associated with weight loss over the hospital stay of 1.1 ± 2.2 kg (SO+FO 0.0 ± 2.9 kg), which did not reach statistical significance. Cumulative nitrogen balance over 5 days was not influenced by the type of lipid emulsion.

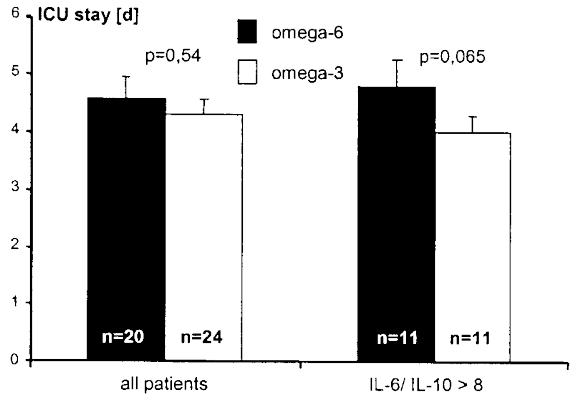

FIGURE 1 – Stay in ICU (mean ± SEM) after major abdominal cancer surgery followed by TPN supplemented with SO (omega-6, solid bars) or FO (omega-3, open bars) emulsion.

Complications were comparably low in both groups. Follow-up data at 18 months did not show any difference in quality of life, health status or mortality between the groups.

Liver and pancreas parameters

Compared to single parenteral supplementation with SO, additional FO application resulted in a significant decrease of the liver enzymes ASAT ($p = 0.001$, Fig. 2) and ALAT ($p = 0.04$) as well as of bilirubin ($p = 0.04$) over the whole observation period. Parameters on postoperative day 5 were ASAT [SO 0.8 ± 0.1 *vs.* SO+FO 0.5 ± 0.1 mmol/(l · sec)], ALAT [SO 0.9 ± 0.1 *vs.* SO+FO 0.6 ± 0.1 mmol/(l · sec)] and bilirubin (SO 16.1 ± 5.3 *vs.* SO+FO 6.9 ± 0.6 mmol/l). Moreover, LDH was reduced ($p < 0.05$) on days 4 and 5 in the SO+FO group [day 5 SO 7.7 ± 0.4 *vs.* SO+FO 6.7 ± 0.4 mmol/(l · sec)].

While levels of α-amylase did not change due to FO administration and regained normal values on day 6 (SO 91 ± 92 *vs.* SO+FO 78 ± 78 U/l), serum concentrations of lipase were significantly lower ($p = 0.04$) after FO supplementation [Fig. 3, day 5 SO 0.6 ± 0.1 *vs.* SO+FO 0.4 ± 0.1 umol/(l · sec)].

Gastrointestinal tract

Parameters of gastrointestinal function were the appearance of bowel sounds (SO 2.4 ± 0.3 days *vs.* SO+FO 2.3 ± 0.3 days), bowel movement (both groups 3.1 ± 0.3 days) as well as the possibility of starting enteral feeding (SO 4.3 ± 0.2 days *vs.* SO+FO 4.7 ± 0.3 days). Considering these variables, no between-group differences were observed.

Inflammatory parameters

Acute-phase parameters are shown in Table III. White blood cell counts as well as body temperature did not differ between the SO and SO+FO groups. Procalcitonin decreased during the postoperative period. No differences between the groups corresponding to the low and comparable need of antibiotics were found.

DISCUSSION

During the past decades, intensive collaborative work has been done in linking research activities in the fields of cancer, immunology and inflammation. These activities resulted in a better understanding of the pathophysiology and diagnosis of these diseases. In the early phase of inflammation, interleukins and lipid mediators are excessively released and play a crucial role in host defense; however, they are also involved in the pathogenesis of organ dysfunction.[9,13] AA is the precursor of the proinflammatory eicosanoids and is released from membrane phospholipids in the course of inflammatory activation and subsequently metabolized to prostaglandins and leukotrienes.[9] Various strategies have been evaluated to control the excessive production of lipid mediators,

