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Intravenous Fish Oil and Serum Fatty Acid Profiles in Pediatric Patients with Intestinal Failure Associated Liver Disease

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Abstract

Background: Intravenous fish oil (FO) treats pediatric intestinal failure associated liver disease (IFALD). There are concerns that a lipid emulsion composed of omega-3 fatty acids will cause an essential fatty acid deficiency (EFAD). This study's objective was to quantify the risk for abnormal fatty acid concentrations in children treated with FO.

Methods: Inclusion criteria for this prospective study was children with intestinal failure. Intravenous soybean oil (SO) was replaced with FO for no longer than 6 months. Serum fatty acids were analyzed using linear and logistic models, and compared to age-based norms to determine the percentage of subjects with low and high concentrations.

Results: Subjects (n=17) started receiving FO at a median of 3.6 months of age (IQR 2.4-9.6 months). Over time, α -linolenic, linoleic, arachidonic and Mead acid decreased, while docosahexaenoic and eicosapentanoic acid increased ($p < 0.001$ for all). Triene:tetraene ratios remained unchanged ($p = 1$). Although subjects were 1.8 times more likely to develop a low linoleic acid while receiving FO vs. SO (95% CI 1.4-2.3, $p < 0.01$), there was not a significant risk for low

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Authorship Statement

K.L. Calkins and M.L. Ong equally contributed to the conception and design of the research; K.L. Calkins, M.L. Ong, R.S. Venick, S.B. Shew, J.C.Y. Dunn equally contributed to the design of the research; K.L. Calkins, M.L. Ong, R.S. Venick, and L. Reyen equally contributed to the acquisition of the data; K.L. Calkins, M.L. Ong, and T.R. Grogan equally contributed to the analysis of the data; K.L. Calkins, M.L. Ong, R.S. Venick, S.B. Shew, J.C.Y. Dunn, L. Reyen, and T.R. Grogan equally contributed to the interpretation of the data; M.L. Ong and K.L. Calkins drafted the manuscript. All authors critically revised the manuscript, agree to fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Conflicts of Interest: KLC received research support from Fresenius Kabi. KLC is a consultant for Fresenius Kabi. Fresenius Kabi did not support, nor were they involved in this study. KLC served on an advisory boards for Baxter, Mead Johnson, and Fresenius Kabi. RSV served on an advisory board for Fresenius Kabi.

Clinical Trial Website: <https://clinicaltrials.gov/show/NCT00969332>

arachidonic acid. Subjects were 1.6 times more likely to develop high docosahexaenoic acid while receiving FO vs. SO; however this was not significant (95% CI 0.9-2.6, $p=0.08$).

Conclusion: In this cohort of parenteral nutrition-dependent children, switching from SO to FO led to a decrease in essential fatty acid concentrations, but an EFAD was not evident. Low and high levels of fatty acids developed. Further investigation is needed to clarify if this is clinically significant.

Trial Identifier: _____

Introduction

Children with intestinal failure depend on lipid emulsions as part of parenteral nutrition (PN). Soybean-based (SO) lipid emulsions were previously considered the standard of care for providing non-protein energy and fatty acids to children with intestinal failure. Prolonged PN and SO causes intestinal failure associated liver disease (IFALD).¹⁻⁴ Recently, the United States Food and Drug Administration approved a fish-oil (FO) based lipid emulsion for the treatment of pediatric intestinal failure associated liver disease (IFALD). Despite mounting efficacy data, many people have expressed concerns that FO will cause an essential fatty acid deficiency (EFAD).¹⁻³

The polyunsaturated fatty acid content of SO and FO is strikingly different (Table 1). SO is typically dosed at 1-3 g/kg/d and contains high concentrations of the traditional essential fatty acids, linoleic and alpha-linolenic acids (LA and ALA, respectively). Because mammals lack enzymes to make LA and ALA, humans depend on dietary sources of LA and ALA. In contrast, FO is dosed at 1 g/kg/d and contains a small amount of LA and ALA. FO also contains a small amount of arachidonic acid (ARA), a downstream metabolite of LA, and large amount of docosahexaenoic (DHA) and eicosapentaenoic acid (EPA), two downstream metabolites of ALA. ARA and DHA play important roles in cellular structure and function, inflammation, immunity, brain development, and overall growth.⁵

