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ORIGINAL RESEARCH

Impact of intravenous fish oil on omega-3 fatty acids and their derived lipid metabolites in patients with parenteral nutrition

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Abstract

Background: Long-term parenteral nutrition (PN) can lead to intestinal failure–associated liver disease (IFALD). Omega-3 (n-3) polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were shown to prevent IFALD. EPA-derived and DHA-derived oxylipins could contribute to this protective effect.

Methods: We analyzed the effect of parenteral fish oil on oxylipins in patients with chronic intestinal failure receiving PN ($n = 8$). Patients first received no fish oil for 8 weeks and then switched to PN with 25% of fat as fish oil for another 8 weeks. Fatty acid profiles of red blood cells, PUFA-derived oxylipins generated by cyclooxygenase, lipoxygenase (LOX), and cytochrome P450 (CYP) pathways, inflammatory markers, and liver function were assessed before and during fish-oil PN.

Results: EPA plus DHA in erythrocytes (the Omega-3 Index) was high with a median of 11.96% at baseline and decreased to 9.57% without fish oil in PN. Addition of fish oil in

Karsten H. Weylandt and Mirjam Karber contributed equally to this study.

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PN increased the median Omega-3-Index to 12.75%. EPA-derived and DHA-derived CYP-dependent and LOX-dependent metabolites increased significantly with fish oil in PN, with less pronounced changes in arachidonic acid and its oxylipins. There were no significant changes of inflammation and liver function parameters.

Conclusions: This study shows that fish oil–containing PN leads to primarily CYP- and LOX-dependent n-3 PUFA–derived inflammation-dampening oxylipins arising from EPA and DHA. Within this short (16-week) study, there were no significant changes in inflammation and clinical readout parameters.

KEYWORDS

cytochrome P450, omega-3 polyunsaturated fatty acids, oxylipins, parenteral nutrition–associated liver disease

CLINICAL RELEVANCY STATEMENT

This study demonstrates that parenteral fish oil leads to very high levels of omega-3 (n-3) polyunsaturated fatty acids (PUFAs) in the blood and demonstrates the formation particularly of potentially beneficial n-3 PUFA epoxy and monohydroxy metabolites with high underlying substrate levels of docosahexaenoic acid and eicosapentaenoic acid.

INTRODUCTION

Intestinal failure–associated liver disease (IFALD) is a problem often complicating the treatment of patients with a reduction of gut function (intestinal failure) and subsequent dependence on intravenous nutrient supplementation. Depending on the criteria used, signs of IFALD affect 2%–90% of adults receiving long-term parenteral nutrition (PN).[1] Clinically, IFALD can manifest as hepatic steatosis and cholestasis. When not resolved, it can result in hepatic fibrosis and/or biliary cirrhosis and liver failure in a small number of cases. One strategy in the prevention and treatment of IFALD is to encourage enteral feeding and to reduce the duration and amount of PN, but this is not feasible for patients with intestinal failure.

In children with intestinal failure and subsequent need for exclusive PN, omega-3 (n-3) polyunsaturated fatty acids (PUFAs) were shown to protect from IFALD.[2–5] Fish oil as a parenteral fat source was able to improve lipid profiles, with decreased levels of serum low-density lipoprotein (LDL), very low-density lipoprotein, total cholesterol, and triglycerides.[6]

Lipids containing essential fatty acids (FAs) are a critical PN component, and in recent years, recommendations have been published to include n-3 PUFA–containing fish oil in PN in a variety of clinical contexts.[7] A range of experimental studies support the notion that an n-3 PUFA as well as an omega-6 (n-6) PUFA supply can be maintained on the basis of arachidonic acid (AA) and docosahexaenoic acid (DHA) with no special need for linoleic acid (LA) and alpha-linolenic acid.[8]

There is a large amount of experimental and clinical data showing anti-inflammatory and immune-modulating effects of n-3 PUFAs, particularly with regard to n-3 PUFA–derived so-called specialized pro-resolving lipid mediators (SPMs).[9,10]

Data from animal models indicate that fish oil protects the liver from PN-induced injury via peroxisome proliferator-activated receptor-gamma signaling mediated by the n-3 PUFA receptor GPR120.[11] Furthermore, n-3 PUFAs protect from acute liver injury and liver tumors through the suppression of cytokine formation.[12,13] Fat-1 transgenic mice, which are capable of endogenous production of n-3 PUFAs from n-6 PUFAs, have an increase in metabolites associated with a pro-resolving lipidome such as 17-hydroxydocosahexaenoic acid (HDHA).[14,15] Antisteatotic effects have been established for cytochrome P450 (CYP)–derived n-3 PUFA epoxides,[16] arguing toward anti-inflammatory protective effects of this class of mediators in the context of liver pathologies.[17] In humans, oral supplementation with n-3 PUFAs is associated with a decrease of liver fat content in patients with nonalcoholic fatty liver disease[18,19] and with an increase in circulating n-3 PUFA–derived lipid mediators in healthy volunteers,[20] as well as in patients with cardiovascular disease and severe hyperlipidemia.[21]

In human infants, a pro-resolving lipidome was found after shifting the lipid source of their PN to fish oil–containing preparations, with formation of monohydroxy metabolites of n-3 PUFAs.[22] However, the effect of parenteral administration of fish oil on the n-3 PUFA–derived inflammation-dampening oxylipins (IDOs) and potentially SPM generation in adults has not been comprehensively assessed yet.

In this study, we assessed the effect of fish oil–enhanced PN on the formation of AA-derived, eicosapentaenoic acid (EPA)–derived, and DHA-derived metabolites. To this end, we conducted a longitudinal study investigating the effect of fish-oil administration in patients with chronic intestinal failure (CIF). We found that fish-oil administration in PN leads to sustained, very high levels of n-3 PUFAs in the blood erythrocyte fraction, as indicated by stable high Omega-3 Index levels. These high levels of n-3 PUFAs were accompanied by high levels of CYP-derived and lipoxygenase (LOX)–derived n-3 PUFA oxylipins implicated in inflammation dampening in other studies.