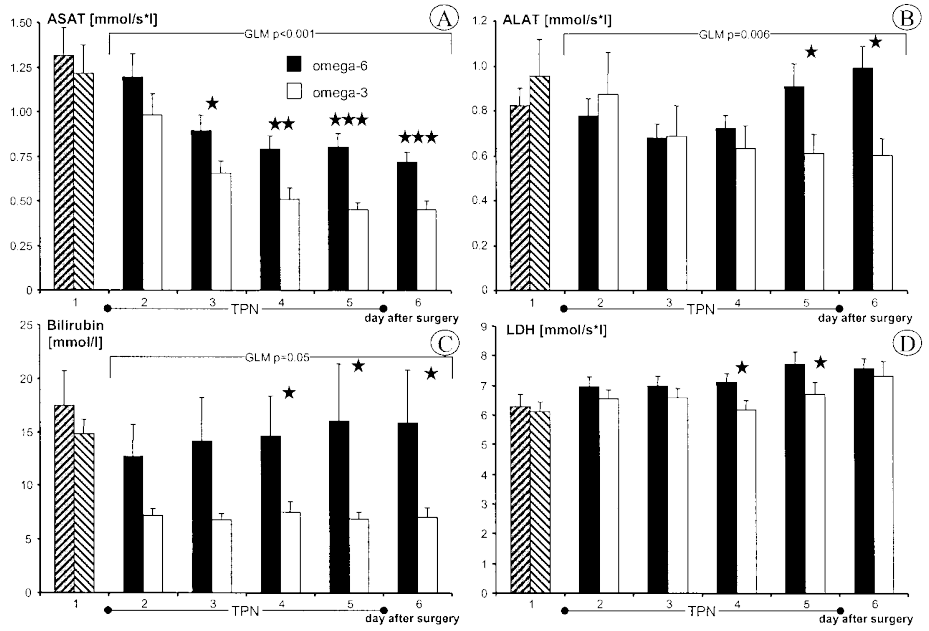

Figure 2 – *(a)* ASAT, *(b)* ALAT, *(c)* bilirubin and *(d)* LDH (means ± SEM) after major abdominal cancer surgery followed by TPN supplemented with SO (omega-6, solid bars) or FO (omega-3, open bars) emulsion. *Post hoc* Bonferroni adjusted daily comparison. $*p < 0.05$, $**p < 0.01$ and $***p < 0.001$; hatched columns, baseline before TPN.

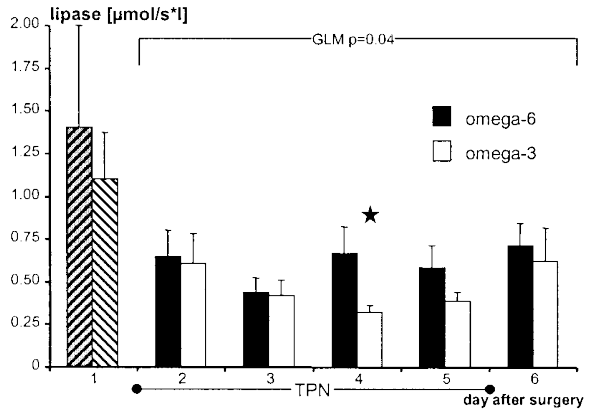

Figure 3 – Lipase (mean ± SEM) after major abdominal cancer surgery followed by TPN supplemented with SO (omega-6, solid bars) or FO (omega-3, open bars) emulsion. *Post hoc* Bonferroni adjusted daily comparison. $*p < 0.05$; hatched columns, baseline before TPN.

such as inhibition of phospholipase A_2, the enzyme catalyzing AA release; blockade of cyclooxygenase and lipoxygenase enzymes; as well as development of receptor antagonists against platelet-activating factor and leukotrienes.[9] However, the reactions of effector cells are not determined by the concentration of a single cytokine or acute-phase reactant but by an array of mediators in concert.[13] Accordingly, monocausal therapeutic interventions could remain without effect if inflammatory signals are transmitted simultaneously and blocked pathways are bypassed or upregulation of corresponding receptors enables signal transduction despite low signal density.[13] For beneficial modulation of immunologic reactions, it appears essential to use substances such as FO, which affect not only one target but a minimum array of signals.[9] Keeping in mind that therapies purely based on immunostimulants are associated with the danger of additional tissue damage[26] and that anti-inflammatory interventions might negatively influence host defense,[15] omega-3 fatty acids could improve the condition of patients during postaggression metabolism after major abdominal surgery.[9]

Besides beneficial effects of long-term intake of omega-3 fatty acid on the development of cancer and cardiovascular disease, encouraging results were obtained in critically ill patients by supplementation with long chain n-3 fatty acids.[10] Because n-3 PUFAs containing lipid emulsions are now available for i.v. administration to humans, the current study was designed to address effects on liver and pancreas during the maximum recommended FO dosage (0.2 g/kg daily) after major abdominal tumor surgery.

