Applied nutritional investigation

# Intravenous lipid emulsions and liver function in adult chronic intestinal failure patients: results from a randomized clinical trial

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## ARTICLE INFO

## ABSTRACT

*Aim:* Intravenous lipid emulsion (ILE) can become a risk factor for intestinal failure associated liver disease (IFALD). Many ILEs are commercially available, however, a direct comparison of their impact on liver has, to our knowledge, never been performed. The aim of the study was to analyse that clinical problem during long term parenteral nutrition (PN).
*Methods:* A randomized, controlled clinical trial was performed at the Intestinal Failure Center in Skawina, Poland. Sixty-seven patients (37 F, 30 M, mean age 53.9 years) enrolled in home parenteral nutrition (HPN) due to stable chronic intestinal failure (CIF) were randomized to receive one the following for 12 months: long-chain triglycerides (LCT), medium/long-chain triglycerides, olive oil/LCT (OO/LCT) and a mix of LCT/MCT/OO/fish oil. Clinical evaluation and biochemical tests (total bilirubin, SGOT, SGTP, GGPT, alkaline phosphatase) were performed at enrolment and after 6 and 12 months.
*Results:* the most common reason for intestinal failure (IF) was short bowel due to mesenteric ischaemia, followed by Crohn's disease, surgical complications and radiation enteritis. PN stabilized liver parameters in all patients. No essential fatty acids deficiency was diagnosed. All four ILEs demonstrated comparable influence on liver in all study periods. The only exception was the decrease in total bilirubin concentration after 12 months ($28.1 \pm 25.3$ vs $11.1 \pm 4.5$, $p = 0.0023$) and GGTP ($222.5 \pm 205.8$ vs $146.6 \pm 197.7$, $p = 0.0079$) when OO/LCT was in use.
*Conclusions:* All four ILEs tested may be safe even during long-term parenteral nutrition. OO/LCT may be more effective than the others, but more studies in the field are needed.

## Introduction

Intravenous lipid emulsions (ILEs), which are essential components of parenteral nutrition (PN), are a good source of energy as well as essential fatty acids (FAs) [1−5]. The first ILEs were based on cotton seed oil or soybean oil (i.e., long-chained triacylglycerols [LCTs]) [3−10] and were useful in metabolically stable patients but deleterious in septic and unstable patients and perhaps also in those who receive long-term nutrition support. Hence, less proinflammatory and immunosuppressive ILEs were developed. These newer ILEs included mixtures of medium-chain triacylglycerols (MCTs) and LCTs, olive oil and LCT (OO/LCT; ClinOleic, Baxter Healthcare), and MCT, LCT, OO, and fish oil (SMOFlipid, Fresenius Kabi) [3,7−11].

In general, there appear to be few differences in patient outcomes when using these different ILEs. A pure fish-oil ILE is also available but although this has been shown to be effective in the intensive care unit after surgery and in patients with liver failure [11], there are concerns that pure fish oil may not supply sufficient essential FAs. On the other hand, a recent study by Anez-Bustillos et al. [12] proved otherwise; hence, patients who do not receive ILEs other than omega-3-polyunsaturated FAs (PUFAs) may not develop essential FAs deficiency.

