Impact of total parenteral nutrition including omega-3 fatty acids on the regulation of plasma lipoproteins and glycemic control after major abdominal surgery

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Introduction

Acute conditions such as surgical trauma, inflammation, and sepsis induce major changes in the concentration, composition, and metabolism of plasma lipoproteins as well as increases in serum glucose levels due to insulin resistance. Changes in lipid metabolism observed during the acute phase response (APR) seem to be of clinical relevance. Elevated triglyceride (TG) levels correlated linearly with mortality in surgical intensive care unit (ICU) patients[1] and reductions in both high-density lipoprotein (HDL) and total cholesterol were associated with poor clinical outcome, infectious complications, and increased concentrations of proinflammatory cytokines in critically ill patients.[2–7] Lipoproteins are thought to be important regulators of the host immune response due to their lipopolysaccharide (LPS)-neutralizing capacities. HDL was essential for the release of bound LPS from cell membranes[8] while binding of LPS in serum and lymph of septic individuals occurred mainly by low density lipoprotein (LDL) and very low-density lipoprotein (VLDL).[9] In addition to their LPS-neutralizing properties, lipoproteins exert anti-inflammatory actions by modulation of adhesion molecule expression, endothelial nitric oxide production and antioxidant properties.

Large epidemiologic studies on long term intake of diets rich in omega-3 fatty acids (omega-3 FA) like eicosapentaeonic acid (EPA) and docosahexaeonic acid (DHA) demonstrated decreased TG levels and increased HDL cholesterol while total cholesterol and LDL levels remained constant or decreased slightly[10–13] Omega-3 FA were also reported to ameliorate insulin resistance[14] although available data are controversial[12,15,16] and in a recent study Tappy and coworkers demonstrated that in healthy volunteers, omega-3 FA did not affect blood glucose regulation and energy expenditure.[17]

Nutritional lipids supplied during critical illness have been shown to modulate the host immune response to inflammation. Previous work from our group demonstrated that omega-3 FA in clinically relevant doses were rapidly incorporated into cell membranes.[18] On the other hand, their effects on leukocyte membrane composition and leukotriene formation during total parenteral nutrition (TPN) were transient and lasted only few days longer than they were delivered as shown by Morlino and coworkers.[19]

Inclusion of omega-3 FA seems to have beneficial effects on cellular immunity even after short term administration and helps to maintain the balance between pro- and anti-inflammatory cytokines thereby preventing hyper-inflammatory complications. Experimental data confirm that omega-3 FA attenuate an overwhelming inflammatory reaction,[20] ameliorate host defense,[21,22] and improve splanchnic blood flow and gut barrier function[23] in septic states. In clinical studies, enteral nutrition with diets containing fish oil had restorative effects on the depressed cellular immunity of patients with critical illness and after major abdominal surgery.[24,25] Further, in an observational multicenter study, we demonstrated a diagnosis-dependent decrease in infectious complications and mortality in 661 patients.[6] Moreover, a prospective study in burn patients demonstrated that a diet containing fish oil significantly reduced wound infection, shortened hospital stay, and reduced mortality compared with standard enteral nutrition.[26] Recently, our group reported that following major abdominal surgery in cancer patients also TPN including omega-3 FA was beneficial and improved liver function compared to treatment with omega-6 FA alone.[27]

The impact of omega-3 FA on glucose and lipid homeostasis during the postoperative period is widely unknown and a recent study by Tappy and coworkers[28] did not detect differences in glucose and lipid oxidation, as well as in hepatic de novo gluco- and lipogenesis in mixed ICU-patients receiving omega-3 FA.

In the present study, we analyzed the effects of TPN including omega-3 FA on the regulation of lipid metabolism and glycemic control in a defined patient group after elective surgery for cancer of the gastrointestinal tract in whom improved liver function had already been reported.[27]

Materials and methods

Study design

Prospective randomized double-blind controlled trial.

Patients

With institutional review board approval (Ref. No: EK-DD 80199) and patient written informed consent, 44 patients suffering from carcinoma of the gastrointestinal tract or the pancreas were prospectively enrolled. Elective surgery was performed between May 1999 and February 2000 (Table 1). Postoperatively the 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 this study, the patients were randomly assigned to receive either TPN supplementation with soybean oil (SO) or with SO+ fish oil (FO) emulsion (Table 2).