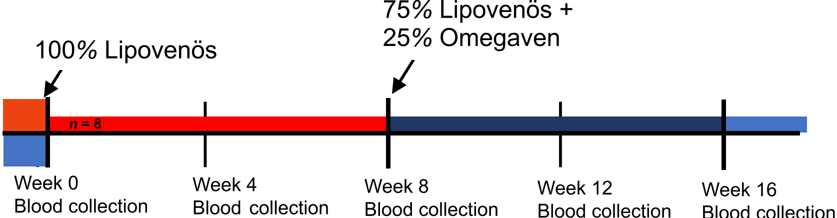

FIGURE 1 Studydesign. Regardless of preceding parenteral nutrition (PN) regimen, patients after inclusion received Lipovenös medium-chain triglyceride (MCT) 20% (Fresenius Kabi AG) during a washout phase of 8 weeks. This was followed by 8 weeks of 75% Lipovenös MCT 20% plus 25% Omegaven (Fresenius Kabi AG) as the lipid component of the PN administered

METHODS

Study population/design

In this prospective longitudinal pilot study, eight patients receiving long-term PN owing to intestinal failure underwent a defined change of their PN FA component according to the protocol shown in Figure 1: Regardless of preceding PN regiment, patients after inclusion received Lipovenös medium-chain triglyceride (MCT) 20% (Fresenius Kabi AG) during a washout phase of 8 weeks. This was followed by 8 weeks of 75% Lipovenös MCT 20% plus 25% Omegaven (Fresenius Kabi AG) as lipid compound. Lipovenös MCT 20% lipid content consists of 50% soybean oil and 50% MCT. Omegaven lipid content consists of 100% fish oil, which is rich in EPA and DHA. The FA composition of Omegaven and Lipovenös MCT 20% is shown in Supporting Information (Supplementary Table S1), with the batch of Omegaven used throughout containing an amount of 15.69 mg/ml EPA and 13.69 mg/ml DHA, as well as small (nanogram) amounts of some oxylipins (Supporting Information: Table S2).

Owing to variations in FA compositions between different batches of these lipid emulsions, lipid components used in this study were from the same batch. The overall quantitative composition of the respective original parenteral support solution—that is, all other nutrients (total energy, amino acids, glucose, micronutrients) were left unaltered.

The following inclusion criteria were applied: patients age ≥18 years, ≥6-month duration of home PN caused by CIF, and PN at least 3 days/week. Exclusion criteria were underlying liver disease not related to PN, malignant disease, chronic ongoing inflammation, and any contraindication to receive Lipovenös MCT 20% or Omegaven lipid. Patients underwent clinical examination, nutrition status assessment, and comprehensive blood tests collected after at least 6 h of fasting, including fasting from PN, every 4–8 weeks (as available in clinical routine). The first time point (baseline) for this study was before switching to 100% Lipovenös MCT 20% (week 0). Blood samples were directly analyzed for routine clinical chemistry parameters. Separate aliquots were stored in liquid nitrogen until further lipidomics analysis, all as described in the following sections. All participants gave written consent. The study was approved by the local ethics committee of Charité – University Medicine, Berlin (EA1/110/14 and EA2/034/13), and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki in its last revision of 2013.

FA analysis

Red blood cell (RBC) FA compositions were analyzed according to HS-Omega-3 Index methodology as described previously.[23,24] In short, RBCs, after being washed twice with phosphate-buffered saline, were stored at −80°C. FA methyl esters generated by acid transesterification were analyzed by gas chromatography using a GC-2010 gas chromatograph (Shimadzu) equipped with an SP-2560 100 m column (Supelco) with hydrogen as the carrier gas. Identification of FAs was done using a standard mix of FAs. The HS-Omega-3 Index is given as EPA plus DHA expressed as a percentage of total identified PUFAs. The coefficient of variation for EPA plus DHA was 5%. Analyses were quality controlled according to DINISO 15189.

Oxylipin analysis

To measure total (free and esterified) LOX-derived and CYP-derived metabolites, plasma samples (500 µl) were subjected to alkaline hydrolysis, and subsequent solid-phase extraction (SPE) was performed exactly as described previously.[20] As described before, free metabolites, including alkaline-sensitive prostaglandins (PGs) and thromboxanes (TXs), were directly extracted via SPE without prior alkaline hydrolysis.[20] In short, liquid chromatography–tandem mass spectrometry analysis was performed using an Agilent 6460 Triple Quad mass spectrometer with JetStream ion source (Agilent Technologies) coupled with an Agilent 1200 HPLC System (degasser, binary pump, well plate sampler, thermostatted column compartment) equipped with a Kinetex column (150 mm × 2.1 mm, 2.6 µm; Phenomenex). For exact conditions of chromatography analysis, please refer to Fischer et al.[20] Internal standards added to the samples before extraction included 10 ng each of 20-hydroxyeicosatetraenoic acid (HETE)-*d6*; 14,15-epoxyeicosatrienoic acid (EET)-*d8*; 14,15-dihydroxyeicosatrienoic acid (14,15-DHET)-*d11*; PGE2-d4; leukotriene B4-d5; and 15-HETE-*d8* (Cayman Chemical) and served for the quantification of groups of similar metabolites. Calibration curves for the quantification of individual metabolites

were established based on the changes in the relative peak area in response to different target compound/internal standard concentration ratios. Linearity was $r^2 > 0.99$ over a range from 1 to 20 ng absolute for any compound. 5,6-EET, 5,6-epoxyeicosatetraenoic acid (EEQ), and 4,5-epoxydocosapentaenoic acid (EDP) were undetectable in the samples, below the limit of validation, or instable. One patient was excluded from oxylipin analysis because of thrombocyte activation before analysis at week 0.

Clinical chemical parameter analysis

Clinical chemistry analysis included parameters of liver function, kidney function, lipid and glucose metabolism, hematology, inflammatory parameters, and electrolytes. Analysis was performed in a standardized setting in Labor Berlin – Charité Vivantes GmbH using clinical routine analysis facilities.

Indirect calorimetry

Resting energy expenditure (REE) was evaluated by means of indirect calorimetry in fasting conditions after a measurement stabilization period of about 10 min and an actual measurement of at least 30 min in a resting horizontal position. Patients were placed under a canopy hood that collected the expired air. Respiratory quotient and REE were assessed based on the measurement of carbon dioxide production and oxygen consumption via a proprietary device (Quark RMR, COSMED).[25]

Statistical analysis

Statistical analysis was performed with IBM SPSS statistics 22 and GraphPad Prism 6 (GraphPad Software). Data were tested for normal distribution and are given as mean ± SEM and median (interquartile range [IQR]). A general linear model with repeated measures was used to analyze the differences between groups. Normally distributed data were evaluated using Pearson correlation coefficient, whereas Spearman correlation coefficient was used for nonnormally distributed data. P values <0.05 were considered significant.

RESULTS

Patient characteristics

Eight patients with CIF were included in this study. Mean age of the group was 49 ± 24 years, with a mean body mass index of 22.8 ± 2.9 kg/m^2. Patients had received PN for a mean duration of 48 ± 33 months before inclusion, with a weekly PN energy intake of 7715 ± 3297 kcal. REE, as measured by indirect calorimetry, was 1553 ± 223 kcal/day, and PN covered 100% ± 22% of the REE (Table 1).