**Table 1**
General characteristics and nutritional parameters by group

| | Lipofundin MCT/LCT | ClinOleic | Smoflipid | Intralipid | P value |
|---|---|---|---|---|---|
| General description | | | | | |
| Number of patients, n | 18 | 17 | 16 | 14 | − |
| Female, n (%) | 10 (55.5%) | 10 (58.8%) | 8 (50%) | 9 (56.25%) | 0.6585* |
| Male, n (%) | 8 (44.5%) | 7 (41.2%) | 8 (50%) | 5 (43.75%) | |
| Mean age, y ± SD | 56.3 ± 15.4 | 54.8 ± 12.9 | 47.8 ± 12.5 | 59.6 ± 17.6 | 0.1190[†] |
| Mean BMI at baseline, kg/m$^2$ ± SD | 19.5 ± 4.2 | 18.9 ± 2.9 | 18.5 ± 4.3 | 22.2 ± 6.5 | 0.1865[†] |
| Mean BMI at 3 mo, kg/m$^2$ ± SD | 21.5 ± 3.9 | 19.9 ± 2.8 | 20.5 ± 4.1 | 22.0 ± 4.5 | 0.4913[†] |
| Mean BMI at 12 mo, kg/m$^2$ ± SD | 21.4 ± 3.3 | 22.3 ± 2.1 | 20.2 ± 4.5 | 24.0 ± 3.9 | 0.0264[†‡] |
| Nutritional support | | | | | |
| Length of PN before admission (d) | 23 ± 3.5 | 22 ± 4.0 | 25 ± 1.5 | 25 ± 2.0 | 0.366 |
| Mean lipid, g/kg body weight/d ± SD | 0.7 ± 0.2 | 0.6 ± 0.4 | 0.7 ± 0.2 | 0.7 ± 0.2 | 0.3412[†] |
| Mean energy, kcal/kg/d ± SD | 20.0 ± 4.4 | 20.8 ± 5.8 | 23.1 ± 6.1 | 18.2 ± 5.4 | 0.0627[†] |
| Mean nitrogen, g/kg/d ± SD | 0.15 ± 0.2 | 0.16 ± 0.1 | 0.15 ± 0.1 | 0.16 ± 0.2 | 0.0333[†§] |
| Mean volume administered, mL/d ± SD | 1332.5 ± 390.9 | 1428.1 ± 233.1 | 1448.2 ± 896.7 | 1446.8 ± 203.2 | 0.0036[†] |
| Mean number of PN bags used per week, ± SD | 6.1 ± 1.0 | 6.1 ± 0.9 | 6.2 ± 1.0 | 5.6 ± 0.7 | 0.0013[†] |
| Cather-related bloodstream infections per 1000 catheter d | 0.55 | 0.7 | 0.35 | 0.6 | 0.667 |

BMI, body mass index; LCT, long-chain triacylglycerols; MCT, medium-chain triacylglycerols; PN, parenteral nutrition; SD, standard deviation.
*χ$^2$ test.
[†]Analysis of variance.
[‡]Smoflipid and Intralipid groups are different.
[§]ClinOleic and Smoflipid groups are different.

Some patients such as those who are critically ill, have chronic intestinal failure (CIF), and receive home parenteral nutrition (HPN) are particularly exposed to intestinal failure-associated liver disease (IFALD) [13–19]. IFALD is one of the most dangerous complications of HPN and is potentially life threatening [13,14]. PN, intestinal failure, and inflammation are etiological factors that influence the risk of developing IFALD [19]. The amount and type of ILE that is used in PN and the possible excess of energy intake are among the possible major causes of IFALD [13]. ILEs at a dose of >1 g fat/kg body weight/d and omega-6-PUFAs as a sole source of lipids are known to play a role in the etiology of IFALD [11]. If decreasing the amount of energy intake and/or the excess of lipids is not effective enough, the antiinflammatory properties of the second or third generation ILEs may be the only method to improve the liver function. The most significant clinical outcome has been observed with omega-3-PUFAs as the sole ILE or in combination with other ILEs. The clinical gain is the most spectacular in the pediatric population [17]. Some authors observed an improvement in the liver function of adults as well; however, this was obvious only for omega-3-PUFAs and the impact of other ILEs remains unknown.

Moreover, no study has directly compared the impact of all commercially available ILEs on the liver in adults who receive long-term HPN. Therefore, the aim of this study was to compare all four ILEs with regard to impact on the liver by assessing the clinical status of patients and liver test results after 12 mo. Total bilirubin and liver tests along with clinical status were selected to describe the liver function because their elevation and particularly the progressive one may indicate an emerging risk of IFALD. The primary hypothesis was that the second generation of ILEs will improve the liver test results and decrease total bilirubin during HPN compared with LCTs.

## Methods

A randomized, controlled, clinical study of four parallel groups was performed at the Intestinal Failure Center of the Stanley Dudricks' Memorial Hospital in Skawina, Poland between January 1, 2010 and December 31, 2015. A total of 88 patients (48 male and 40 female patients; mean age: 54.5 y) who were admitted to start HPN due to stable CIF were randomly assigned during the recruitment period (January 2010−March 2014) to receive PN with one the following lipid emulsions: LCTs (LCT group; Intralipid, Fresenius Kabi, Germany); MCTs/LCTs 50:50 (MCT/LCT group; Lipofundin, B Braun Germany); OO/LCTs 80:20 (OO group; ClinOleic, Baxter Healthcare); and MCTs/LCTs/OO/fish oil (SMOF group; SMOFLipid, Fresenius Kabi,

Germany). The solutions were mixed with other macro- and micronutrients at the compounding unit of the Skawina Hospital pharmacy.