Concerning demographic data at study entry, both groups were comparable (Table I). As expected, the operative trauma had a major influence on the various parameters measured as well as on the patients' acute physiologic condition as assessed by SAPS II. Regarding reference values (see Material and Methods), the function of the liver and pancreas was affected in particular (Figs. 2, 3).

From the first postoperative day until day 5, patients in both groups received TPN, which was individually body weight–adapted, isocaloric and isonitrogenic (Table II). Regarding the type of administered fatty acid, the length of neither the ICU stay nor the in-hospital stay changed in the whole study population. In those at risk for sepsis (IL-6/IL-10 ratio >8 at day 1[24]), there was a tendency to reduced ICU stay by 0.8 days after FO+SO, which gained statistical significance when the analysis was restricted to patients with gastrectomies and Whipple procedures (–1.3 ± 0.5 days, $p = 0.02$).

In addition, weight loss of 1.1 kg was found after SO, which was completely abolished in the FO+SO group. Despite a 0.5 l lower cumulative ICU fluid balance after FO+SO, the difference in ICU weight loss was not significant. Similar improvements in the nutritional state in cachectic cancer patients receiving omega-3 PUFAs were reported by Barber *et al.*[4] Weight loss at baseline of 2.9 kg/month was reversed by omega-3 PUFAs. Even weight gain at both 3 (median 1 kg) and 7 (median 2 kg) weeks was achieved. Moreover, dietary intake increased significantly by almost 400 kcal/day. In a former study of this group, parameters of inflammation state were significantly reduced after FO.[27]

TABLE III – APR (MEAN ± SD) AFTER MAJOR ABDOMINAL SURGERY, BEFORE AND AFTER 5 DAYS OF PARENTERAL SUPPLEMENTATION OF SO OR SO + FO

	Day 1 (baseline)		Day 6		GLM p
	SO	SO + FO	SO	SO + FO	
Body temperature (°C)	37.0 ± 0.4	37.0 ± 0.6	36.5 ± 0.4	36.6 ± 0.5	0.92*
White blood cells (GPt/l)	13.6 ± 4.6	11.9 ± 4.8	11.4 ± 4.9	12.0 ± 5.9	0.45
CRP (mg/l)	9 ± 13	9 ± 10	64 ± 45	89 ± 64	0.06
Fibrinogen (g/l)	3.1 ± 0.7	3.1 ± 0.7	5.5 ± 1.3	6.2 ± 1.7	0.32
Procalcitonin (ng/ml)	0.8 ± 0.7	0.8 ± 0.9	0.2 ± 0.6	0.2 ± 0.2	0.76

*Subgroup analysis of patients at risk for sepsis undergoing Whipple procedure or gastrectomy (IL6/IL10 > 8, $n = 19$) showed reduced mean body temperature during ICU stay under FO (SO 36.9 ± 0.3°C *vs.* SO+FO 36.6 ± 0.3°C, $p = 0.05$).

Molecular insights into the mechanisms of EPA-derived prevention of tumor growth are provided by Whitehouse *et al.*[28] Soleus muscles from mice bearing a cachexia-inducing tumor (MAC16) showed increased protein degradation *in vitro.* EPA suppressed catabolism through inhibition of an ATP-dependent proteolytic pathway. Proteasome activity was completely suppressed together with attenuation of the expression of 20S proteasome α subunits and the p42 regulator, suggesting that EPA induces attenuation of the upregulation of proteasome expression in cachectic mice and that this is correlated with an increase in skeletal muscle protein expression.

The liver enzymes ASAT and ALAT as well as their ratio significantly increased after surgery. Serum levels of ASAT might be confounded by surgery-associated tissue injury and may, therefore, not exclusively reflect the hepatic condition. Considering type and duration of surgical procedure, tissue trauma was distributed homogeneously over both groups. Subsequent supplementation with FO was associated with significant reductions of ASAT, ALAT, bilirubin and LDH (Fig. 2) and, thus, exhibited liver-protective effects. Similar effects were reported by Hwang *et al.*[29] in septic mice, who found reduced liver enzymes and mortality after FO administration, which was attributed to downregulation of hepatocellular apoptosis. In addition, we observed favorable effects of FO to the pancreas, as documented by significantly reduced levels of serum lipase over the 5 postoperative days.