Exclusion criteria

Exclusion criteria were age <18 or >80 yr, ASA-status >3, BMI <16 or $>30\,kg/m^2$, hypertriglyceridemia, pregnancy, hyperthyroidism, chronic liver disease, pancreatitis, HIV infection or hepatitis, severe cardiac or renal disease, medication with insulin, corticoids, cytostatics or cyclooxygenase inhibitors. Secondary exclusion criteria were withdrawal of consent, considerable side effects of lipid application, TG levels above 3.99 mmol/l on two consecutive days, surgical complications which lead to interruption of TPN, and septic shock.

Interventions

All patients received TPN for 5 days postoperatively (according to Table 2) by an indwelling central venous 3 lumen catheter. Glucose (Glucosteril 40%, Fresenius-Kabi, Bad Homburg, Germany), amino acids (Aminosteril 10%, Fresenius-Kabi) and a SO emulsion (Lipovenoes® 10% PLR, Fresenius-Kabi) were provided to both groups by means of infusion pumps (Volumed μVP5000, Fresenius-Kabi, Bad Homburg, Germany). 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/kgBW/d, which is the maximum approved daily Omegaven® dosage and which was associated with most favorable patient outcome.[6] The resulting ratio of omega-3/omega-6 ratio was 1:6.6 in the SO group and 1:2.6 in the FO+SO group, respectively. All patients daily received fat-(Vitalipid®, Pharmacia, Erlangen, Germany) and water soluble vitamins (Soluvit®, Pharmacia) as well as trace elements (Addel N®, Pharmacia). Calculated on body mass the nutrition in both groups was isonitrogenic and isocaloric. When blood glucose levels exceeded 10 mmol/l intravenous insulin was given continuously.

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 the first postoperative day (day 1), baseline values were obtained before TPN was started (8:00 a.m.).

Blood samples

For laboratory measurements, 10 ml of whole blood were withdrawn from an arterial line daily at 8:00 a.m.. Analysis of parameters of lipid metabolism and serum glucose were immediately done by the Department of Clinical Chemistry (DCC), University Hospital of Dresden, Germany, according to standard laboratory procedures. Triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol, and serum glucose were determined from serum samples using the following test kits on Hitachi 917 (all from Roche Diagnostics, Mannheim, Germany): TG (GPO-PAP), CHOL (CHOD–

Table 1 Demographic characteristics (mean ± SD) of patients in the soybean oil (SO) and the fish oil (FO)+SO group.

Group	SO ($n = 20$)	SO+FO ($n = 24$)	p-Value
Age (yr)	60.8 ± 10.9	61.0 ± 12.6	0.96
Gender (male/female)	14/6	18/6	1.00
Body mass index	24.5 ± 4.1	25.2 ± 4.4	0.56
SAPS II	12.0 ± 5.2	12.4 ± 5.2	0.80
Albumin (g/l)	52.88 ± 7.63	49.43 ± 7.67	0.14
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	

Table 2 Regimen of total parenteral nutrition in the soybean oil (SO) and the fish oil (FO)+SO group (given as g/kg body weight/day and as percent of total energy supplied).

Day	Both groups		SO n-3:n-6 = 1:6.6	FO+SO N3:n6 = 1:2.6
	Glucose 40% (Glucosteril 40%)	Amino acids (Aminosteril KE 10)	Lipids (Lipovenoes 10% PLR)	Lipids (Lipovenoes 10% PLR) (Omegaven 10%)
1	2.0 g/kg/d 46%	0.5 g/kg/d 12%	0.8 g SO/kg/d 42%	0.64 g SO/kg/d+0.16 g FO/kg/d 42%
2–5	3.0 g/kg/d 46%	1.2 g/kg/d 19%	1.0 g SO/kg/d 35%	0.8 g SO/kg/d+0.2 g FO/kg/d 35%

PAP), HDL-C plus 2nd generation, LDL-C plus 2nd generation, and Gluco-quant (Hexokinase). Plasma glycerol levels were determined photometrically using a test kit for free glycerol (Freies Glycerin-Testkit, WAK-Chemie, Germany). The TG values were corrected for the glycerol values obtained.

VLDL-cholesterol was calculated by the cholesterol content of the lipoprotein fraction migrating with preβ-mobility (REP Ultra HDL, VLDL/LDL Cholesterol System, Helena Laboratories, Mount Waverley, Australia).

Glycemic control

Blood glucose values determined by point of care blood gas information system (Radiometer, Copenhagen, Denmark) and insulin infusion rates were recorded. Mean glucose values and insulin infusion rates were calculated for 4 h periods:A (8:00–12:00), B (12:00–16:00), C (16:00–20:00), D (20:00–24:00), E (0:00–4:00), and F (4:00–8:00). For comparison of differences in glycemic control between the two groups, blood glucose levels were normalized to the insulin doses applied.