Assignment to the treatment groups was performed after assessment and check of the inclusion and exclusion criteria. The randomization and blinding were performed by the chief of the hospital pharmacy. The study treatment was blinded for the physician and patient. Consecutive patients were randomly assigned to one of the four treatment groups using sequentially numbered, sealed, and opaque envelopes. Patients were matched on the basis of age, sex, body mass index, type of nutrition, and diagnosis.

Patients were referred to the intestinal failure center from other hospitals around the country. All patients received all-in-one PN with ILE before inclusion in the study; however, detailed data on the type of emulsion were unavailable because hospitals are not obliged to report these data at the time of discharge. Detailed characteristics of the patients are presented in Tables 1 and 2.

### Intervention

The test emulsion was added to the regular PN admixture, which was used to feed patients at home. The study lasted 12 mo. The treatment period was defined as the time from the first administration of the study drug until the final infusion and the follow-up period included 4 wk after the last administration of the tested emulsion drug.

The study was terminated if the laboratory test results showed a serum triacylglycerol concentration >3 mmol/L (>262.5 mg/dL), an intolerable or serious adverse event was observed, or a failure of therapeutic safety or tolerability caused an unacceptable risk/benefit ratio.

**Table 2**
Causes of intestinal failure by group

| Cause of intestinal failure | Lipofundin MCT/LCT (n = 18) | ClinOleic (n = 17) | Smoflipid (n = 16) | Intralipid (n = 14) |
|---|---|---|---|---|
| Vascular | 7 | 8 | 7 | 6 |
| Crohn's disease | 3 | 3 | 4 | 2 |
| Surgical | 2 | 2 | 2 | 2 |
| Radiation enteritis | 2 | 1 | − | 1 |
| GI fistula (Crohn's disease excluded) | 1 | − | 1 | 1 |
| Malabsorption | 1 | 1 | − | − |
| Motility disorders | 1 | − | − | 1 |
| Benign GI obstruction | 1 | − | − | − |
| Trauma | − | 1 | 1 | − |
| Necrotizing enterocolitis | − | − | 1 | − |
| Other | − | 1 | − | 1 |

GI, gastrointestinal; LCT, long-chain triacylglycerols; MCT, medium-chain triacylglycerols.

*Inclusion and exclusion criteria*

The inclusion criteria were ≥18 y of age, CIF while on PN including lipids, metabolic stability (i.e., absence of pathologic laboratory testing that resulted in a change of PN regime for at least 1 mo), and ability to tolerate up to 1.0 g lipids/kg body weight per day as a part of PN. The exclusion criteria were preexisting liver dysfunction (i.e., elevated levels of serum glutamic oxaloacetic transaminase, serum glutamate pyruvate transaminase, total bilirubin, gamma-glutamyl transpeptidase [GGTP], and alkaline phosphatase >3 × normal value), history of cancer and anticancer treatment within the last 5 y, severe hyperlipidemia, severe coagulopathy, severe renal insufficiency, acute thromboembolic events, positive test for HIV, Hepatitis B or C (from medical history), known or suspected drug or alcohol abuse, and participation in another interventional clinical trial in parallel or within 3 mo before the start of this clinical trial. Women with childbearing potential (i.e., female patients who are not chemically or surgically sterile or not postmenopausal), of childbearing potential who tested positive on a standard pregnancy test (e.g., urine dipstick), and/or those who are lactating were also excluded from the study.

*Clinical management*

ILEs were infused via a central venous catheter as part of all-in-one solutions along with amino-acids, glucose, electrolytes, vitamins, and trace elements. For each patient, the required nutritional supply was calculated per day. The lipid delivery rate was established to stay between 0.6 and 0.8 g/kg/d. All patients were allowed to consume food orally. The oral provision of nutrients did not exceed 10% of the entire energy and protein intake, which was assessed by a dietitian.

Biochemistry, hematologic, coagulation, and inflammatory parameters as well as vital signs were determined. All adverse events were documented and evaluated. The laboratory variables included for biochemistry were triacylglycerols, total cholesterol, alkaline phosphatase, serum glutamic oxaloacetic transaminase, GGTP, serum glutamate pyruvate transaminase, sodium, potassium, chloride, magnesium, calcium, phosphate, total bilirubin, creatinine, urea, glucose, albumin, and total protein. Hematologic laboratory variables were leucocytes, platelets, erythrocytes, hemoglobin, and hematocrit. Coagulation was determined using the international normalized ratio.