SO was originally designed for adults to prevent an EFAD when enteral nutrition was limited. When essential fatty acid intake is low (particularly LA), oleic acid, an omega-9 fatty acid, is converted to Mead acid, a triene. At the same time, ARA, a tetraene, decreases. As a result, the triene:tetraene ratio increases. Historically, a triene:tetraene ratio >0.2 has been considered diagnostic of an EFAD and precedes clinical manifestations of an EFAD, which include growth failure, dermatitis, thrombocytopenia, poor wound healing, and elevated liver function tests.⁶ With improved technology, age-specific triene:tetraene ratios have been published, and ratios <0.2 have been considered diagnostic of an EFAD.⁶ Because FO contains a small amount of LA, ALA, and ARA and a large amount of DHA and EPA - 2 downstream omega-3 fatty acids that suppress the hepatic desaturase enzyme that converts LA to ARA - many people have postulated that FO would cause an EFAD.⁷ On the contrary, in animals with an EFAD that receive oral FO, Mead acid decreases.⁸ Likewise, in children with IFALD who are treated with FO, Mead acid decreases and triene:tetraene ratios remain normal.^{2,9-11}

In this study, we aimed to quantify the risk for low and high concentrations of fatty acids in children whose SO was replaced with FO for IFALD treatment. We believe this information is clinically relevant since the availability of FO will increase in the United States, and there is a need to understand the fatty acid profiles of children with intestinal failure who are treated with different lipid emulsions.

Methods

Study Design and Outcomes

This is an observational study. Subjects were prospectively followed during a six month treatment course with FO.³ The primary outcome of this study was the risk for a low-serum or high-serum fatty acid concentration when compared to age-based norms.¹² Secondary outcomes were changes over time in fatty acids and triene:tetraene ratios.

Patient Population

Inclusion criteria for this study included >2 weeks and <18 years of age, 2 serum fatty acid measurements, intestinal failure (gastrointestinal disorder plus >60% of one's energy from PN), and cholestasis (a serum conjugated bilirubin ≥ 2 mg/dL on 2 consecutive measurements).³ Exclusion criteria have been described in previous publications, but also included oral fish oil supplements and liver transplant.³

Study Procedures and Methods

FO (Omegaven®, Fresenius Kabi, Bad Homburg, Germany) replaced SO (Intralipid®, Fresenius Kabi, Uppsala, Sweden) as the sole source of parenteral fat. FO was dosed at 1 g/kg/d for six months or until death, transplant, or PN discontinuation. All other aspects of medical care were managed by the medical team.

Because of the concern for an EFAD, the primary medical team opted to routinely measure serum fatty acid profiles during FO treatment. For this study, results for this laboratory test were collected at baseline (while receiving SO and prior to FO) and at approximately 3 and 6 months of FO treatment. Intravenous fat was suspended for at least 2 hours prior to sample collections. Samples were analyzed at the Mayo Clinic Laboratories via gas chromatography-mass spectrometry. Low or high concentrations of individual fatty acids were defined based on age-based normal ranges for <1 month, 1 month - 1 year, 1 year - 17 years, and >17 years of age.¹¹ Low was defined as a serum fatty acid concentration below the lower limit of normal for the subject's age; high was defined as a serum fatty acid concentration above the upper limit of normal for the subject's age.¹¹

Written informed consent was obtained from a parent or legal guardian. The study was approved by the University of California Los Angeles Institutional Review Board. The Food and Drug Administration approved 2 emergency investigational new drug (EIND) applications (104,951 and 104,766) and an investigational new drug (IND) application (105,326) for FO. This study is registered at <http://www.clinicaltrials.gov> ().

Statistical Methods and Analysis

Logistic generalized estimating equation models were constructed to analyze the risk for low or high fatty acid concentrations over time. Generalized estimating equation linear models were constructed on log-transformed values to assess fatty acid concentrations, triene:tetraene ratios, and liver function tests over time. Paired t-test and McNemar's test were used for PN and enteral nutrition at the start and end of the study. P-value <0.05 was defined as statistical significance.