Impact of parenteral fish oil on FA composition of erythrocyte membranes

FA composition of erythrocyte membranes was determined at baseline. Median Omega-3 Index was 11.96% (IQR, 9.74%–14.38%), reflecting widespread use of fish oil–containing PN in standard care. Patients then entered a washout period of 8 weeks, during which they received only minimal amounts n-3 PUFA present in Lipovenös MCT 20% as part of their PN. The incorporation of FAs in erythrocyte membranes was a dynamic process and directly influenced by parenteral fish oil. After these 8 weeks, the Omega-3 Index had decreased to 9.57% (IQR, 8.25%–10.61%) at week 8. From week 9 to week 16, the eight patients received intravenous EPA plus DHA by administering 25% of FAs as fish-oil preparation; this led to the Omega-3 Index rising to 12.75% (IQR, 12.22%–15.02%) (Figure 2A).

TABLE 1 Patients' characteristics

Descriptive data	Baseline
Demographic, anthropometric, and disease characteristics	
Number of patients, *n* (f/m)	8 (7/1)
Age, mean ± SEM, years	49 ± 24
BMI, mean ± SEM, kg/m^2	22.8 ± 2.9
Anatomical SBS type, I/II/III, *n* (%)[a]	4/4/0 (50/50/50)
Underlying primary disease as cause of CIF, *n* (%)	
Mesenteric infarction	3 (37.5)
Inflammatory bowel disease	2 (25)
Bowel obstruction	1 (12.5)
Trauma	2 (25)
Home PN	
Duration, month, mean ± SEM, months	48 ± 33
Median (range), months	33 (9–122)
PN, mean ± SEM, days/week	5 ± 2
PN, mean ± SEM, kcal/infusion	1538 ± 275
PN, mean ± SEM, kcal/week	7715 ± 3297
Composition of PN, mean ± SEM	
Lipid, g/week	334 ± 146
Fish oil, g/week	47 ± 21
Glucose, g/week	747 ± 358
Amino acids, g/week	350 ± 138
REE, kcal	1553 ± 223 (*n* = 4)
REE covered by PN, mean ± SEM, %	100 ± 22 (*n* = 4)

Note: Composition of PN in g/week takes PN-days/week into account.
Abbreviations: BMI, body mass index; CIF, chronic intestinal failure; f, female; m, male; PN, parenteral nutrition; REE, resting energy expenditure measured with indirect calorimetry; SBS, short bowel syndrome.
[a]According to Messing et al.[26]

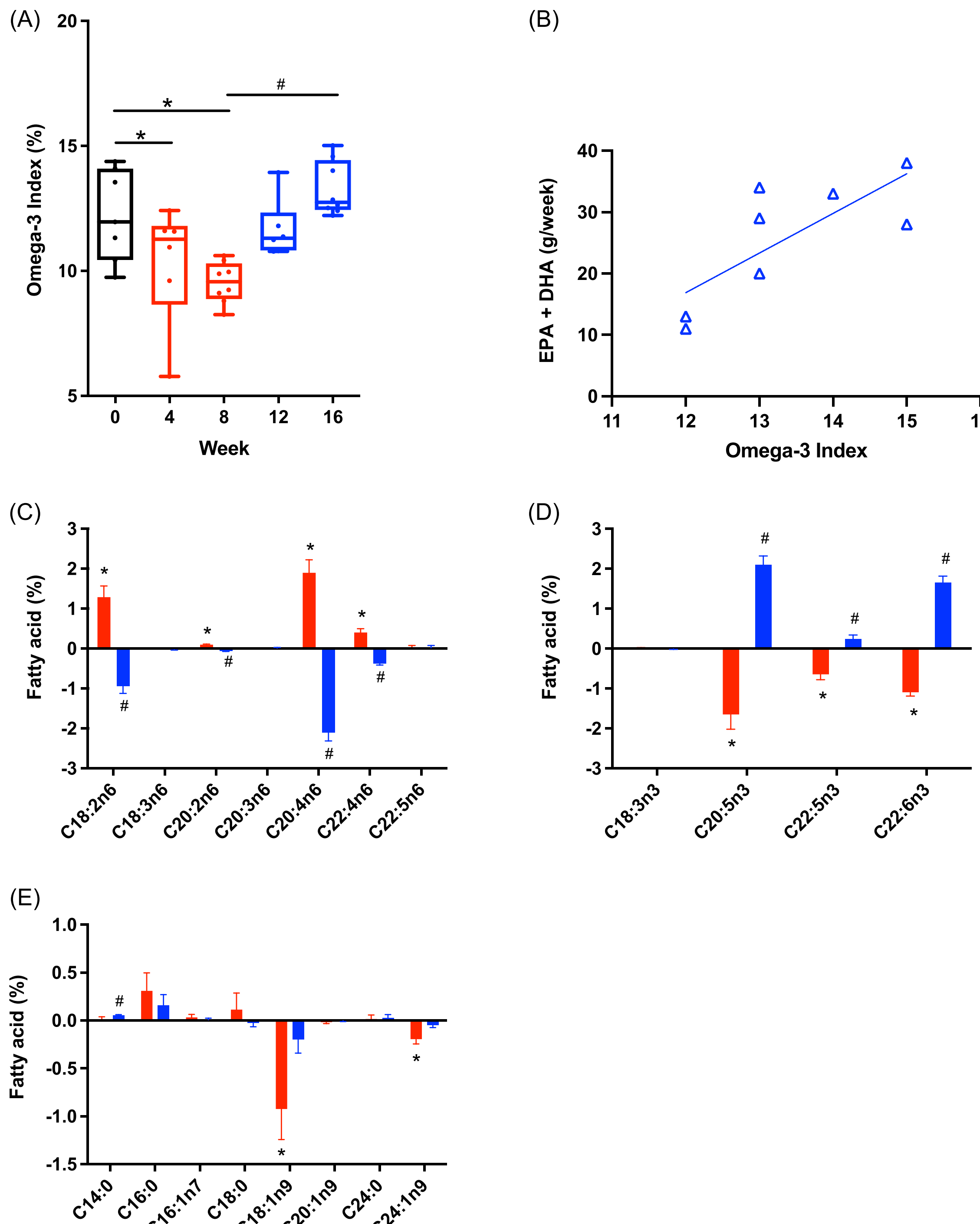

FIGURE 2 Effect of fish-oil supplementation on HS-Omega-3 Index and fatty acid composition. (A) Time-dependent changes of the Omega-3 Index during the fish oil–free washout period of 8 weeks and the fish-oil administration phase of 8 weeks from week 9 to week 16. (B) Omega-3 Index at the end of week 16 as a function of weekly supplementation of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) in grams during weeks 9–16. (C–E) Percentage change of omega-6 (n-6) polyunsaturated fatty acids (PUFAs), omega-3 (n-3) PUFAs, and other individual fatty acids in the red blood cell fraction at two points of the study (week 8 vs week 0; week 16 vs week 8). Data are given as mean ± SEM or median (range). A general linear model for repeated measurements was used for analysis. *Significant ($P < 0.05$) change vs baseline (week 0). #Significant ($P < 0.05$) change vs week 8

EPA plus DHA doses given per week ranged from 11.13 to 38.43 g, depending on the individual patient's PN requirements (Figure 2B). Fish oil–containing PN was able to modulate the FA composition of erythrocyte membranes: LA (18:2n-6), eicosadienoic acid (EDA; 20:2n-6), AA (20:4n-6), and adrenic acid (AdA; 22:4n-6) levels were significantly higher (Figure 2C), whereas EPA (C20:5n-3), docosapentaenoic acid (DPA; C22: 5n-3), DHA (C22:6n-3) (Figure 2D), and oleic acid (OA) (C18:1n-9) were significantly lower (Figure 2E) during the absence of n-3 PUFA. By contrast, under fish-oil administration, the relative amounts of LA, AdA, AA, and EDA were significantly lower (Figure 2C), whereas those of myristic acid (C14:0), EPA, DPA, and DHA in erythrocyte membranes were significantly higher (Figure 2D,E).