*Clinical variables*

The clinical variables for the study were incidence of cholestasis (defined as either conjugated bilirubin >3-fold upper limit of normal and either GGTP or alkaline phosphatase >3-fold upper limit of normal, or conjugated bilirubin alone >2 mg/dL without an explanation for another etiology such as viral hepatitis), adverse events, and vital signs (blood pressure [mmHg], heart rate [beats/min], and body temperature [°C]). The laboratory safety variables and vital signs were recorded every 3 mo, 12 h after completion of an infusion and before the start of the next infusion.

Adverse events were registered during the entire study period and during the 4 wk of follow-up time. An adverse event was defined as any untoward medical occurrence in a patient that did not necessarily have a causal relationship with the treatment. A serious adverse event was any untoward medical occurrence that at any dose resulted in death, was life threatening ("life threatening" in the definition of "serious" referred to an event in which the patient was at risk of death at the time of the event but not an event that hypothetically might have caused death if it were more severe), required inpatient hospitalization or the prolongation of an existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect.

The intensity of all adverse events was rated in accordance with the Common Terminology Criteria for Adverse Events version 3.0. Each adverse event was classified in one of the five categories and represented the maximum intensity that was reported during the evaluation period in question. The classifications were grade 1 mild, grade 2 moderate, grade 3 severe, grade 4 life threatening or disabling, and grade 5 death-related adverse event.

*Ethics and consent*

The ethics committee of the Jagiellonian University Medical School approved the study [KBET/39/L/2010]. Patients were approached and enrolled by one of two investigators (SK, KSz). Informed written consent was obtained from each participant before enrollment. The study was carried out in accordance with the international ethical recommendations of the Helsinki Declaration and registered under number NCT03044639 at ClinicalTrials.gov.

*Statistical analysis and sample size calculation*

All data were analyzed with Statsoft STATISTICA version 12. The results are presented as either mean ± standard deviation (SD) or median as appropriate. The study of the categorical variables used the $\chi^2$ test of independence. The Shapiro-Wilk test was used to check for normal distribution of data. For non-normally distributed quantitative variables, the Kruskal Wallis test was used and for normally distributes variables, when the remaining test assumptions were met, an analysis of variance was conducted. Post hoc analyses included the Tukey and Dunn tests. The results were considered statistically significant when the *P* value was <0.05.

The decrease/increase of the liver parameters after 12 mo was assumed to be approximately 100% and a dropoff rate of 20% was anticipated. To detect an increase or decrease in the concentration of liver parameters by 100% due to lipid emulsion, approximately 15 patients were allocated to each of the two compared arms (α=0.05 two-sided; power=0.80). The sample size was calculated using SamplePower 2 (SPSS Inc, Chicago, IL).

## Results

Eighty-eight patients were randomized but only 65 patients (37 female and 28 male patients; mean age: 53.9 y) completed the 12-mo study period and were eligible for the analysis per the protocol (Fig. 1).

Relatively many patients were lost to follow-up (n = 16) due to transfer to another HPN center (n = 11), elective surgery for gastrointestinal fistula (n = 3), and weaning off/ reduction of HPN due to improved function of the gastrointestinal tract (n = 3). There were no significant differences among the study groups with regard to sex, age, body mass index, underlying disease, and intake of energy, proteins and lipids (Tables 1 and 2).

The liver test results are presented in Table 3. The results normalized with time in all groups to the extent that after the 12-mo period, no statistically significant differences were observed between the groups (Table 3). Thus, the primary hypothesis of the study was not supported because none of the alternative ILEs was more effective than LCTs (Intralipid).

No serious adverse events were observed during the study period and no patients were prematurely terminated from the study due to an adverse event or serious adverse event. No signs of essential FA deficiency were diagnosed.

Oral intake was analyzed in all patient groups and changed/ increased with time; however, the time differences among the groups were not significant. The omega-9 FA-rich ILE based on OO (ClinOleic); however, reduced the bilirubin concentration (28.1 ± 25.3 μmol/L at the beginning versus 11.1 ± 4.5 μmol/L at the end; P=0.0023) and GGTP (222.5 ± 205.8 IU/L versus 146.6 ± 197.7 IU/L; P=0.0079). No other lipid emulsion exerted such an effect but this group started from the higher values at the beginning of the study. Nonetheless, this was the only group to demonstrate the trend between the 6th and 12th month.

## Discussion

ILE is an indispensable constituent of PN because it is a very good source of energy and essential FAs [1—5]. The oldest emulsion is LCT, which is soybean-derived and has been used for decades. LCT has been proven to be safe and well tolerated but potentially harmful because of the overzealous production of inflammatory mediators during long-term PN. New-generation ILEs such as MCTs, OO, and fish oil have been proven to be safer and have been gaining more attention. Also, these new ILEs have proven their clinical effectiveness in some patient groups. For example, the use of MCT/LCT emulsion helped to reduce the length of mechanical ventilation in patients in intensive care units, improved the condition of patients with chronic obstructive pulmonary disease, and improved albumin synthesis [15—18]. In surgical patients, a reduction of postoperative complications was observed even with the reduction of morbidity after hemihepatectomy [19,20].

OO has been observed to decrease oxidation and improve lymphocyte function [20]. Sala-Vila et al. [21] have summarized the
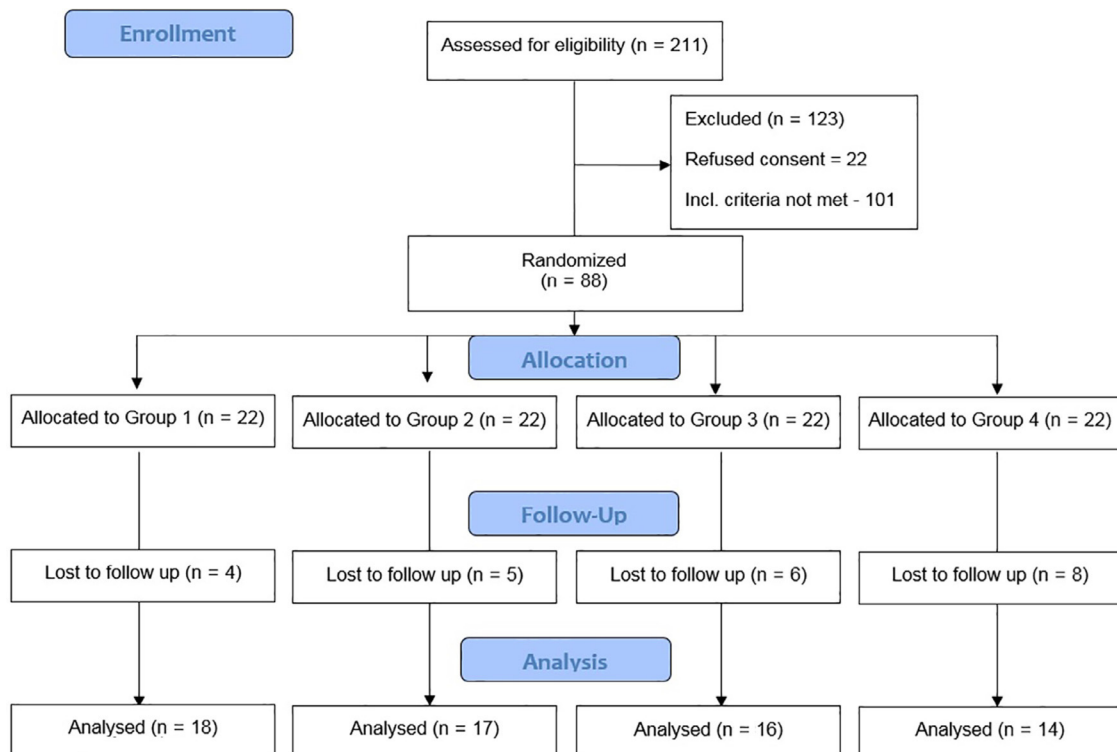
**Fig. 1.** CONSORT diagram.

**Table 3**
Liver function markers by group

| | Lipofundin MCT/LCT | ClinOleic | Smoflipid | Intralipid | P value |
|---|---|---|---|---|---|
| **Day 0** | | | | | |
| Median SGPT (UI/L, IQR) | 26.0 (15–38) | 38.5 (26–106) | 33.5 (25.5–41.5) | 34.0 (18–74) | 0.0144*,† |
| Normal range: < 40 IU/L | | | | | |
| Median SGOT (UI/L, IQR) | 23.3 (15.1–33) | 35 (27–68) | 22 (16.5–29.5) | 28 (19.9–38) | 0.0109* |
| Normal range: < 40 IU/L | | | | | |
| Median GGTP (UI/L, IQR) | 68 (28–112.3) | 165 (77–202) | 66 (32–90) | 60 (40–174) | 0.0220*,† |
| Normal range: < 40 IU/L | | | | | |
| Median alkaline phosphatase (UI/L; IQR) | 128.5 (92–219.3) | 175.5 (102–330) | 163 (112–324) | 134.5 (89–219) | 0.5380* |
| Normal value: < 270 IU/L | | | | | |
| Median bilirubin (μmol/L, IQR) | 9.4 (5.9–16.0) | 18.0 (11.6–33.7) | 9.4 (7.6–12.3) | 9.4 (5.9–18.5) | 0.0045*,† |
| Normal range, 3.42–20.6 μmol/L | | | | | |
| Median oral energy intake (kcal/d) | 534.5 (150–760) | 605.1 (95–810) | 555.5 (205–790) | 608.2 (170–780) | >0.05 |
| **After 6 mo of HPN** | | | | | |
| Median SGPT (IQR) | 25 (18–47) | 40 (22.5–59.5) | 37.6 (21.5–56.5) | 28 (20–48) | 0.1679* |
| Mean SGOT ± SD | 28.1 ± 17.4 | 33.0 ± 13.6 | 31.7 ± 15.5 | 30.0 ± 14.7 | 0.1709‡ |
| Median GGTP (IQR) | 44.3 (25–105.9) | 83.8 (27.5–246.5) | 74 (27.5–94.6) | 47 (25–81) | 0.3416* |
| Mean fatty acids ± SD | 194.0 ± 159.8 | 231.8 ± 192.0 | 203.1 ± 128.4 | 192.2 ± 100.5 | 0.7817‡ |
| Mean bilirubin ± SD | 12.3 ± 9.8 | 13.1 ± 6.8 | 18.4 ± 16.7 | 20.0 ± 34.6 | 0.0857‡ |
| Median oral energy intake (kcal/d) | 1380.4 (400–2200) | 1290 (550–2350) | 1352.5 (500–2350) | 1432.5 (490–2100) | >0.05 |
| **After 12 mo of HPN** | | | | | |
| Mean SGPT ± SD (U/L) | 36.1 ± 29.2 | 53.8 ± 54.7 | 47.3 ± 48.7 | 38.0 ± 29.5 | 0.8779‡ |
| Mean SGOT ± SD (U/L) | 29.6 ± 23.3 | 50.1 ± 56.0 | 42.7 ± 45.7 | 31.1 ± 23.0 | 0.5749‡ |
| Median GGTP (U/L; IQR) | 45.5 (23–80.5) | 29 (19–91.8) | 78 (27.5–80) | 65 (32.6–103) | 0.3616* |
| Mean alkaline phosphatase ± SD (U/L) | 214.3 ± 213.7 | 188.5 ± 124.5 | 280.2 ± 427.5 | 233.4 ± 318.6 | 0.9565‡ |
| Mean bilirubin ± SD μmol/L | 14.0 ± 10.2 | 11.1 ± 4.5 | 14.0 ± 10.9 | 16.8 ± 13.5 | 0.8466‡ |
| Median oral energy intake (kcal/d) | 1480.5 (510.1–2405) | 1510.7 (525–2240) | 1520.7 (670–2350) | 1476.5 (510–2211) | >0.05 |

GGTP, gamma-glutamyl transpeptidase; HPN, home parenteral nutrition; IQR, interquartile range; LCT, long-chain triacylglycerols; MCT, medium-chain triacylglycerols; SD, standard deviation; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamate pyruvate transaminase.
*Kruskal-Wallis H test.
†Significant difference between the Lipofundin and Clinoleic groups.
‡Analysis of variance.

literature on OO-based emulsions and concluded that they are safe, well tolerated, and present advantages in the liver function of patients with burns. Fish oil is a source of bioactive omega-3-PUFAs, eicosapentaenoic, and docosahexaenoic, which are recognized to reduce inflammation [4] and modify lipid metabolism, blood lipid concentrations, coagulation, inflammation, and immune function [10].

As mentioned previously, the PN regimen and particularly the type of ILE can be the etiological factor in the development of IFALD [19]. Therefore, the new ILEs should be beneficial in terms of hepatoprotection. Surprisingly, there has been a scarcity of valuable research on ILEs and IFALD in adults and a direct comparison of commercially available ILEs that are used for long-term PN has never been performed.