Regarding splanchnic vasculature, Pscheidl *et al.*[21] demonstrated improved perfusion and fewer translocations of viable bacteria from the gut into mesenteric lymph nodes and the liver after omega-3 fatty acids. This mechanism could have contributed to the beneficial effects on the pancreas and liver after TPN supplemented with FO.

Part of the immunostimulant FO effects was the amplification of the "positive" hepatic APR,[30] as measured by CRP and fibrinogen. This immune augmentation could partially be ascribed to the improved liver function, which was reflected by lower transaminases (Fig. 2), bilirubin and LDH. The strengthened hepatic production of proteins of humoral host defense or of coagulation factors[30] correlates with the higher serum levels of opsonizing CRP and fibrinogen (Table III). Conversely, weakened APR after burn injury was associated with elevated mortality rates.[31] However, the issue of the APR appears to be double-edged. The APR is a condition *sine qua non* for initiating repair mechanisms in states of a properly regulated inflammatory response, as observed in early recovery from burn injury[31] or in the current postoperative patients. If, however, an inadequately prolonged or overwhelming APR is present, as in advanced sepsis[25,31] or in patients with tumor cachexia,[27] the APR turns from friend into foe, becoming a part of the pathomechanism and possibly inducing an unfavorable outcome.

Today's standard of care in patients after major abdominal tumor surgery, as investigated in the current study, is early postoperative (12 hr) enteral feeding, *e.g.,* by intraoperatively placed small bowel catheters[32] or other multimodal concepts.[33,34] However, the current literature contains a vast number of studies concerning enteral and parenteral immunonutritional mixes[35] but lacks data regarding definite impact of single pharmaconutritional approaches, such as omega-3 fatty acids. TPN was chosen to guarantee bioavailability of the omega-3 fatty acids, which could not be assured during enteral nutrition in which gastrointestinal transport and mucosal uptake function may be unpredictably impaired in a number of patients and, thus, could confound study outcome.

However, particular studies from the late 1980s raised concerns that TPN might increase infectious complications and induce a fatty liver in critically ill patients.[32,36] Critical review of the data suggests that, in humans, TPN does not cause mucosal atrophy or increase bacterial translocation[36] and increased sepsis with TPN can be ascribed to overfeeding.[37] Accordingly, Wolfe *et al.*[38] concluded that clinical phenomena, such as existing liver disease, renal failure and abdominal sepsis, rather than administration of TPN, had a predominant effect on liver histopathology.

Nutritional goals have changed over the last 2 decades from immunosuppressant hyperalimentation to more reasonable objectives,[39] and the quality of i.v. lipid emulsions has evolved likewise.[40] TPN is an equally effective alternative to EN when a risk of malnutrition is present and EN is not tolerated or when gut failure is present.[32,36] Considering the above, the setting of TPN in the current trial is unlikely to have induced TPN-associated liver dysfunction.

Our study was not undertaken to prove the superiority of TPN over EN. Rather, it was designed to investigate the impact of omega-3 fatty acids on the postoperative course after major abdominal tumor surgery. Consequently, the next step must be investigation of the observed omega-3 effects in early enterally fed patients as part of a multimodal concept.[33]

Various causes may account for our failure to detect differences in patient outcome parameters. Firstly, a short single nutritional intervention is unlikely to produce extensive effects on outcome in a small cohort of postoperative patients who do not present signs of severe illness (SAPS II at entry[12]). To detect changes in outcome parameters, our study was clearly underpowered. This problem was previously addressed in a large meta-analysis investigating immunonutrition.[35] In a cohort of elective postoperative patients, mortality is fortunately such a rare event that changes in mortality remain statistically undetectable. Secondly, individual patients may incorporate the lipids into their cell membranes to different degrees, which may explain the variability in parts of the results.

Considering the results of Tanigushi *et al.,*[24] who observed reduced mortality rates in SIRS patients with lower IL-6/IL-10 ratios, it could be postulated that omega-3 fatty acids may have favorable effects in these patients as shown by ICU stay in subgroup analysis. This effect must, however, be proven in a larger number of patients.

ACKNOWLEDGEMENTS

The authors thank the staff of the ICUs of the Departments of Anesthesiology and Surgery, University Hospital Dresden, for their kind and generous support. The technical assistance of Dipl.-Pharmaz. E. Tydecks (Central Pharmacy) and Dipl.-Math. E. Kuhlisch (Institute of Medical Informatics and Biometry) of the University Hospital Dresden is especially acknowledged.

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