Impact of parenteral fish oil on circulating CYP-derived oxylipin levels

Blood content of n-3 PUFAs modified the amounts of CYP-derived epoxy metabolites of essential FAs. We calculated the Omega-3–Epoxymetabolite Index,[20] which reflects the relative abundance of CYP-epoxygenase–derived metabolites from n-3 PUFAs (DHA and EPA) in relation to those synthesized from AA. Without n-3 PUFAs in the PN, the median Omega-3–Epoxymetabolite Index was 0.86% at the end of the washout period (after week 8) and increased to 2.19% after week 16 under defined fish-oil administration in the PN (Figure 3G). As shown in Figure 3, 14,15-EET was the most abundant isomeric form among the EETs measured and was the only EET determined as having significantly higher levels during n-3 PUFA starvation (Figure 3A). Among the DHETs (5,6-DHET, 8,9-DHET, 11,12-DHET, and 14,15-DHET), 5,6-DHET was the most abundant isoform (Figure 3B). EEQs (8,9-EEQ, 11,12-EEQ, 14,15-EEQ, and 17,18-EEQ) and dihydroxyeicosatetraenoic acids (5,6-DiHETE, 8,9-DiHETE, 11,12-DiHETE, 14,15-DiHETE, and 17,18-DiHETE) all increased significantly with fish oil in the PN (Figure 3C,D). Similarly, EDPs and dihydroxy docosapentaenoic acids (DiHDPAs) also had the highest concentration at week 16, and 16,17-EDP and 7,8-DiHDPA were the dominating components (Figure 3E,F).

Regarding the omega-hydroxylase products, AA-derived 20-HETE showed almost no variation at the end of the washout period and decreased after readministration of fish oil in the PN, whereas EPA-derived 20-hydroxyeicosapentaenoic acid (20-HEPE) was significantly decreased at the end of the washout period and increased with administration of fish oil. On the other hand, the level of DHA-derived 22-HDHA was not affected by the washout period but significantly increased with fish-oil administration (Figure 3H). The ratios of 20-HETE:20-HEPE:22-HDHA changed dynamically from 32:21:47 (week 0) to 34:15:51 (week 8) to 27:28:45 (week 16).

Impact of parenteral fish oil on LOX-dependent and cyclooxygenase-dependent oxylipins

5-LOX catalyzes the formation of 5-HETE from AA, 5-HEPE from EPA, and the metabolites 4-HDHA and 7-HDHA from DHA as parenteral FA. 5-HEPE and 7-HDHA were significantly reduced at the end of the washout period when compared with baseline levels, which was not the case for 4-HDHA. After introduction of PN with fish oil for 8 weeks, EPA-derived and DHA-derived 5-LOX products increased significantly when compared with their levels in week 8. By contrast, we observed a significant reduction in 5-HETE formation 8 weeks after the introduction of fish oil (Figure 4A).

12-LOX converts AA to 12-HETE, whereas it converts EPA and DHA to 12-HEPE and 14-HDHA, respectively. 14-HDHA is of special biological interest, as it is the precursor of pro-resolving mediator maresin-1.[27] The level of 12-HETE remained unaffected during the whole study period, whereas the levels of 12-HEPE and 14-HDHA were lower during the washout period. Upon administration of parenteral fish oil, 12-HEPE and 14-HDHA increased again (Figure 4B). Similar results could be observed with 15-LOX–dependent metabolites 15-HETE, 15-HEPE, and 17-HDHA, which are derived from their corresponding FAs: AA, EPA, and DHA. The level of 15-HETE did not change throughout the study period, whereas fish oil in PN significantly increased plasma levels of 15-HEPE and 17-HDHA (Figure 4C).

18-HEPE, precursor of the anti-inflammatory E-resolvin family generated from EPA, is possibly formed through several mechanisms, including autoxidation and cyclooxygenase-2 (COX-2) activity,[26] and alternatively through microbial CYP monooxygenases.[28] The plasma level of 18-HEPE was highly responsive to parenteral fish-oil administration, being significantly reduced at the end of the very low n-3 PUFA period and significantly increased after 8 weeks of parenteral fish-oil administration, exhibiting a threefold increase after week 16 compared with week 8 (Figure 4D).

However, within the limitations of our analytical setup, we were not able to detect dihydroxy and trihydroxy SPMs such as maresin-1 or resolvin D1, D3, D5, or E1. We found small amounts of EPA-derived lipoxin A5, but only in a few samples, and there were no differences between the different time points (Figure 4E).

PGs and TXs are products of the action of COX enzymes on PUFAs. PGE_3 and TXB_3 levels at week 0 were below the limit of detection. The concentration of TXB_2 did not change during the washout period but decreased significantly at week 16. PGE_2—a paradigmatic lipid mediator with context-dependent, mostly proinflammatory actions—was not affected by fish-oil administration (Figure 4E).

9-HETE and 9-HEPE are produced via nonenzymatic oxidation from AA and EPA. The plasma level of 9-HETE remained unaltered during the washout period but showed a significant reduction with parenteral fish-oil administration. The level of 9-HEPE showed a significant decrease to the minimum values after the washout period but increased threefold after the introduction of fish oil compared with that at week 8 ($P < 0.01$) (Figure 4F).