Results

From March 2009 to November 2015, 47 children received FO at our institution. Seventeen subjects satisfied inclusion and exclusion criteria; 2 subjects were excluded because they received liver transplants prior to FO treatment. The remaining subjects were excluded because they did not have 2 serum fatty acid profiles. At baseline, 13 fatty acid profiles were available. At approximately 3 months of FO, 16 profiles were available. At approximately 6 months of FO, 15 profiles were available.

The subjects' median age (interquartile range [IQR] Q1-Q3) was 3.6 months (2.4-9.6 months) (Table 2). Serum conjugated bilirubin and other markers of liver injury decreased significantly over time (Table 3). Cholestasis resolved (serum conjugated bilirubin < 2 mg/dL on 2 consecutive occasions) in 94% of the subjects (n=16). During the study, 1 subject expired secondary to sepsis and 1 subject received a multi-visceral transplant for liver failure. At the end of the study, 100% of the subjects remained PN-dependent.

At the start of the study on SO, PN comprised the majority of energy intake (81.7 (71.6-91.5) kcal/kg/d PN vs 4.5 (0.2-20.4) kcal/kg/d enteral nutrition). By the end of the study, enteral intake increased; however, the majority of energy intake was from PN (62.7 (54.2-82.1) kcal/kg/d PN vs 25.9 (6.5-53.8) kcal/kg/d enteral nutrition) (Table 4). Prior to the start of the study, subjects were receiving SO with an average 378±191 mg/kg of LA and 68±34 mg/kg of ALA with no ARA, DHA or EPA. At the end of the study, subjects were receiving FO with <9±2 mg/kg of LA, and an average of 5±1 to 32±8 mg/kg of ALA, 5±1 to 18±5 mg/kg of ARA, 66±17 to 142±37 mg/kg of DHA, and 59±1 to 130±34 mg/kg of EPA.

While receiving SO and prior to the start of FO, 31% of subjects had high LA and ALA concentrations, whereas no subjects had low LA and ALA concentrations. Over time on FO, LA and ALA concentrations decreased (−307 µmol/L per month, 95% CI −402, −211 and −17 µmol/L per month, 95% CI −26, −9, respectively, p<0.001 for both) (Figure 1, Table 5). Subjects were more likely to develop low LA concentrations on FO vs. SO (odds ratio [OR] 1.8, 95% CI 1.4, 2.3, p<0.01). However, this was not case with ALA. On SO, 23% of subjects were noted to have high ARA concentrations. Over time with FO, ARA concentrations decreased (−45 µmol/L/mo, 95% CI −95, 4, p<0.001), without a concomitant risk for low ARA concentrations at 6 months (Figure 2, Table 5).

On SO, 46% and 15% of subjects had high DHA and EPA concentrations, respectively. Over time with FO, DHA and EPA concentrations increased (144 µmol/L/mo, 95% CI 29, 258 and 226 µmol/L/mo; 95% CI 66, 386, respectively; p<0.01 for both). After 6 months of FO,

87% and 100% of subjects had high DHA and EPA concentrations. Subjects were more likely to develop high DHA concentrations on FO vs. SO (OR 1.6, 95% CI 0.9-2.6); however this not statistically significant ($p=0.08$). The risk for high EPA concentrations could not be calculated, since 100% of the subjects had high EPA concentrations throughout FO treatment (Figure 2, Table 5). Overall, specific fatty acid percentages of total fatty acids followed a similar pattern of change (Table 5).

There was no evidence of an EFAD. Mead acid decreased over time ($-1.0 \mu\text{mol/L/mo}$, 95% CI $-2, -0.2$, $p<0.001$) (Figure 3, Table 5). Mean triene:tetraene ratios ($\pm\text{SD}$) were unchanged and normal when compared to age-specific ranges (0.02 ± 0.01 at baseline and 3 and 6 months; $p=1$). There were no physical manifestations of an EFAD.

Discussion

In this study, children with IFALD, who received some enteral nutrition and whose SO was replaced with FO, did not develop an EFAD as measured by a triene:tetraene ratio. As expected, changes in circulating fatty acids reflect changes in lipid emulsions. Serum concentrations of traditional essential fatty acids, LA and ALA, decreased significantly over time. 67% of subjects had low LA levels after 6 months of FO. However, only 1 subject had a low ARA level at 3 months, and none of the subjects had low ARA levels at 6 months of FO. The subject who had a low ARA level at 3 months was born premature at 34 weeks gestational age and was receiving some enteral feeds at the time of the fatty acid measurement. Very few subjects developed low ALA levels while receiving FO, and Mead acid levels decreased. Lastly, no one had low DHA or EPA levels on either lipid emulsion.