Statistics

Data are presented as arithmetic mean $\pm$ standard error of means (SEM) if not stated otherwise. Repeated measurement analysis within and between groups was achieved with general linear model (GLM) according to a two 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 for MS Windows (Release 12.0.1, SPSS, Chicago, IL).

Results

Clinical characteristics of the patients

Data of all randomized patients were eligible for statistical analysis which was carried out on an intention to treat basis. Demographic characteristics of the patients concerning age, gender, SAPS II at entry, body mass index (BMI) and surgical procedures are summarized in Table 1. There were no significant differences between groups at entry. Distribution of cancer stages according to the classification of the international union against cancer 1997 did not differ between groups (Table 3). One patient in each group underwent chemotherapy or radiochemotherapy prior to surgery. Mean albumin values did not differ between groups, however, 2 patients in the SO+FO group exhibited preoperative hypoalbuminemia suggestive of impaired nutritional status

Table 3 Cancer stage according to the classification of the International Union against Cancer (UICC 1997).

	SO ($n = 20$)	SO+FO ($n = 24$)	p-Value
Stage 0	1	1	0.7
Stage I	7	6	
Stage II	2	3	
Stage III	1	4	
Stage IV	3	3	
Radiochemotherapy	1	0	
Chemotherapy	0	1	
Undefined (beninge)	4	5	

General data

All patients were extubated at the end of surgery and transferred to the ICU spontaneously breathing. The body mass adjusted nutritional goal of TPN was met in all cases.

Levels of C-reactive protein (CRP) increased temporarily reaching maximum values at the second and third postoperative day and then declined again. During the 5 days of parenteral nutrition no significant differences in CRP levels were observed between the groups.

Lipid metabolism

Baseline values for plasma levels of total cholesterol, LDL-, HDL-, and VLDL-cholesterol as well as TGs and glyerol were obtained at the first postoperative day before start of TPN and did not differ between groups (see Table 4).

During the course of TPN, plasma cholesterol as well as LDL-cholesterol increased in both groups while HDL-cholesterol remained nearly unchanged (Figure 1). LDL-cholesterol was significantly higher in the SO group compared to the SO+FO group at the third and fourth postoperative day. TGs and VLDL-cholesterol also increased during TPN (Figure 2). While TG values were similar in both groups, the rise in VLDL levels occurred earlier under SO+FO and reached higher values compared to SO. After discontinuation of TPN, VLDL levels were similar in both groups while serum glycerol was lower in the SO+FO group compared to SO (Figure 2).

Glycemic control

Patients in both groups had comparable serum glucose levels preoperatively and at the first postoperative day before

Table 4 Metabolic parameters after major abdominal surgery before onset of total parenteral nutrition with either soybean oil (SO) or SO+fish oil (FO) emulsions. All values are given in mmol/l (mean $\pm$ SEM).

	SO ($n = 20$)	SO+FO ($n = 24$)	GLM p-value
Total cholesterol	2.10 $\pm$ 0.49	2.28 $\pm$ 0.43	0.19
LDL-cholesterol	0.90 $\pm$ 0.36	1.03 $\pm$ 0.36	0.25
HDL-cholesterol	0.82 $\pm$ 0.25	0.82 $\pm$ 0.22	0.99
VLDL-cholesterol	0.41 $\pm$ 0.28	0.50 $\pm$ 0.28	0.31
Glycerol	0.16 $\pm$ 0.08	0.14 $\pm$ 0.08	0.39
Triglycerides	0.49 $\pm$ 0.25	0.61 $\pm$ 0.43	0.26
Serum glucose	5.8 $\pm$ 1.3	5.9 $\pm$ 1.0	0.80