To our knowledge, our study is the first to be performed for such a long time period and prove that liver tests may normalize with time regardless of ILE type. Therefore, it can be assumed that none of the alternative ILEs was more effective than LCT (Intralipid), which proves the point that it is the quality of PN that matters the most. On the other hand, omega-9 FA-rich ILE that is based on OO (ClinOleic) reduced the bilirubin concentration ($28.1 \pm 25.3$ at the beginning versus $11.1 \pm 4.5$ at the end; $P=0.0023$) as well as GGTP ($222.5 \pm 205.8$ versus $146.6 \pm 197.7$; $P=0.0079$). No other lipid emulsion exerted such an effect. Therefore, we may speculate that some ILEs may be more effective than others. The pure omega-3-PUFA solution (Omegaven, Fresenius Kabi, Germany) was not included in the study because the use of pure fish oil solutions as the sole lipid source in PN may lead to essential FAs deficiency. In addition, to our knowledge, this is the first study to compare ILEs in patients with CIF who are totally dependent on HPN. The other strengths of the study include the long-time duration, a direct comparison of all four available ILEs, and the homogenous study group.

Nonetheless, the authors are aware of some limitations of the study such as the relatively significant loss to follow-up, lack of intent-to-treat (ITT) analysis or incomplete assessment of the laboratory parameters (including C-reactive protein and conjugated bilirubin), and lack of precise data on the PN used in other hospitals in terms of total energy provision and type of ILE used. These data were unobtainable because discharge papers do not have to contain that kind of data; hence, if the physician-in-charge did not provided us with that information, it was impossible to obtain. The same applies to the lack of length of PN in those units. The reason for the lack of ITT analysis was the doubt whether ITT including all patients (even those who received HPN for 1 to 2 mo) would contribute to the full picture of long-term PN and long-term use of ILEs.

Other available studies suffer from drawbacks as well. First, the research is short-term and generally not longer than 4 wk. Only two trials lasted longer (but only up to 6 mo), which disqualifies them as CIF studies [7,22−26]. Second, these studies were mostly non-inferiority studies, which did not prove any advantage of the newer emulsion over the traditional one [22−25]. Finally, many of the trials suffer from poor methodology (e.g., small groups and lack of randomization) or are just case reports [22−27].

Our results differ from those of the majority of available studies. A new systematic review on non-alcoholic fatty liver disease (NAFLD) showed that in 12 of 17 trials, a decrease in liver fat and/or other markers of NAFLD after supplementation with omega-3 PUFAs was reported [28]. Those findings suggest a leading key role for omega-3-PUFAs in the prevention of liver failure. However, not all of the included results can be applied to IFALD because patients with NAFLD do not suffer from intestinal failure and do not use PN. Pediatric trials have suggested much promise from inclusion of omega-3 PUFAs in PN and prevention or reversal of IFALD. de Meijer et al. [29] and Vernick et al. [30] observed the positive

impact of fish oil in liver disease in newborn infants. In our study, fish oil-containing ILE did not demonstrate any favorable clinical impact, which is consistent with the meta-analysis by Seide et al. [31], who demonstrated a lack of sufficient high-quality data to support the use of parenteral omega-3 PUFAs in children.

The impact of oral intake was analyzed in our patients' group. However, we did not find any differences among the groups; hence, we assumed that oral intake could not influence the outcomes.

The scale of positive impact of OO-based ILE in our study was only partially surprising. Some authors observed a hepatoprotective effect of OO in their studies but never in long-term observations [32−36]. Moreover, OO has been known for its resistance to oxidative stress and the lowest proinflammatory effect, which has been observed in both in vitro and in vivo studies [21,32,33]. OO is an important component of the Mediterranean diet, which is considered the healthiest diet in the world. Nevertheless, one could have expected an intravenous effect that was different from the oral one.

## Conclusions

In our opinion, the present study shows that if designed properly, PN is a safe therapy even in patients with CIF. This was proven by the normalization of the liver test results in all patients after the introduction of ILE as part of HPN. Moreover, all ILEs are safe and effective with regard to the liver even during long-term PN. We may hypothesize that OO-based ILE is more promising than other ILEs during long-term PN; however, some limitations of our study (e.g., highest initial total bilirubin concentration for that group) clearly demonstrate the need for more studies.

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