EFAD was first described in the 1930s in experiments in rats fed fat-free diets.¹³ These rats grew poorly, were sterile, developed scaly skin, and died.¹³ These symptoms were reversed with a small amount of LA.¹³ Although ALA is also considered an essential fatty acid because it serves as a precursor to DHA and EPA, its role in growth, reproduction, skin integrity and other physiological processes is less important. In the 1960s, Holman defined an EFAD as a triene:tetraene ratio >0.4 based on animal experiments.¹³ This triene:tetraene threshold was thought to capture the minimum dietary requirement for LA.¹³ In 1979, based on experiments in humans, Holman revised this threshold to 0.2. Since then, lower thresholds that are age-specific have been proposed and reflect more precise fatty acid measurements.¹⁴ In this study, the mean triene:tetraene ratio was 0.02, which is considered normal.¹²

This study reconfirms results of previously published studies; FO contains sufficient downstream fatty acids to compensate for its small amount of LA and ALA.^{2,9-11} Le *et al* followed 79 pediatric patients with short bowel syndrome treated with FO and found decreased LA, ALA, and ARA, and increased DHA and EPA in the context of decreasing Mead acid.² In the aforementioned study, a rapid decrease in omega-6 fatty acids and rapid increase in omega-3 fatty acids was observed.² This pattern is slightly different than the pattern we observed in our study. This is because we measured fatty acids at only three time points, whereas Le *et al* measured fatty acids weekly.² In this same study, triene:tetraene ratios with FO ranged from a median 0.022 (IQR 0.016-0.031) at the start of FO to 0.028

(IQR 0.019-0.042) at the end of FO.² Another study of premature infants treated with FO showed a clinically nonsignificant increase in the mean triene:tetraene ratio ($\pm$ SD) after 1 month of FO (0.013 ± 0.005 with SO and 0.028 ± 0.017 with FO). However, after 3 months of FO, the triene:tetraene ratios were comparable to values obtained at the start of the study on SO.¹⁰

With FO, DHA and EPA increased dramatically. Increased EPA concentrations may also be secondary to DHA retroconversion.¹⁵ There are concerns that increased EPA concentrations may increase the risk for bleeding.^{16,17} However, this concern remains controversial. In addition, there is a concern that elevated DHA and EPA levels will suppress LA's conversion to ARA, and this decline may have adverse consequences since ARA is essential for growth and neurodevelopment.^{5,18-21} In this study and other studies, ARA decreased over time.^{2,9-11} However, we only observed 1 low ARA concentration at 3 months of FO treatment. These findings are most likely because FO contains some ARA and/or dietary ARA intake. Studies have not demonstrated growth faltering with FO; in fact, some studies demonstrate improved growth.³ To date, there is only 1 randomized controlled trial that investigated neurodevelopmental scores in infants who received either FO or SO.²² Although this study was stopped early for futility concerns and was underpowered, there was no difference between the 2 groups for neurodevelopment.²²

In contrast to our study population, preterm neonates receiving PN with SO, even when dosed at 3 g/kg/d, demonstrate a postnatal decline in ARA and DHA over the first couple weeks of age.^{23,24} Although SO provides the parent essential fatty acids, LA and ALA, many people believe there is a need for preformed ARA and DHA in lipid emulsions in the neonatal intensive care unit. First, preterm infants have an increased demand for ARA and DHA.^{5,23,24} Second, in preterm and cholestatic infants, endogenous synthesis of ARA and DHA from their parent essential fatty acid is inefficient.²³⁻²⁵ Third, in preterm infants, low DHA and ARA levels are linked to sepsis, retinopathy of prematurity, chronic lung disease, and developmental delays.^{5,23,24} Although substituting SO for FO may appear like an attractive option to mitigate this deficiency, FO may exacerbate this postnatal ARA deficit and have adverse consequences in preterm infants.^{18-20,26} In a meta-analysis of preterm infants who received a composite lipid emulsion (7 studies with lipid composed of 30% soybean oil, 30% medium-chain triglycerides and 25% olive oil and 1 study with a lipid composed of 50% medium-chain triglycerides, 40% soybean oil, and 10% FO), plasma and erythrocyte ARA levels were lower when compared to preterm infants who received SO (mean difference, 1.27% and 0.92%, respectively with $p<0.001$ and $p=0.02$).²⁷ It remains unclear how fatty acid levels will evolve on long-term composite lipid emulsions in preterm infants, and after switching from a composite lipid emulsion to FO for IFALD treatment. It should be noted that the associations between fatty acids and specific co-morbidities in preterm infants without cholestasis who receive SO may not translate to children with IFALD who receive FO.