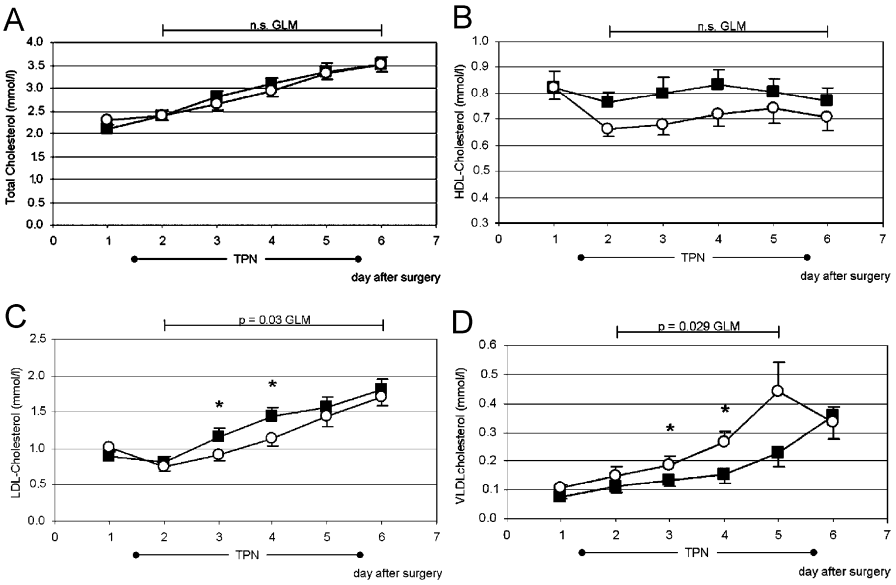

Figure 1 Changes in plasma levels of (A) total cholesterol, (B) high-density lipoprotein (HDL)-cholesterol, (C) low density lipoprotein (LDL)-cholesterol, (D) very low density lipoprotein (VLDL)-cholesterol (means ±SEM) after major abdominal cancer surgery followed by total parenteral nutrition (TPN) supplemented with soybean oil (SO, black squares) or with fish oil+soybean oil (FO+SO, open circles) emulsions. *Post hoc* Bonferroni adjusted daily comparison: * $p<0.05$.

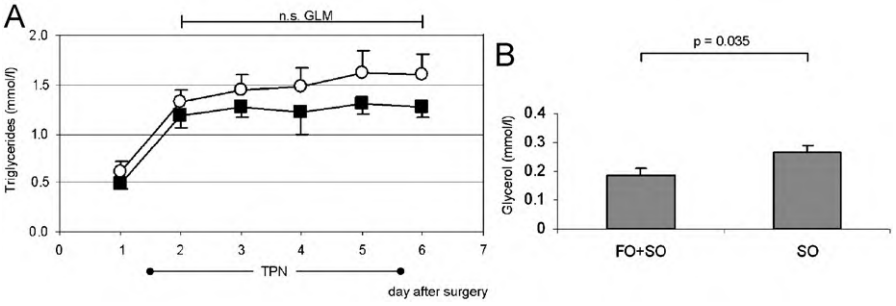

Figure 2 (A) Time course of triglyceride plasma levels (mean±SEM) after major abdominal cancer surgery followed by total parenteral nutrition (TPN) supplemented with soybean oil (SO, black squares) or with fish oil+soybean oil (FO+SO, open circles) emulsions. (B) Glycerol plasma levels (mean±SEM) at the sixth postoperative day when TPN using either FO+SO or SO emulsions was discontinued.

start of TPN. After start of TPN, there was a rise in blood glucose levels in both groups. While in the SO group, blood glucose levels fell significantly over time from the second postoperative day until the end of the observation period, blood glucose levels remained high in the SO+FO group. Correlation coefficients of insulin doses versus blood glucose levels were similar in both groups and blood glucose levels normalized to the insulin doses applied did not differ between the two groups (Figure 3).

Discussion

Omega-3 FA exert diverse effects on different cell types thereby modulating immune function, proinflammatory signaling, as well as glucose and lipid metabolism. Inclusion of omega-3 FA into both enteral and parenteral nutrition of critically ill patients lead to improved outcome and also reduced costs.[6,26,29–31] While improvements in cellular immunity and organ function as well as attenuation of hyperinflammatory states and infectious complications by omega-3 FA in critically ill patients have been reported previously,[25,27] the impact of short-term parenteral nutrition including omega-3 FA on glucose and lipid homeostasis during the postoperative period is widely unknown.

We investigated cancer patients after major admonial surgery and applied TPN for the first 5 postoperative days. This allowed us to study metabolic parameters under constant, well controlled substrate delivery without fluctuations due to complications of enteral nutrition.

We hypothesized that omega-3 FA may exert beneficial effects on acute-phase related alterations of plasma lipoproteins and glycemic control. It is known that elevated plasma TG levels contribute to peripheral insulin resistance by impairing insulin-receptor signaling ultimately leading to decreased cellular glucose uptake and serum hyperglycemia.[32] In previous studies in insulin-resistant and obese individuals long-term oral intake of omega-3 FA ameliorated elevated TG-levels,[12–14,16,25] inhibited hepatic VLDL apoB secretion[33] and increased beta-oxidation of fatty acids.[34–36]

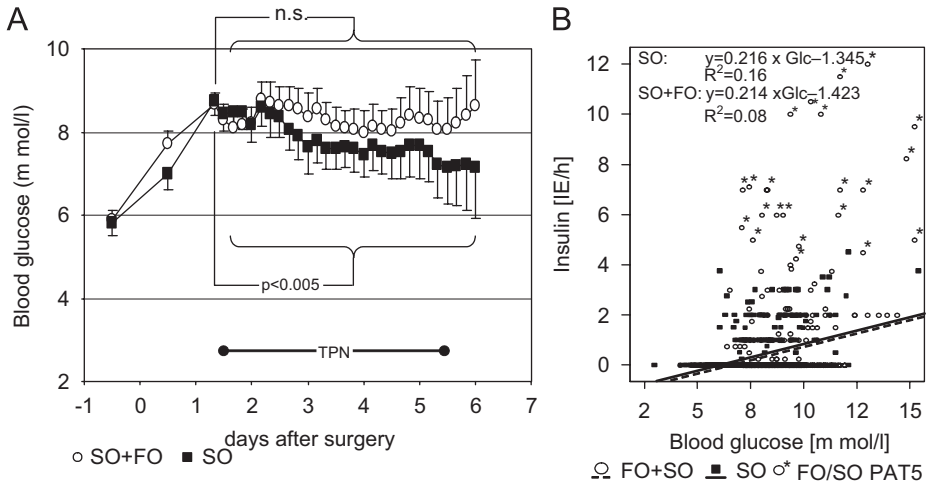

Figure 3 Time course of (A) blood glucose levels (mean ± SEM) ($p < 0.0005$ within group effect over time in 2 way ANOVA only in the SO-group) and (B) correlation of blood glucose levels with insulin doses infused in patients after major abdominal cancer surgery followed by total parenteral nutrition (TPN) supplemented with soybean oil (SO, black squares) or with fish oil+soybean oil (FO+SO, open circles) emulsions. Patient 5 of the FO/SO group was an outlier and is therefore marked with an asterisk.

So, omega-3 FA might be favorable during the postoperative course and could promote a more rapid recovery of metabolic homeostasis.

Omega-3 FA diferentially affected plasma levels of lipids and lipoproteins in our study. In both groups, we observed immediate reductions in both HDL- and LDL-cholesterol reaching minimum levels at the second postoperative day. These findings corresponded with increasing CRP values and are in line with the inverse correlation of serum HDL levels and SAPS II score in septic patients.[37] HDL-cholesterol did not change significantly during the course of TPN and there were no differences between treatment groups. So, omega-3 FA obviously are not capable of influencing the APR-induced down regulation of HDL-cholesterol.

LDL-cholesterol increased in both treatment groups and was significantly higher in the SO group compared to the FO+SO group at days 3 and 4 of TPN. In the case of VLDL, we observed elevations in both the SO and FO+SO group with plasma VLDL-cholesterol values being significantly higher in the FO+SO group compared to the SO group at days 3 and 4 of TPN. Elevation of hepatic TG synthesis and VLDL secretion are characteristic for the APR due to increased flux of free fatty acids (FFA) to the liver which is further enhanced by exogenous administration of nutritional lipids. In addition, the inhibitory actions of insulin on hepatic TG and VLDL synthesis[38,39] are impaired due to hepatic insulin resistance during the APR which might further sensitize the hepatic apoB secretory pathway to enhanced FFA flux. Previous work showed that the regulation of hepatic TG and VLDL secretion is modified by the kind of fatty acids supplied. In this context, omega-3 FA take an exceptional position among polyunsaturated fatty acids as studies both in healthy human subjects and in in vitro cell culture experiments demonstrated an inhibitory effect of omega-3 FA on VLDL secretion.[33,40] In contrast to these observations, inclusion of omega-3 FA into TPN further increased VLDL levels in our study compared to TPN with omega-6 FA alone while TG levels did not differ significantly between the two groups. So, our study demonstrates that the inhibitory effect of omega-3 FA on hepatic VLDL secretion is not present during the early postoperative course after major abdominal surgery. Rather we observed an immediate rise in VLDL levels in the FO+SO group whereas the increase in VLDL levels seemed to be delayed in the SO group. Levels of CPR, reflecting the severity of the APR, and caloric intake did not differ between groups.