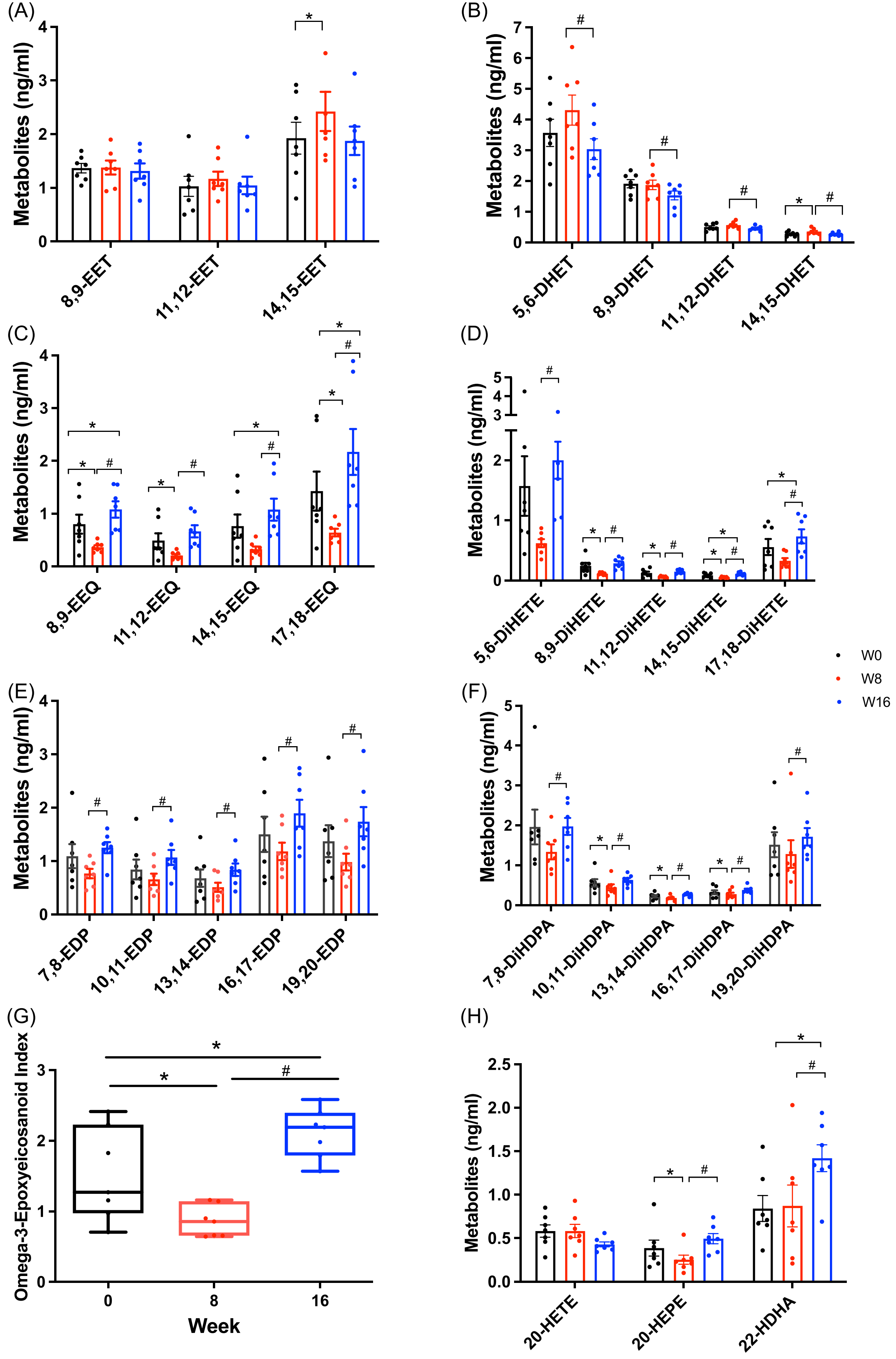

FIGURE 3 (See caption on next page)

Association of n-3, n-6 PUFAs with their metabolites and HS-Omega-3 Index

In our study, n-3 PUFA–derived LOX-dependent and CYP-dependent metabolites were strongly associated with their respective precursors under fish oil–containing PN. We plotted the ratios of EPA-derived/AA-derived and DHA-derived/AA-derived metabolites from the LOX- and CYP-epoxygenase/soluble epoxide hydrolase pathways against the precursor ratios (EPA/AA and DHA/AA, respectively) (Figure 5). The slopes of the correlation lines indicate that among the LOX enzymes, 5-LOX–derived metabolites displayed the highest susceptibility toward parenteral EPA and DHA administration (Figure 5A,B). Efficiency for lipid mediator conversion for EPA-derived and DHA-derived epoxy metabolites was similar (Figure 5C,D). Likewise, we observed a positive correlation between the HS-Omega-3 Index and the n-3 PUFAs EPA and DHA, with EPA contributing higher amounts at higher HS-Omega-3 Indices, whereas the n-6 PUFAs LA and AA were inversely correlated with a more pronounced decrease of AA with higher HS-Omega-3 Indices (Figure 5E,F).

Impact of parenteral fish oil on clinical parameters

We also analyzed the correlation between parenteral fish oil and clinical parameters of liver function and inflammatory markers (Table 2). Liver synthesis parameters such as pseudocholinesterase and serum albumin level or lipid parameters such as total cholesterol, high-density lipoprotein, LDL, and triglycerides were not affected. The mean value of alanine transaminase decreased from 41.13 U/L in week 8 to 33.63 U/L in week 16, albeit not by a significant level. Indicators of inflammation such as leukocyte count and high-sensitivity C-reactive protein remained unchanged.

DISCUSSION

This longitudinal study investigated the effect of fish oil–containing PN in patients with CIF. Patients in our study were characterized by a high Omega-3 Index of 11.96% at the start of the study, which decreased to 9.57% after a period of 8 weeks without any fish oil in PN and increased to 12.75% upon giving 25% of fat as a fish-oil component in PN for 8 weeks.

The high values of n-3 PUFAs in the blood at baseline already reflect the paradigm shift that occurred in recent years, with the use of fish oil laid out in practice guidelines for PN,[7] thereby modifying essential FA composition in PN.[8] Studies in children with IFALD in whom PN containing n-3 PUFAs improved prognosis and prevented IFALD led to Omegaven, a parenteral lipid component manufactured from fish oil, being approved for use as a drug in this context in the United States since 2018.[29]

Fish oil–containing lipid emulsions in long-term PN were shown to be adequate regarding nutrition requirements.[30] Studies using soybean oil/MCT/olive oil (OO)/fish oil[31] or soybean/MCT/OO/fish oil–based lipid emulsions[32] established changes in FA composition toward n-3 PUFAs.

However, there are few data about the clinical effects of fish oil in PN. Comparing fish oil–containing (SMOFlipid) baseline PN against pure fish oil–containing (Omegaven) PN found complex changes in lipopolysaccharide-induced cytokine profiles.[33] SMOFlipid did not alter liver function markers or inflammation, whereas OO-based ClinOleic (without fish oil) decreased some markers of liver function and inflammation in another study.[34] In acutely ill adult patients, SMOFlipid, as compared with a 100% soybean oil–based lipid emulsion, decreased the n-6:n-3 PUFA ratio, but there were no significant differences in biochemical measurements, Sequential Organ Failure Assessment score, length of intensive care unit stay, and mortality.[35] A comparison of four different lipid emulsion substitutions (long-chain triglycerides [LCTs], MCTs/LCTs, OO/LCTs, and a mix of LCTs/MCTs/OO/fish oil) in adult patients with intestinal failure receiving long-term PN showed that OO/LCT, but not the fish-oil lipid emulsion, led to a significant decrease in total bilirubin concentration and gamma-glutamyl transferase after 12 months.[36]

As outlined in the Introduction, a previous study showed a shift to a pro-resolving lipidome with fish oil–containing PN in infants,[22] and with this study, we aimed to assess this also in adult patients with short bowel syndrome. The Omega-3 Index in our patients was markedly higher than in healthy individuals receiving an oral administration of EPA and DHA using capsules of prescription-grade fish oil.[20] To precisely define the amounts of n-3 PUFAs given in the PN, we used a defined batch of n-3 PUFA–containing fish-oil lipid emulsion (Supporting Information: Table S1). This was done to control for the high natural variation of n-3 PUFA content in fish oil–containing parenteral lipid emulsions: For Omegaven (used in this study), the specification gives a broad range of possible n-3 PUFA content, ranging from 1.25 to 2.82 g EPA and from 1.44 to 3.09 g

FIGURE 3 Effect of fish-oil supplementation on cytochrome P450 (CYP)–epoxygenase and CYP-hydroxylase metabolites derived from arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). (A–F) Dynamic changes of AA-derived, EPA-derived, and DHA-derived regioisomeric epoxy metabolites and their corresponding vicinal diols under parenteral fish-oil supplementation. (G) Changes of the Omega-3–Epoxyeicosanoid Index under parenteral fish-oil supplementation. Modulation of the Omega-3–Epoxyeicosanoid Index was calculated as follows: [(EEQs + DiHETEs) + (EDPs + DiHDPAs)]/(EETs + DHETs). (H) Changes on CYP-epoxygenase and CYP-hydroxylase monohydroxy products under parenteral fish-oil supplementation. Data are given as mean ± SEM. A general linear model for repeated measurements was used for analysis. *Significant ($P < 0.05$) change vs baseline level (W0). #Significant ($P < 0.05$) change vs W8. DiHDPA, dihydroxy docosapentaenoic acid; DiHETE, dihydroxyeicosatetraenoic acid; DHET, dihydroxyeicosatrienoic acid; EDP, epoxydocosapentaenoic acid; EEQ, epoxyeicosatetraenoic acid; EET, epoxyeicosatrienoic acid; HDHA, hydroxydocosahexaenoic acid; W, week

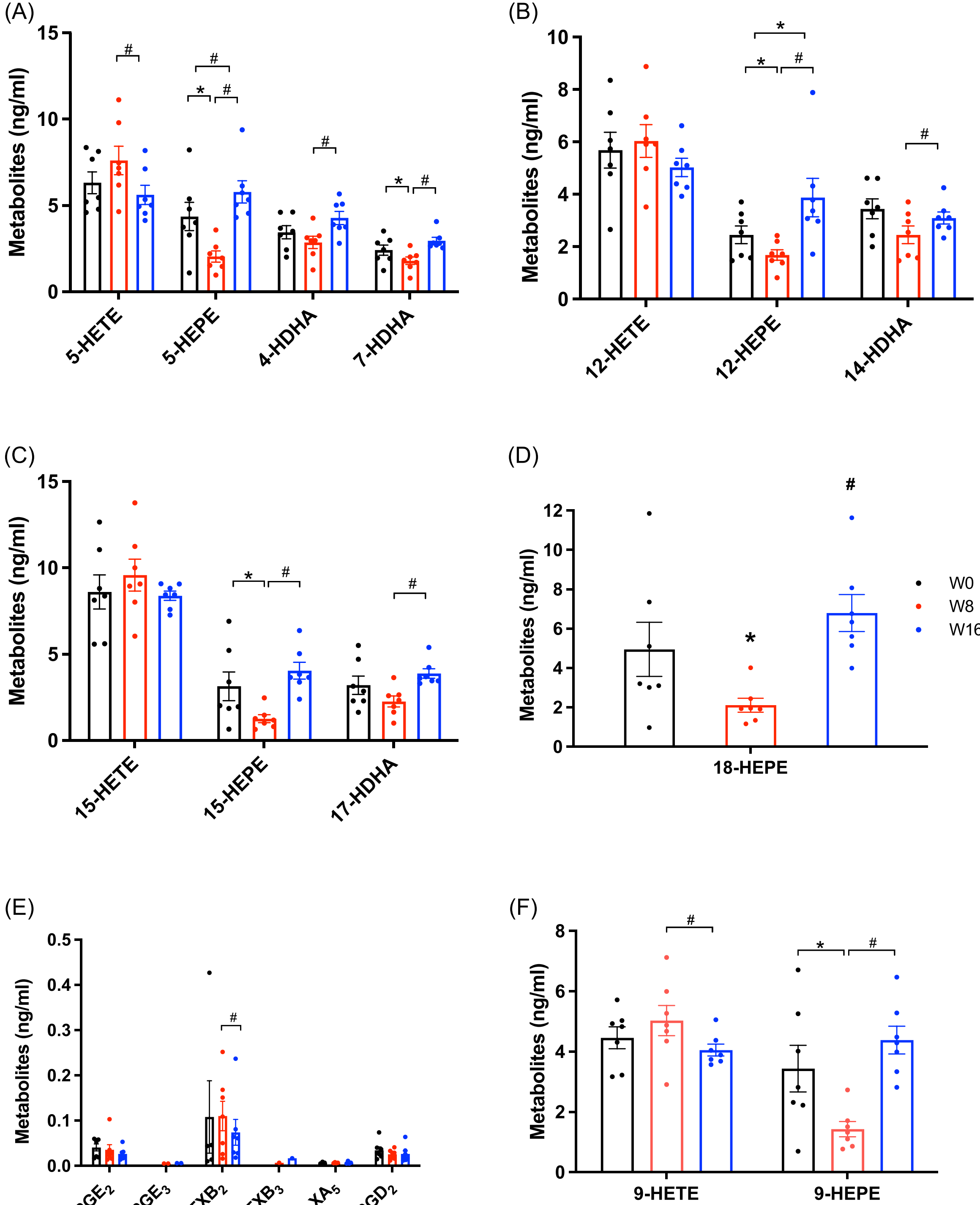

FIGURE 4 Effect of fish-oil supplementation on lipoxygenase (LOX)–dependent and cyclooxygenase (COX)–dependent monohydroxy and nonenzymatic oxidation metabolites derived from arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). (A–C) Dynamic changes of AA-derived, EPA-derived, and DHA-derived 5-LOX, 12-LOX, and 15-LOX metabolites under parenteral fish oil. (D) Change of 18-HEPE concentration. (E) Changes on COX-dependent metabolites and lipoxin A5 (LXA_5) due to fish-oil administration. (F) Nonenzymatic oxidation metabolites derived from AA and EPA. A general linear model for repeated measurements was used for analysis. *Significant ($P < 0.05$) change vs basal level (W0). #Significant ($P < 0.05$) change vs W8. HDHA, hydroxydocosahexaenoic acid; HEPE, hydroxyeicosapentaenoic acid; HETE, hydroxyeicosatetraenoic acid; PGE, prostaglandin E; TXB, thromboxane B; W, week

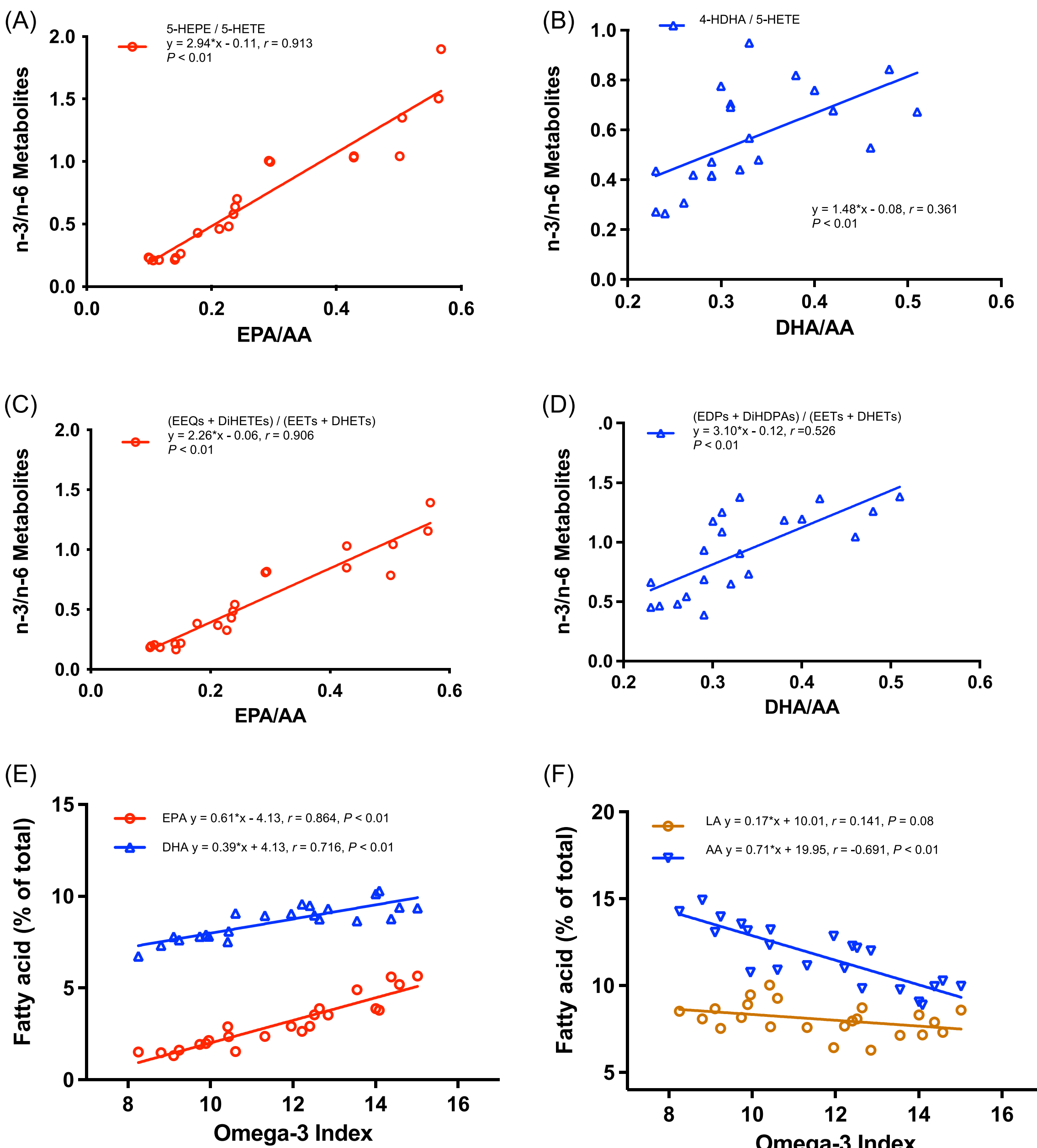

FIGURE 5 Relationship between omega-3, omega-6 polyunsaturated fatty acids (PUFAs) and some of their oxylipins and the HS-Omega-3 Index. (A–D) Correlation of omega-3, omega-6 PUFA–derived oxylipins with their respective precursor fatty acids. (E and F) Correlation of some omega-3, omega-6 PUFAs with HS-Omega-3 Index. For relative efficiencies, Pearson (B, D–F) or Spearman (A, C) coefficient correlation was performed, depending on whether the data were normally distributed. AA, arachidonic acid; DiHDPA, dihydroxy docosapentaenoic acid; DiHETE, dihydroxyeicosatetraenoic acid; DHA, docosahexaenoic acid; DHET, dihydroxyeicosatrienoic acid; EDP, epoxydocosapentaenoic acid; EEQ, epoxyeicosatetraenoic acid; EET, epoxyeicosatrienoic acid; EPA, eicosapentaenoic acid; HDHA, hydroxydocosahexaenoic acid; HEPE, hydroxyeicosapentaenoic acid; HETE, hydroxyeicosatetraenoic acid; LA, linoleic acid

DHA per 100 ml of lipid emulsion. For SMOFlipid, only the amount of n-3 PUFA–rich fish oil is given (as 30 g per 1000 ml lipid emulsion), without further specification of the EPA and DHA content.

Based on the high level of the Omega-3 Index, our data indicate that the administration of PN with fish oil is accompanied by a predominant accumulation of EPA-derived and DHA-derived LOX-epoxygenase–dependent and CYP-epoxygenase–dependent oxylipins. In contrast, AA-derived, CYP- and LOX-metabolites were not significantly affected by fish oil in the PN. Furthermore, we observed a positive correlation between the ratios of EPA-derived and DHA-derived to AA-derived metabolites and the ratio of their precursor PUFAs (Figure 5). By contrast, we could only observe small or no changes of plasma PGs and TXs in response to fish oil–containing PN. Only plasma TXB_2 (the stable intermediate of proinflammatory TXA_2) was reduced by the reintroduction of fish oil.

TABLE 2 Clinical parameters of patients with chronic intestinal failure

Clinical parameter	Week 0	Week 8	Week 16
Sodium, mmol/L	140.75 ± 3.06	140.3 ± 1.35	140.1 ± 0.69
Potassium, mmol/L	4.14 ± 0.47	4.16 ± 0.15	4.18 ± 0.12
Calcium, mmol/L	2.27 ± 0.12	2.27 ± 0.06	2.30 ± 0.04
Phosphate, mmol/L	1.14 ± 0.17	1.18 ± 0.06	1.12 ± 0.07
Magnesium, mmol/L	0.79 ± 0.08	0.76 ± 0.06	0.80 ± 0.03
Creatinine, mg/dl	0.87 ± 0.26	0.75 ± 0.06	0.82 ± 0.08
Estimated GFR, ml/min	75.00 ± 18.42	81.50 ± 5.20	75.75 ± 6.56
Urea, mg/dl	37.50 ± 19.77	35.38 ± 2.80	32.38 ± 2.67
Bilirubin, total, mg/dl	0.84 ± 0.75	0.93 ± 0.30	0.81 ± 0.18
Bilirubin, direct, mg/dl	0.28 ± 0.15	0.28 ± 0.07	0.29 ± 0.04
Serum albumin level, g/L	40.23 ± 4.51	41.53 ± 1.16	40.65 ± 1.27
Protein, g/L	74.29 ± 6.21	72.50 ± 2.47	74.43 ± 1.27
Total cholesterol, mg/dl	149.57 ± 50.22	140.40 ± 15.03	136.4 ± 13.39
HDL cholesterol, mg/dl	50.71 ± 27.16	43.75 ± 4.86	40.38 ± 6.35
Non-HDL cholesterol, mg/dl	106.71 ± 46.08	96.75 ± 13.02	95.88 ± 12.04
LDL cholesterol, mg/dl	84.57 ± 37.50	74.13 ± 10.50	71.50 ± 8.97
Triglycerides, mg/dl	133.86 ± 96.57	107.8 ± 30.40	114.0 ± 37.11
ALT, U/L	38.50 ± 22.17	41.13 ± 9.00	33.63 ± 7.39
AST, U/L	34.00 ± 7.45	36.5 ± 4.68	33.5 ± 2.76
AP, U/L	134.25 ± 68.10	123.80 ± 24.18	110.9 ± 20.62
Pseudocholinesterase, kU/L	6.61 ± 2.07	6.77 ± 0.67	6.71 ± 0.71
GGT, U/L	57.63 ± 51.89	51.38 ± 12.95	48.88 ± 14.70
Insulin, mU/L	15.19 ± 15.29	13.23 ± 5.88	8.41 ± 1.36
C-peptid, µg/L	4.18 ± 2.96	2.97 ± 0.88	2.31 ± 0.33
hs-CRP, mg/L	2.93 ± 2.82	1.16 ± 0.41	3.13 ± 0.75
Transferrin, g/L	2.87 ± 0.36	3.17 ± 0.29	3.04 ± 0.26
Hemoglobin, g/dl	12.58 ± 1.38	12.88 ± 0.49	12.26 ± 0.38
Hematocrit, %	0.38 ± 0.04	0.39 ± 0.01	0.37 ± 0.01
Erythrocyte count, per pl	4.49 ± 0.65	4.53 ± 0.24	4.33 ± 0.18
Leukocyte count, per nl	6.00 ± 1.59	6.73 ± 0.96	6.01 ± 0.72
Thrombocyte count, per nl	206.25 ± 104.01	189.9 ± 24.47	173.1 ± 22.83
MCV, fl	85.75 ± 8.03	86.13 ± 2.25	86.13 ± 1.73
MCH, pg	28.44 ± 3.13	28.64 ± 0.98	28.55 ± 0.77
MCHC, g/dl	32.81 ± 1.12	33.21 ± 0.48	33.18 ± 0.52
MPV, fl	11.34 ± 1.33	11.33 ± 0.48	11.14 ± 0.34
RDW-CV, %	15.21 ± 1.71	14.65 ± 0.74	14.66 ± 0.79
INR, %	1.11 ± 0.09	1.25 ± 0.12	1.12 ± 0.08

(Continues)

TABLE 2 (Continued)

Clinical parameter	Week 0	Week 8	Week 16
aPPT, s	38.66 ± 6.32	40.56 ± 3.80	43.58 ± 7.44
HbA_{1c}, %	5.08 ± 0.85	5.09 ± 0.16	5.03 ± 0.18

Note: A general linear model for repeated measurements was used for analysis. Data are mean ± SEM.

Abbreviations: ALT, alanine transaminase; AP, alkaline phospatase; aPPT, activated partial thromboplastin time; AST, aspartate aminotransferase; GFR, glomerular filtration rate; GGT, gamma-glutamyl transferase; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; INR, international normalized ratio; LDL, low-density lipoprotein; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; s, second.

*Significant ($P < 0.05$) change compared with baseline week 0.

#Significant ($P < 0.05$) change compared with week 8.

These results regarding LOX-epoxygenase–dependent and CYP-epoxygenase–dependent oxylipins are consistent with previous studies. Several CYP enzymes are obviously more efficient in the formation of EEQs from EPA compared with the generation of EETs from AA.[37] Moreover, DHA was shown to significantly inhibit CYP2J2-mediated AA metabolism.[38] As seen in Figure 3, all isoforms of EEQ and EDP measured were significantly increased, whereas the levels of EET remained mostly stable. The shift toward EPA/DHA-derived metabolites might have a beneficial effect on endothelial cells, vascular smooth muscle cells, and the humoral regulation system.[39] Furthermore, these oxylipins were shown in experimental models to protect from steatosis and steatohepatitis.[16] The average Omega-3–Epoxymetabolite Index reached 2.1 after fish-oil administration among our participants, which is, in general, consistent with that found by Fischer et al. (2.1 ± 0.15).[20]

Additionally, 14-HDHA, 17-HDHA, 15-HEPE, and 18-HEPE, which could be the precursors and/or pathway indicators[10] of the resolvin and protectin families of SPMs, were also significantly increased after the introduction of fish oil in PN, raising the possibility that the enhanced formation of 17-HDHA and 18-HEPE may improve liver function and dampen inflammation in our patients receiving PN, similar to their protective role in animal studies.[40,41] 18-HEPE was recently shown to be metabolized by different human LOX isoforms to different resolving products.[42] However, within the limitations of our analysis, we were not able to detect dihydroxy and trihydroxy SPMs such as maresin-1, resolvin D1 (RvD1), RvD3, RvD5, and RvE1, which might reflect differences in methodology, as discussed in a recent review in this field.[43]

Our data show that fish oil–containing PN leads to a CYP-based and LOX-based n-3 inflammation-dampening lipidome (rather than just a pro-resolving lipidome based on SPMs) that could account for many of the inflammation-limiting mechanisms that have been described for n-3 PUFA–derived CYP-oxylipins and LOX-oxylipins and suggest that these n-3 IDOs can contribute to the prevention of IFALD.

AUTHOR CONTRIBUTIONS

Ulrich F. Pape, Wolf H. Schunck, and Karsten H. Weylandt contributed to the conception and design of the research. Mirjam Karber contributed to the design of the research. Ulrich F. Pape, Mirjam Karber, Elisabeth Blüthner, and Sophie Pevny performed the acquisition of the data. Michael Rothe and Clemens von Schacky contributed to the analysis of the data. Ingrid W. Zhang, Yanan Xiao, and Karsten H. Weylandt contributed to the analysis and interpretation of the data and the writing of the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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CONFLICT OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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