In contrast to the above studies in preterm infants, in our study, subjects were less premature and FO was initiated at a median of 3.6 months of age.^{11,23} In fact, contrary to traditional thinking, in our study, young children receiving SO were not deficient in ARA and DHA at baseline. In fact, prior to switching to FO, 23% of the subjects had high ARA

concentrations, and 46% had high DHA concentrations. When SO was replaced by FO, 1 subject developed a low ARA concentration at 3 months, and 1 subject had a high ARA concentration at 6 months. At the same time, while receiving FO, the majority of subjects had high DHA concentrations.

Many have postulated that one of the causes of IFALD is the pro-inflammatory environment induced by high concentrations of omega-6 fatty acids and low concentrations of DHA.¹⁻³ Contrary to this hypothesis, in our previous study, ARA was inversely correlated with conjugated bilirubin.⁴ It remains to be determined if this is a type I error or if it is clinically relevant. In a previous study of children with non-IFALD cholestasis, ARA and DHA concentrations were inversely correlated with liver function tests.²⁵ The authors of this study proposed that these results were secondary to impaired hepatic desaturase activity. Unfortunately, in children with IFALD who are receiving an infusion of fatty acids, it is difficult to determine the liver's impact on serum fatty acids.

The optimal enteral ARA-DHA is controversial.²⁶ When compared with infants who were fed formulas supplemented with fish oil and ARA, infants fed formulas supplemented with fish oil without ARA did not grow well, had lower psychomotor scores, and poorer attention spans.^{5,18-20} These findings are attributed to low ARA concentrations, which most likely occur secondary to competitive inhibition by high EPA and DHA levels.⁷ Animal studies demonstrate that high DHA provisions without ARA provisions that match or exceed DHA during fetal and neonatal life cause growth failure and adverse neurobehavioral outcomes.^{18,19} For these reasons, since the early 2000s, infant formulas contain preformed ARA in equal or higher amounts than DHA.²⁶ The ARA-DHA ratio of FO does not fulfill this recommendation. Hence, it is important that FO be reserved for children with IFALD and not used as the sole source of parenteral fat in children without IFALD. It remains unclear what the optimal ARA-DHA ratio in lipid emulsions is and whether it should be similar or different than the ratio in breast milk or formulas.

We recognize the limitations of our study. The sample size is small, and fatty acids were measured at only 3 time points. We also could not account for enteral absorption of fatty acids. It is difficult to accurately quantify enteral nutrition in children with malabsorption who eat *ad libitum*. As a result, it remains unclear if we would observe the same results in children with IFALD who were not receiving enteral nutrition while being treated with FO. We chose to compare our subject's values to published ranges by the Mayo Clinic.¹² Although these ranges are accepted for defining fatty acid norms, these ranges are based on a small sample size (n=37 for <1 month, n=79 for 1 month-12 months, n=37 for 1 year-17 years, n=43 for >17 years of age).¹² Improvements on the originally described method for measuring fatty acids have been reported in larger sample sizes and provide additional reference values.²⁸ Overall, there remains a paucity and lack of consensus in the literature delineating normal values of fatty acid concentrations and triene:tetraene ratios in different groups of children.

In conclusion, in this study of children with IFALD who were supplemented with some enteral nutrition, 1 g/kg/d of FO was not associated with an EFAD. Unless clinically indicated, routine, longitudinal measurements of fatty acid profiles may not be warranted for

all children who receive FO treatment for IFALD. The clinical significance of high and low levels of specific fatty acids warrants further study. Considering the increasing number of options of intravenous lipid emulsions for children, it is important for clinicians to be able to interpret fatty acid patterns and understand how to diagnose an EFAD.