From our observations, one might speculate that the VLDL-lowering effect of omega-3 FA is offset by acute regulatory changes during the APR and that the early rise in VLDL levels induced by TPN including omega-3 FA may reflect improvements in liver function in these patients, which have been reported previously.[27,41] In this context, changes in the hepatocellular redox state might contribute to the observed increase in VLDL by omega-3 FA: There is evidence from experimental studies that changes in microsomal triglyceride transfer protein (MTP) expression can modify apoB and VLDL secretion. Omega-3 FA increased MTP expression under pro-oxidant and stimulated both MTP and apoB expression under pro-reducing conditions.[42] These changes could ultimately lead to the stronger increase in hepatic VLDL secretion seen in our patients receiving omega-3 FA. This hypothesis is supported by the findings of Antebi et al.[41] and Wichmann et al.[31] who reported improved plasma antioxidant capacity by parenteral nutrition including omega-3 FA. In addition, we cannot exclude that there might be changes in the kinetics of the conversion from VLDL- to LDL-lipoprotein particles which may contribute to the observed inverse effects of omega-3 FA on plasma levels of VLDL- and LDL-cholesterol.

Effects of omega-3 FA on blood glucose regulation were subtle but showed persistently high blood glucose levels in patients receiving SO+FO in contrast to the SO group where blood glucose levels decreased over time. Experimental data point towards diabetogenic effects of omega-3 FA as shown by Holness and coworkers[43] who reported impaired suppression of hepatic endogenous glucose production in rats. In vitro, pretreatment of HepG2 cells with EPA

resulted in reduced basal and insulin-stimulated glucose incorporation into glycogen compared to control cells and cells treated with the omega-6- FA linoleic acid.[44] In addition, EPA slowed down the kinetics of insulin receptor phosphorylation suggestive of impaired cellular insulin signal transduction. With respect to insulin kinetics, inclusion of omega-3 FA lowered the fat-induced basal insulin-secretion of isolated pancreatic islets and augmented the clearance rate of exogenously infused insulin.[43] All together, these mechanisms might account for the sustained elevation of blood glucose levels over time observed in our patients treated with TPN including omega-3 FA compared to omega-6 FA alone.

Studies in insulin-resistant human individuals led to controversial results: while in some studies glucose homeostasis was not affected by a diet including omega-3 FA,[12,13] both improvement[14] and deterioration[15,16] of glycemic control were reported by others. In patients with non-insulin-dependent diabetes mellitus, Puhakainen and coworkers observed increased gluconeogenesis from glycerol by omega-3 FA.[45] In healthy human volunteers Tappy and coworkers did not observe significant effects of omega-3 FA on energy metabolism[17] however, this study like the above-mentioned studies in insulin-resistant and diabetic patients investigated long-term effects of orally applied omega-3 FA and were performed either in the fasting state or under a nutritional regime that markedly differs from TPN applied to the patients in our study thereby limiting their validity in our context. Interestingly, in a further trial, the group of Chioléro demonstrated reduced energy expenditure in a mixed ICU patient population ($n = 12/24$ with sepsis) receiving omega-3 FA compared to soy bean lipid emulsion while glucose oxidation, glucose production, and gluconeogenesis as well as lipid oxidation and hepatic de novo lipogenesis did not differ between groups.[28] However, data from this study is also not easily applicable to our group of elective surgical patients. In particular, difficulty exists in comparison as the patient population was rather heterogenous and the time point when TPN was initiated varied between day 1 to day 4 after trauma or surgery. Nonetheless, the distinct observations in critically ill patients[28] and in surgical patients point to different conditions in which the effects of omega-3 FA on regulative systems may be surpassed to different degrees.

Taken together, our study demonstrates that the presence of insulin resistance during the postoperative period after major abdominal cancer surgery affects the metabolic effects of omega-3 FA on lipid and glucose homeostasis. Our study can provide some insights into the metabolic effects of omega-3 FA, further conclusions, however, are limited by the small number of patients studied. Outcome data in postoperative patients indicate beneficial effects of omega-3 FA in the postoperative course in terms of lower infection rates, less overall complications,[6,26] and shorter length of hospital stay.[31] Whether these positive effects can be further improved by either reducing caloric intake according to measured metabolic demand as suggested by the work of Tappy and coworkers[28] or by tighter blood glucose control according to the study by van den Berghe and coworkers[46] has to be investigated in future clinical trials.

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