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Abbreviations:

(ALA)	alpha-linolenic
(ARA)	arachidonic acid
(CI)	confidence interval
(DHA)	docosahexaenoic
(EFAD)	essential fatty acid deficiency
(EPA)	eicosapentaenoic acid
(FO)	fish oil
(IFALD)	intestinal failure associated liver disease
(LA)	linoleic acid
(OR)	odds ratio
(PN)	parenteral nutrition
(SO)	soybean oil

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Clinical Relevancy Statement:

Fish oil-based (FO) lipid emulsions are a common treatment of pediatric intestinal failure associated liver disease. Unlike soybean-based lipid emulsions, FO is composed primarily of the downstream omega-3 fatty acids (docosahexaenoic and eicosapentaenoic acids) and contains a small amount of the essential fatty acids (linoleic and alpha-linolenic acids). For these reasons, there are concerns that FO will cause an essential fatty acid deficiency (EFAD). In this prospective study, children who received FO had low and high levels of specific fatty acids. However, while linoleic and arachidonic acid concentrations decreased over time, there was not a significant risk for an arachidonic acid deficiency. Moreover, Mead acid concentrations decreased and triene-tetraene ratios remained stable. We conclude that FO does not cause an EFAD as measured by triene-tetraene ratios in children with intestinal failure.

Figure 1.

Serum concentrations of ALA and LA are expressed as mean $\pm$ SD in $\mu\text{mol/L}$, $p < 0.01$ for both over time. The percentage of subjects with low or high fatty acid concentrations and risk for low or high fatty acid concentrations with fish oil (FO) are depicted. ALA, alpha-linolenic; LA, linoleic acid. Dotted lines represent upper limits of normal; dashed lines represent lower limits of normal by age.¹³

Figure 2.

Serum concentrations of EPA, DHA and ARA are expressed as mean $\pm$ SD in $\mu\text{mol/L}$, $p < 0.01$ for all 3 over time. The percentage of subjects with low or high fatty acid concentrations and risk for low or high fatty acid concentrations with fish oil (FO) are depicted. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; ARA, arachidonic acid. Dotted lines represent upper limits of normal; dashed lines represent lower limits of normal by age.¹³

Figure 3.

Serum concentrations of OA and MA are expressed as mean $\pm$ SD in $\mu\text{mol/L}$, $p=0.01$ for OA and $p<0.01$ for MA over time. The percentage of subjects with low or high fatty acid concentrations and risk for low or high fatty acid concentrations with fish oil (FO) are depicted. OA, oleic acid; MA, mead acid. Dotted lines represent upper limits of normal; dashed lines represent lower limits of normal by age.¹³

Table 1.

Soybean and fish oil fatty acid composition

Emulsion	Soybean Oil	Fish Oil
Oil		
Soybean	100	0
Fish	0	100
Fatty acids (g)		
Linoleic acid	5	0.1-0.7
α -linolenic acid	0.9	<0.2
Arachidonic acid	0	0.1-0.4
Docosahexaenoic acid	0	1.44-3.09
Eicosapentaenoic acid	0	1.28-2.82
Oleic acid	2.6	0.6-1.3
Palmitic acid	1	0.25-1
Stearic acid	0.35	0.05-0.2

10g fat per 100mL solution.

Table 2.**Demographics**

Age at the start of FO (months)	3.6 (2.4-9.6)
Gender, male	10 (59%)
Race, White	15 (88%)
Ethnicity, Hispanic	14 (82%)
Gestational age, weeks	36 (33.5-37.8)
Small bowel length, cm	15 (8.5-29)
Intestinal surgeries before enrollment	2 (1-3)
Late-onset sepsis during study	1 (0-2)
Intestinal surgeries during study	0 (0-0.5)
PN duration at the start of FO, months	3.5 (2.3-8.1)
PN duration during the study, months	5.5 (5.3-5.5)

Data are represented as median (interquartile range Q1-Q3) or n (%). Analyses for small-bowel length were based on available data (n=13). FO, fish oil; PN, parenteral nutrition.

Table 3.

Liver function tests over time

	Soybean Oil	Fish Oil 3 months	Fish Oil 6 months	Slope unit/month (95% CI)	P- value
Total bilirubin	10±5	5±9	0.5±0.2	-1.5 (-2.0,-1.1)	0.001
Conjugated bilirubin	6±3	3±5	0.2±0.1	-1.0 (-1.2,-0.7)	0.001
AST	182±139	108±94	57±38	-21 (-33,-9)	0.01
ALT	153±120	107±70	72±72	-13 (-23,-3)	0.03

Data are represented as mean ± SD. AST, aspartate aminotransferase; ALT, alanine aminotransferase. Bilirubin values are expressed in mg/dL; AST and ALT are expressed in U/L.

Table 4.

Nutrition at the start of the study and end of the study

	Soybean Oil (n=17)	Fish Oil 6 months (n=17)	p- value
PN calories, kcal/kg/d	81.7 (71.6-91.5)	62.7 (54.2-82.1)	0.002
Glucose delivery rate, mg/kg/min	14.2 (13-17.1)	15.6 (12.2-19.1)	0.9
Amino acid, g/kg/d	2.8 (1.7-3.1)	1.8 (1.4-2.1)	0.001
Lipid, g/kg/d	1.5 (1-1.8)	1 (0.9-1)	0.01
Breast milk, %	29 (5)	12 (2)	0.25
Solids, %	18 (3)	65 (11)	0.008
Enteral calories, kcal/kg/d	4.5 (0.2-20.4)	25.9 (6.5-53.8)	0.08

Data are represented as median (interquartile range Q1-Q3). PN, parenteral nutrition.

Table 5.

Fatty acid percent concentrations over time

$\mu\text{mol/L}$	Soybean Oil	Fish Oil 3 months	Fish Oil 6 months	Slope $\mu\text{mol/L/month}$ (95% CI)	P-value
LA	3381 $\pm$ 1154	1273 $\pm$ 567	1461 $\pm$ 1203	-307 (-402, -211)	<0.001
ALA	146 $\pm$ 115	39.4 $\pm$ 21.1	41.1 $\pm$ 45.7	-17 (-26, -9)	<0.001
ARA	815 $\pm$ 337	452 $\pm$ 199	521 $\pm$ 524	-45 (-95, 4)	<0.001
EPA	49.2 $\pm$ 23.8	1080 $\pm$ 513	1390 $\pm$ 1899	226 (66, 386)	<0.001
DHA	235 $\pm$ 119	905.3 $\pm$ 474	1085 $\pm$ 1406	144 (29, 258)	<0.001
Oleic acid	1486 $\pm$ 446	1240 $\pm$ 302	1235 $\pm$ 582	-39 (-79, 2)	0.02
Mead acid	14.5 $\pm$ 8.1	7.4 $\pm$ 2.4	8.1 $\pm$ 4.4	-1 (-2, -0.2)	<0.001
% total FA	Soybean Oil	Fish Oil 3 months	Fish Oil 6 months	Slope %/month (95% CI)	p-value
LA	33 $\pm$ 7	15 $\pm$ 4	16 $\pm$ 7	-2.7 (-3.5, -1.9)	<0.001
ALA	1 $\pm$ 0.8	0.5 $\pm$ 0.2	0.4 $\pm$ 0.2	-0.14 (-0.2, -0.07)	<0.001
ARA	8 $\pm$ 2.3	5 $\pm$ 1	6 $\pm$ 1	-0.4 (-0.58, -0.15)	<0.001
EPA	0.5 $\pm$ 0.2	13 $\pm$ 3	14 $\pm$ 5	2.1 (1.6, 2.6)	<0.001
DHA	2 $\pm$ 0.7	11 $\pm$ 3	11 $\pm$ 5	1.3 (0.9, 1.8)	<0.001
Oleic acid	14 $\pm$ 2	15 $\pm$ 2	15 $\pm$ 2	0.07 (-0.08, 0.23)	0.37
Mead acid	0.1 $\pm$ 0.1	0.1 $\pm$ 0.0	0.1 $\pm$ 0.0	-0.006 (-0.011, -0.001)	0.02

Data are represented as mean $\pm$ SD. P-values calculated from log-transformed values for fatty acid concentrations only. LA, linoleic acid; ALA, alpha-linolenic; ARA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic.