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Randomized Control Trials

Biomarkers of oxidation, inflammation and intestinal permeability in persons with diabetes mellitus with parenteral nutrition: A multicenter randomized trial

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SUMMARY

Background and aims: Parenteral nutrition (PN) composition could play a role in the management of systemic inflammatory response and intestinal barrier disruption. We aimed to evaluate changes in biomarkers of inflammation, oxidative status and intestinal permeability in patients with type 2 diabetes mellitus (T2DM) who received different PN lipid formulas.

Methods: This was a prospective study, including 94 patients with T2DM who received omega (n)-3 polyunsaturated fatty acids (PUFA)-enriched PN, a mixture of medium and long chain triglycerides (MCT/LCT) PN, or an olive oil-based PN. Serum levels of biomarkers of oxidative status, intestinal permeability and inflammation biomarkers were determined at day 1 and day 5 after PN initiation. Registered under ClinicalTrials.gov Identifier no. NCT02706119.

Results: At day 5 after the onset of PN, the MCT/LCT group had a significant reduction of 2 proinflammatory cytokines [interleukin (IL)-15, IL-17A], elevation of the anti-inflammatory cytokine IL-13 and increase of zonulin and indoxylsulfate. The olive oil group showed a statistically significant reduction of 5 proinflammatory cytokines [IL-1β, IL-17A, IL-6, cytokine-leukemia inhibitory factor (LIF) and tumor necrosis factor alpha (TNF-α)] and reduced concentrations of the anti-inflammatory cytokine IL-1RA, while the n-3 PUFA-enriched group presented a statistically significant reduction of 8 proinflammatory cytokines (interferon-gamma, IL-1β, IL-15, IL-17A, IL-6, LIF, monocyte chemoattractant protein 1, and TNF-α). In the between-group comparisons, indoxylsulfate significantly increased in the MCT/LCT group compared to the n-3 PUFA-enriched group, while 8-isoprostane and indoxylsulfate significantly increased in the MCT/LCT group compared to the other groups and superoxide dismutase significantly decreased in the MCT/LCT group compared to the other groups.

Conclusion: In patients with T2DM, PN lipid composition exerts a profound impact on proinflammatory, prooxidative and intestinal permeability biomarkers.

1. Introduction

Medical nutrition therapy (MNT) is an evidence-based process aiming to treat or manage a disease through nutrition. Despite enteral nutrition is the first choice in patients requiring MNT, parenteral nutrition (PN) is the appropriate therapy in patients with non-functioning gastrointestinal tract who are malnourished or at risk of malnutrition, as it has shown to reduce complications and mortality [1].

In patients receiving PN, the underlying disease leads to a systemic inflammatory response. Moreover, the lack of enteral feeding may cause microbiome alterations, facilitating a hyperpermeable intestinal barrier with dysregulation of the inflammatory response that favour translocation of pathogens and microbial metabolites [2].

Importantly, PN lipid composition could play a significant role in the management of these disturbances. Thus, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are omega (n)-3 polyunsaturated fatty acids (PUFA) derived from fish, have shown anti-inflammatory and antioxidative properties [3]. Accordingly, there has been increasing evidence in recent years supporting the use of fish oil-enriched lipid emulsion in PN [4], as they could reduce triglyceride levels, inflammatory markers and liver function enzymes, and improve morbidity and mortality in hospitalized patients, especially in post-surgical and oncology patients [3,5–7], when compared to PN based on soybean oil or mixtures of medium and long chain triglycerides (MCT/LCT) [8]. Moreover, the oleic acid, a n-9 monounsaturated fatty acid (MUFA), has also been associated with a lower risk of inflammatory disease, and olive oil-based PN could have advantages over those based on soybean oil or on MCT/LCT [9].

On the other hand, type 2 diabetes mellitus (T2DM) is a very prevalent condition in patients admitted to the hospital, predisposing to a pro-inflammatory environment. In line with this, hyperglycemia can upregulate proinflammatory factors and lead to oxidative stress, and in turn, increased oxidative stress and inflammation contribute to insulin resistance and impaired insulin secretion [10]. Furthermore, there is increasing evidence that gut microbiota dysbiosis and intestinal permeability are closely related to the pathogenesis of T2DM, favouring a proinflammatory state [11].

Previously, we demonstrated in the INSUPAR study that, in hospitalized adults with T2DM and indication for PN, an acceptable glycemic control can be both achieved with 100 % of insulin

requirements administered as regular insulin on PN bag or with 50 % administered as regular insulin on PN bag and 50 % administered as subcutaneous glargine insulin [12]. However, there are no available studies in patients with T2DM receiving PN that have assessed the role of different lipid emulsions on inflammation, oxidative status and intestinal permeability.

Taken all this together, in this study we aimed to assess the changes in biomarkers of inflammation, oxidative status and intestinal permeability, in patients with T2DM receiving PN with different lipid formulas.

2. Methods

2.1. Study design and participants

The present article is a substudy of the INSUPAR clinical trial, a prospective, randomized, open-label trial done in 26 centers in Spain (23 university hospitals and 3 non-university hospitals) [12]. In this trial, 163 inpatient adults with T2DM on a non-critical setting, with indication for PN, were randomly assigned, in a 1:1 ratio, to receive one of these two insulin regimens: 81 patients received 100 % of insulin requirements administered as regular insulin on PN bag and 82 patients received 50 % of insulin requirements administered as regular insulin on PN bag and 50 % administered as subcutaneous glargine insulin. Main results of the INSUPAR trial can be found elsewhere [3,12,13].

For the present study, all patients from the INSUPAR trial that had an available blood sample obtained on day 1 and day 5 after the initiation of PN (stored at −80 °C in the Hospital-IBIMA biobank, part of the Andalusian Public Health System Biobank) were included, dividing the full cohort into 3 groups depending on the type of PN used: olive oil group, MCT/LCT group, or n-3 PUFA group (Fig. 1).

The study was approved by the Spanish Agency for the Regulation of Drug and Healthcare Products (EUDRACT 2015-003954-42), the Research Ethics Committee provincial of Málaga, and was registered at clinicaltrials.gov (NCT02706119).

2.2. Lipid formulations

SMOFlipid (Fresenius Kabi AB, Uppsala, Sweden) or Lipoplus (B. Braun Melsungen AG, Melsungen, Germany) were used in the n-3 PUFA group, Lipofundina MCT/LCT 20 % (B. Braun Medical, Rubí, Barcelona, Spain) in the MCT/LCT group, and Clinoleic 20 % (Baxter, Ribarroja del Turia, Valencia, Spain) in the olive oil group. Detailed composition of these lipid formulations is shown in Supplementary Table 1.

2.3. Biomarkers

We determined the serum levels of biomarkers of oxidative status by enzyme immunoassay techniques following manufacturer's instructions in Versamax (MTX Lab System, Barcelona, Spain). These were 8-isoprostane (Cayman Chemical Company, MI, USA; intra-assay CV = 7.6–12 %; inter-assay CV = 9.7–19.9 %), superoxide dismutase (SOD) (Cayman Chemical Company, MI, EE. UU.; CV intra-assay = 3.2 %; CV inter-assay = 3.7 %) and total antioxidant capacity (TAC) (Cayman Chemical Company, MI, USA; intra-assay CV = 3.4 %; inter-assay CV = 3 %).

In addition, we measured intestinal permeability markers (ELISA technique), including lipoprotein binding protein (LBP) (MyBioSource, Inc., CA, USA; intra-assay CV ≤ 8 %; inter-assay CV ≤ 10 %), bacterial lipopolysaccharides (LPS) and zonulin (Wuhan Huamei Biotech Co., Ltd. China; intra-assay CV ≤ 8 %; inter-assay CV ≤ 10 %) as well as indoxylsulfate (MyBioSource, Inc., CA, USA; intra-assay CV ≤ 10 %; inter-assay CV ≤ 15 %).

Finally, inflammation parameters were measured in duplicate in 25 μl of serum with ProcartaPlex multiplex Immunoassay (Thermo Fisher Scientific, Waltham, MA, USA) following manufacturer's instructions. These included interferon-gamma, interleukin (IL)-1α, IL-1β, IL-10, IL-12p70, IL-13, IL-15, IL-17A (CTLA-B), IL-1RA, IL-6, IL-8 (CXCL8), cytokine-leukemia inhibitory factor (LIF), monocyte chemoattractant protein 1 (MCP-1), tumor necrosis factor alpha (TNF-α) and fibroblast growth factor 23 (FGF23) (Wuhan Fine Biotech Co., Ltd., China; intra-assay CV ≤ 8 %; inter-assay CV ≤ 10 %). Measurements were also made of C-reactive protein (CRP) levels (with an autoanalyzer) in the laboratory of the hospitals participating in the study.

2.4. Statistical analysis

We estimated that, to detect a mean difference between study groups of 5 pg/ml in the concentrations of IL-6 (standard deviation 5), assuming a statistical power of 80 %, and a significance level of 5 %, 17 patients were required to be included in each study group [14].

Data were analyzed using SPSS V.26.0 for Windows (SPSS Inc., Chicago, Illinois, USA). We used descriptive statistics with means ± SDs or n (%) for participants' baseline characteristics. In the case of biomarkers, a log transformation was applied. To test normality of the study variables, a Kolmogorov–Smirnov test was applied and Levene's test was used in order to check homogeneity. Differences in the baseline characteristics among groups were assessed by an ANOVA test. All the variables tested over repeated time were also analyzed using repeated measures multiple analysis of variance according to time and group of PN used. Values are shown as means and 95 % CIs, if not indicated otherwise. Significance for all statistical tests was set at $P < 0.05$ for bilateral contrast.

3. Results

3.1. Study population

A total of 94 patients were included in the study; 52 patients (55.3 %) received PN enriched with n-3 PUFA, 22 patients (23.4 %) received a mixture of MCT/LCT, and 20 patients (21.3 %) received PN based on olive oil. Of note, no significant differences were found between these cohorts and the rest of the INSUPAR cohort regarding age, sex, reason to start PN, duration and composition of PN, assigned insulin regimen, metabolic control or other variables studied.

Baseline characteristics of these three cohorts are shown in Table 1; no significant between-group differences were observed in baseline characteristics, except for a lower percentage of men receiving PN based on olive oil, and a different amount of grams of lipids in PN bag/kg of adjusted body weight in each group (Table 1).

Regarding potential confounding effects of other variables, no statistically significant differences were observed in neither assigned insulin regimen, insulin dose or in capillary mean blood glucose during PN infusion in the different groups. Likewise, no significant differences were found in terms of kilocalories from enteral feeding at day 5 after the onset of PN in the different study groups.

3.2. Biomarkers of oxidative status

In patients receiving PN enriched in n-3 PUFA, the biomarker of oxidative stress 8-isoprostane showed a significant decrease at day 5 ($p = 0.048$), while the anti-oxidant biomarker TAC significatively decreased at day 5 ($p = 0.006$). On the other hand, in patients under

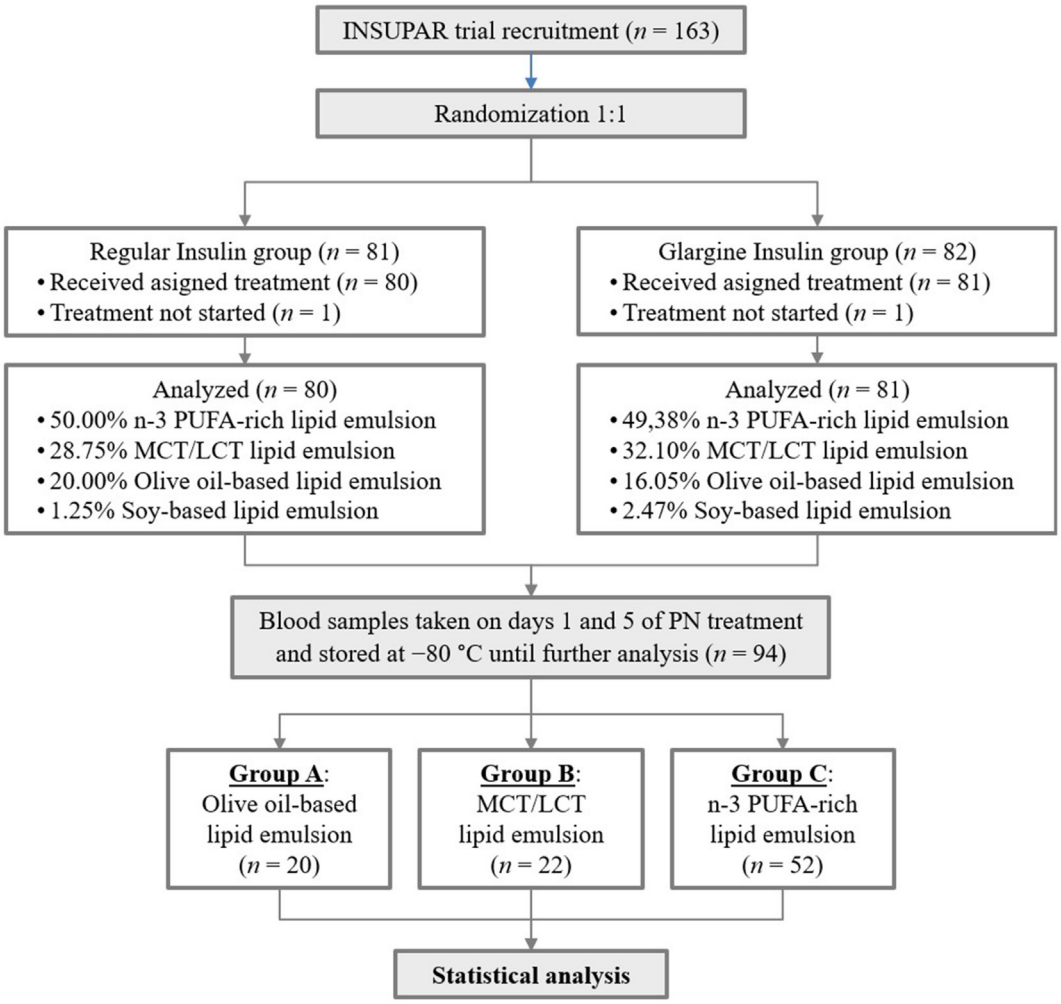

Fig. 1. Screening, randomization, and follow-up. The study groups included an olive oil-based PN group, a mixture of MCT/LCT PN group, and an enriched n-3 PUFA PN group.

treatment with PN based on MCT/LCT, TAC also decreased significantly at day 5 ($p = 0.026$) (Table 2).

In the between-group comparison, at day 5 MCT/LCT group presented significantly higher 8-isoprostane and lower SOD than the olive oil group ($p = 0.005$ and $p = 0.012$, respectively) and n-3 PUFA group ($p < 0.001$ and $p = 0.017$, respectively) (Table 2).

3.3. Intestinal permeability markers and indoxylsulfate

Zonulin and indoxylsulfate increased at day 5 in patients receiving MCT/LCT PN ($p = 0.044$ for both). In addition, LBP increased in patients with n-3 PUFA PN ($p = 0.005$) (Table 3).

3.4. Inflammation parameters

Patients receiving MCT/LCT PN had a significant reduction of the proinflammatory cytokines IL-15 ($p = 0.010$) and IL-17A ($p = 0.036$) at day 5, but also of the anti-inflammatory cytokine IL-13 ($p = 0.008$) (Table 4). Patients with olive oil-based PN showed a statistically significant reduction of five proinflammatory cytokines: IL-1β ($p = 0.013$), IL-17A ($p = 0.010$), IL-6 ($p = 0.003$), LIF ($p = 0.040$) and TNF-α ($p = 0.025$), but reduced values of the anti-inflammatory cytokine IL-1RA ($p = 0.028$) (Table 4). Finally, the group of patients receiving n-3 PUFA PN presented a statistically significant reduction of 8 proinflammatory cytokines: IFN-γ ($p = 0.049$), IL-1β ($p = 0.049$), IL-15 ($p = 0.011$), IL-17A ($p = 0.009$), IL-6 ($p = 0.049$), LIF ($p = 0.005$), MCP-1 ($p = 0.013$) and TNF-α ($p = 0.018$) (Table 4).

3.5. Comparison of profiles between groups

Patients receiving MCT/LCT PN presented a more pro-oxidative and pro-inflammatory profile compared to the other two groups. Accordingly, on day 1 and day 5 after initiation of PN these patients presented significantly higher 8-isoprostane concentrations than in the olive oil group ($p = 0.005$ and $p = 0.005$ respectively) and the n-3 PUFA group ($p = 0.001$ and $p < 0.001$ respectively), as well as higher indoxylsulfate than the n-3 PUFA group ($p = 0.027$ and $p = 0.017$ respectively). Moreover, the MCT/LCT group showed at day 5 significantly lower SOD than the olive oil and n-3 PUFA group ($p = 0.012$ and $p = 0.017$, respectively), and significantly higher FGF23 than the olive oil and n-3 PUFA group ($p = 0.047$ and $p = 0.003$, respectively). When comparing olive oil and n-3 PUFA groups, patients who received olive oil-based PN showed statistically significant lower values of TAC and higher values of IL-8 at day 1 ($p = 0.041$ and $p = 0.002$, respectively), as well as higher values of IL-15 and IL-8 at day 5 ($p = 0.014$ and $p = 0.007$, respectively) (Tables 2–4).

On the other hand, when repeated measures multiple analysis of variance according to time and group of treatment were carried out, 8-isoprostane, FGF23 and indoxylsulfate increased significantly over time in the MCT/LCT group compared to the n-3 PUFA group

Table 1
Baseline characteristics[a].

	Olive (n = 20)	MCT/LCT (n = 22)	n-3 PUFA (n = 52)	P value
Age (years)	72.1 ± 13.0	71.1 ± 7.7	69.6 ± 9.5	0.634
Men (%)	7 (35)	14 (63.6)	40 (76.9)	**0.004**
BMI (kg/m^2)	26.2 ± 4.3	27.8 ± 4.3	27.3 ± 5.9	0.597
Duration of diabetes (years)	12.7 ± 9.7	13.2 ± 9.9	11.2 ± 6.5	0.588
HbA1c (%)	6.7 ± 1.1	6.6 ± 1.0	6.6 ± 1.3	0.927
Albumin (g/dl)	2.5 ± 0.4	2.7 ± 0.5	2.4 ± 0.6	0.316
Creatinine (mg/dl)	0.8 ± 0.2	0.9 ± 0.2	0.8 ± 0.3	0.174
Reason to start PN				0.854
Acute pancreatitis	4 (20)	1 (4.5)	2 (3.8)	
Digestive oncological resection	4 (20)	6 (27.3)	12 (23.1)	
Inflammatory bowel disease	1 (5)	0 (0)	1 (1.9)	
Intestinal perforation	1 (5)	1 (4.5)	3 (5.8)	
Oral intolerance after radiotherapy/chemotherapy	4 (20)	5 (22.7)	14 (26.9)	
Mucositis after bone marrow transplant	1 (5)	2 (9.1)	5 (9.6)	
Post-surgical complications (dehiscence, paralytic ileus, infection…)	5 (25)	7 (31.8)	14 (26.9)	
Upper digestive tract bleeding	0 (0)	0 (0)	1 (1.9)	
Duration of PN (days)	9.9 ± 5.1	8.2 ± 3.2	11.9 ± 7.5	0.061
Grams of carbohydrates in PN bag/kg of adjusted body weight	3.0 ± 0.5	2.9 ± 0.4	2.8 ± 0.4	0.278
Grams of aminoacids in PN bag/kg of adjusted body weight	1.2 ± 0.3	1.3 ± 0.1	1.2 ± 0.2	0.366
Grams of lipids in PN bag/kg of adjusted body weight	1.0 ± 0.2	0.9 ± 0.1	0.8 ± 0.1	**<0.001**
Total daily kilocalories	1630.3 ± 329.5	1710.7 ± 215.2	1655.7 ± 167.8	0.473
Total daily insulin (IU)	51.4 ± 30.4	49.8 ± 29.8	50.1 ± 26.4	0.980
Insulin (IU/kg)	0.8 ± 0.3	0.7 ± 0.3	0.7 ± 0.4	0.613
Charlson comorbidity index	0.2 ± 0.3	0.1 ± 0.2	0.1 ± 0.2	0.582

Bold font indicates statistically significant results.
[a] Values are means ± SDs or percentages. BMI, body mass index; PN, parenteral nutrition; LCT, long-chain triglycerides; MCT, medium-chain triglycerides; n-3 PUFA, omega-3 polyunsaturated fatty acids.

Table 2
Biomarkers of oxidative status[a].

		Olive (n = 20)	MCT/LCT (n = 22)	n-3 PUFA (n = 52)	Olive vs MCT/LCT	Olive vs n-3 PUFA	MCT/LCT vs n-3 PUFA
8-isoprostane	Baseline	1.26 ± 0.63	1.71 ± 0.51	1.27 ± 0.31			
(pg/ml)	Day 5	1.38 ± 0.48	1.83 ± 0.66	1.19 ± 0.31			
	Change	p = 0.158	p = 0.121	**p = 0.048**	**−0.45 (−0.79, −0.11) p = 0.005**	0.19 (−0.09, 0.48) p = 0.308	**0.64 (0.37, 0.92) p < 0.001**
SOD (U/ml)	Baseline	0.03 ± 0.02	0.03 ± 0.01	0.03 ± 0.02			
	Day 5	0.04 ± 0.02	0.02 ± 0.02	0.03 ± 0.02			
	Change	p = 0.341	p = 0.331	p = 0.228	**0.02 (0.01, 0.04) p = 0.012**	0.01 (−0.01, 0.02) p = 0.287	**−0.01 (−0.02, −0.01) p = 0.017**
TAC (mmol)	Baseline	0.47 ± 0.13	0.52 ± 0.06	0.54 ± 0.11			
	Day 5	0.44 ± 0.13	0.47 ± 0.10	0.49 ± 0.15			
	Change	p = 0.439	**p = 0.026**	**p = 0.006**	−0.03 (−0.13, 0.07) p = 1.000	−0.05 (−0.14, 0.03) p = 0.406	−0.02 (−0.11, 0.06) p = 1.000

Bold font indicates statistically significant results.
[a] All values shown in this table come from the logarithm of the correspondent parameter. Data are presented as mean ± SD or mean (95 % CI). LCT, long-chain triglycerides; MCT, medium-chain triglycerides; n-3 PUFA, omega-3 polyunsaturated fatty acids; SOD, superoxide dismutase; TAC, total anti-oxidant capacity.

Table 3
Intestinal permeability biomarkers and indoxylsulfate[a].

		Olive (n = 20)	MCT/LCT (n = 22)	n-3 PUFA (n = 52)	Olive vs MCT/LCT	Olive vs n-3 PUFA	MCT/LCT vs n-3 PUFA
Indoxylsulfate	Baseline	1.67 ± 1.20	2.37 ± 0.26	1.32 ± 1.25			
(ng/ml)	Day 5	1.70 ± 1.21	2.48 ± 0.31	1.34 ± 1.27			
	Change	p = 0.389	**p = 0.044**	p = 0.305	−0.78 (−1.80, 0.24) p = 0.190	0.36 (−0.49, 1.20) p = 0.904	**1.14 (0.16, 2.11) p = 0.017**
LBP (ng/ml)	Baseline	2.57 ± 0.16	2.60 ± 0.12	2.52 ± 0.52			
	Day 5	2.62 ± 0.11	2.47 ± 0.59	2.68 ± 0.41			
	Change	p = 0.136	p = 0.283	**p = 0.005**	0.16 (−0.16, 0.47) p = 0.672	−0.05 (−0.32, 0.22) p = 1.000	−0.21 (−0.47, 0.05) p = 0.157
LPS (pg/ml)	Baseline	1.70 ± 0.40	1.81 ± 0.27	1.58 ± 0.46			
	Day 5	1.78 ± 0.30	1.79 ± 0.32	1.56 ± 0.49			
	Change	p = 0.077	p = 0.735	p = 0.733	−0.01 (−0.33, 0.30) p = 1.000	0.21 (−0.05, 0.48) p = 0.165	0.23 (−0.03, 0.49) p = 0.106
Zonulin (ng/ml)	Baseline	0.42 ± 0.58	0.19 ± 0.31	0.33 ± 0.41			
	Day 5	0.42 ± 0.62	0.34 ± 0.42	0.31 ± 0.37			
	Change	p = 0.956	**p = 0.044**	p = 0.688	0.09 (−0.24, 0.43) p = 1.000	0.11 (−0.18, 0.40) p = 1.000	0.02 (−0.26, 0.29) p = 1.000

Bold font indicates statistically significant results.
[a] All values shown in this table come from the logarithm of the correspondent parameter. Data are presented as mean ± SD or mean (95 % CI). LBP, lipoprotein binding protein; LCT, long-chain triglycerides; LPS, bacterial lipopolysaccharides; MCT, medium-chain triglycerides; n-3 PUFA, omega-3 polyunsaturated fatty acids.

Table 4
Inflammation parameters[a].

		Olive (n = 20)	MCT/LCT (n = 22)	n-3 PUFA (n = 52)	Olive vs MCT/LCT	Olive vs n-3 PUFA	MCT/LCT vs n-3 PUFA
FGF23 (pg/ml)	Baseline	1.13 ± 1.07	1.79 ± 1.43	0.92 ± 1.17			
	Day 5	1.03 ± 0.97	2.07 ± 1.33	0.69 ± 1.14			
	Change	p = 0.621	p = 0.195	p = 0.202	**−1.04 (-2.07, -0.01) p = 0.047**	0.34 (−0.51, 1.20) p = 0.98	**1.38 (0.39, 2.36) p = 0.003**
IFN-γ (pg/μl)	Baseline	1.02 ± 0.18	1.00 ± 0.07	0.97 ± 0.10			
	Day 5	0.99 ± 0.12	0.98 ± 0.09	0.94 ± 0.06			
	Change	p = 0.113	p = 0.376	**p = 0.049**	0.01 (−0.05, 0.07) p = 1.000	0.05 (−0.01, 0.11) p = 0.052	0.04 (−0.01, 0.10) p = 0.146
IL-1α (pg/μl)	Baseline	0.30 ± 0.31	0.19 ± 0.10	0.22 ± 0.30			
	Day 5	0.27 ± 0.31	0.19 ± 0.11	0.22 ± 0.32			
	Change	p = 0.119	p = 0.974	p = 0.996	0.08 (−0.13, 0.29) p = 1.000	0.04 (−0.14, 0.22) p = 1.000	−0.04 (−0.21, 0.14) p = 1.000
IL-1β (pg/μl)	Baseline	0.91 ± 0.03	0.90 ± 0.01	0.90 ± 0.02			
	Day 5	0.90 ± 0.02	0.91 ± 0.06	0.89 ± 0.01			
	Change	**p = 0.013**	p = 0.432	**p = 0.049**	−0.01 (−0.03, 0.01) p = 0.918	0.01 (−0.01, 0.02) p = 1.000	0.01 (−0.01, 0.03) p = 0.242
IL-10 (pg/μl)	Baseline	0.87 ± 0.20	0.87 ± 0.25	0.83 ± 0.10			
	Day 5	0.82 ± 0.10	0.85 ± 0.17	0.80 ± 0.03			
	Change	p = 0.051	p = 0.437	p = 0.085	−0.03 (−0.10, 0.04) p = 0.925	0.02 (−0.04, 0.08) p = 1.000	0.05 (−0.01, 0.11) p = 0.136
IL-12p70 (pg/μl)	Baseline	1.05 ± 0.23	1.00 ± 0.04	0.98 ± 0.04			
	Day 5	1.03 ± 0.19	0.99 ± 0.03	0.98 ± 0.04			
	Change	p = 0.065	p = 0.058	p = 0.339	0.04 (−0.03, 0.11) p = 0.413	0.05 (−0.01, 0.11) p = 0.130	0.01 (−0.05, 0.06) p = 1.000
IL-13 (pg/μl)	Baseline	0.88 ± 0.03	0.87 ± 0.01	0.87 ± 0.03			
	Day 5	0.87 ± 0.02	0.86 ± 0.01	0.86 ± 0.01			
	Change	p = 0.097	**p = 0.008**	p = 0.071	0.01 (−0.01, 0.02) p = 0.335	0.01 (−0.01, 0.02) p = 0.134	0.00 (−0.01, 0.01) p = 1.000
IL-15 (pg/μl)	Baseline	1.18 ± 0.02	1.18 ± 0.00	1.18 ± 0.01			
	Day 5	1.18 ± 0.01	1.17 ± 0.00	1.17 ± 0.01			
	Change	p = 0.107	**p = 0.010**	**p = 0.011**	0.0041 (−0.0004, 0.0086) p = 0.082	**0.0046 (0.0007 to 0.0084) p = 0.014**	0.0004 (−0.0033 to 0.0041) p = 1.000
IL-17A (pg/μl)	Baseline	0.99 ± 0.09	0.98 ± 0.04	0.97 ± 0.05			
	Day 5	0.97 ± 0.08	0.96 ± 0.03	0.95 ± 0.02			
	Change	**p = 0.010**	**p = 0.036**	**p = 0.009**	0.00 (−0.03, 0.03) p = 1.000	0.02 (−0.01, 0.05) p = 0.346	0.02 (−0.01, 0.04) p = 0.464
IL-1RA (pg/μl)	Baseline	2.82 ± 0.67	2.71 ± 0.66	2.56 ± 0.73			
	Day 5	2.56 ± 0.48	2.75 ± 0.70	2.58 ± 0.74			
	Change	**p = 0.028**	p = 0.678	p = 0.762	−0.20 (−0.71, 0.32) p = 1.000	−0.03 (−0.47, 0.41) p = 1.000	0.17 (−0.26, 0.59) p = 1.000
IL-6 (pg/μl)	Baseline	1.56 ± 0.58	1.63 ± 0.59	1.45 ± 0.51			
	Day 5	1.29 ± 0.44	1.47 ± 0.61	1.34 ± 0.42			
	Change	**p = 0.003**	p = 0.257	**p = 0.049**	−0.18 (−0.54, 0.18) p = 0.667	−0.05 (−0.35, 0.26) p = 1.000	0.13 (−0.16, 0.43) p = 0.844
IL-8 (pg/μl)	Baseline	1.06 ± 0.29	0.93 ± 0.29	0.80 ± 0.27			
	Day 5	0.98 ± 0.27	0.92 ± 0.27	0.76 ± 0.25			
	Change	p = 0.105	p = 0.877	p = 0.287	0.06 (−0.14, 0.25) p = 1.000	**0.21 (0.05, 0.38) p = 0.007**	0.16 (0.00, 0.32) p = 0.056
LIF (pg/μl)	Baseline	0.64 ± 0.07	0.63 ± 0.05	0.63 ± 0.04			
	Day 5	0.62 ± 0.06	0.62 ± 0.02	0.61 ± 0.03			
	Change	**p = 0.040**	p = 0.195	**p = 0.005**	0.00 (−0.03, 0.03) p = 1.000	0.01 (−0.02, 0.03) p = 1.000	0.01 (−0.02, 0.03) p = 1.000
MCP-1 (pg/μl)	Baseline	1.97 ± 0.36	1.99 ± 0.45	1.75 ± 0.43			
	Day 5	1.87 ± 0.41	1.87 ± 0.42	1.65 ± 0.37			
	Change	p = 0.146	p = 0.051	**p = 0.013**	0.00 (−0.29, 0.30) p = 1.000	0.22 (−0.03, 0.47) p = 0.105	0.22 (−0.02, 0.46) p = 0.094
TNF-α (pg/μl)	Baseline	1.39 ± 0.11	1.39 ± 0.09	1.36 ± 0.07			
	Day 5	1.35 ± 0.05	1.37 ± 0.09	1.34 ± 0.03			
	Change	**p = 0.025**	p = 0.338	**p = 0.018**	−0.02 (−0.06, 0.02) p = 0.741	0.00 (−0.03, 0.04) p = 1.000	0.02 (−0.01, 0.06) p = 0.236

Bold font indicates statistically significant results.
[a] All values shown in this table come from the logarithm of the correspondent parameter. Data are presented as mean ± SD or mean (95 % CI). IFN, interferon; IL, interleukine; LCT, long-chain triglycerides; LIF, Cytokine-Leukemia Inhibitory Factor; MCT, medium-chain triglycerides; MCP-1, Monocyte Chemoattractant Protein 1; n-3 PUFA, omega-3 polyunsaturated fatty acids; TNF-α, tumor necrosis factor-alpha.

(p = 0.038, p = 0.028 and p = 0.029 respectively). Likewise, SOD decreased significantly over time in the MCT/LCT group compared to the olive oil group (p = 0.042). Lastly, C Reactive Protein (CRP) increased significantly over time in the MCT/LCT group compared to the olive oil group (p = 0.049) (Fig. 2).

4. Discussion

In this study, we report that patients with T2DM who received MCT/LCT PN had the more pronounced oxidative and proinflammatory profile between all study groups. Also, we show that olive oil-based PN had a more oxidative and proinflammatory profile compared with n-3 PUFA-enriched PN.

Lipid emulsions are an essential component of PN. The first available was soybean oil-based, that provides concentrated energy and essential fatty acids. However, the high levels of LCT n-6 PUFA could be associated with worsening clinical outcomes, including increase of infections and longer intensive care and hospital stay [15]. Therefore, efforts have been made to use alternative oils (olive oil, MCT, and fish oil) in order to reduce the soybean-oil content of PN.

In our study, the MCT/LCT group showed a more unfavorable profile of oxidative status, with decreasing TAC over time as well as higher levels of the oxidative stress marker 8-isoprostane and lower levels of the anti-oxidant enzyme SOD, compared to other PN.

Previous studies have also analyzed oxidative status parameters in patients receiving PN, with dissimilar results. Thus, Demirer et al. measured total antioxidant status (TAS) and thiobarbituric acid reactive substances (TBARS), an index of lipid peroxidation, in adult patients receiving received MCT/LCT, olive oil-based or fish oil-enriched PN after major abdominal surgery. They reported the lowest decrease of TAS in the olive oil group (as in our study), and the highest reduction of TBARS also in the olive oil group, maybe

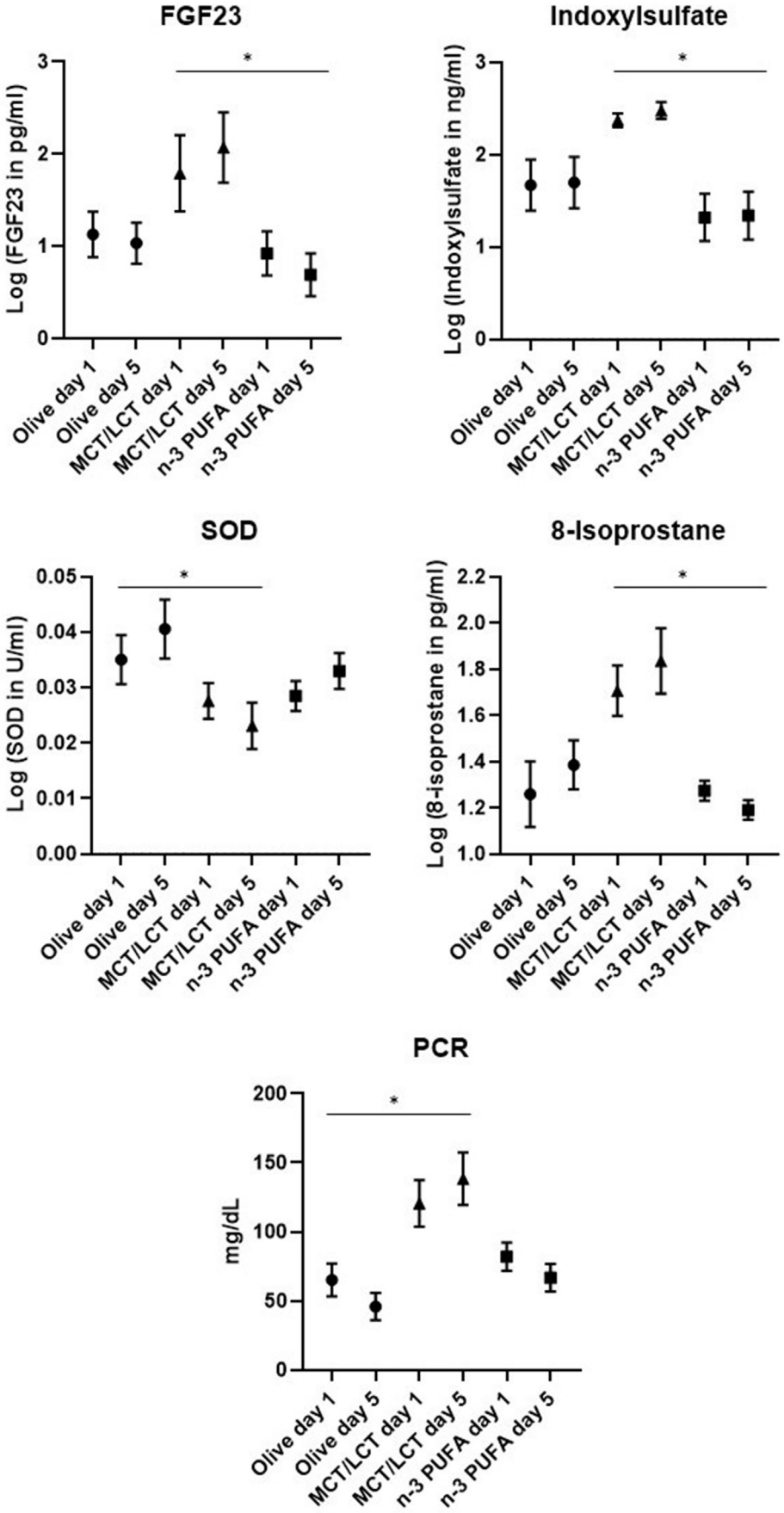

Fig. 2. Parameters that showed statistically significative differences when repeated measures multiple analysis of variance according to time and group of treatment were carried out. The asterisk represents significant differences in evolution over time and between groups.

due to a less prone lipid peroxidation of MUFA compared to PUFA [16]. Moreover, Chen et al. [17] compared MCT/LCT and 100 % fish oil-based PN in newborn piglets, obtaining that TAC and expression of genes encoding antioxidant enzymes (such as SOD) were higher in the fish oil group after 14 days, in consonance with our results.

However, other studies comparing oxidative status between olive oil and MCT/LCT PN found no significant differences. Thus, authors like Roggero [18] or Wang [19] did not detect significant differences in any oxidative status parameter, including total antioxidant potential but also F2-isoprostane and SOD, when comparing these two PN in preterm infants after 7 days of PN. Moreover, when Deshpande et al. [20] compared olive oil (Clinoleic®) and fish oil-enriched (SMOFlipid®) PN in 34 very preterm neonates, found that F2-isoprostane did not change at day 7 in the olive oil group, but decreased in the fish oil group, which is consistent with our results.

Regarding inflammation parameters, in our study n-3 PUFA-enriched PN was associated with the more positive evolution. In line with our results, Suárez-Lledó et al., when comparing fish oil, MCT/LCT, and a combination of both PN in 28 patients after esophagectomy, found that the maximum values of IL-6 were reached at day 1, without significant differences among the groups studied [21]. On the other hand, they did not find differences in the concentrations of IL-10, IL-8 or TNF-α, while our study showed a significant decrease of TNF-α in n-3 enriched-PUFA group on day 5 that did not occur in MCT/LCT group, probably due to our larger sample size. Moreover, Ma et al. [14] compared n-3 enriched-PUFA and MCT/LCT formulas in 99 postsurgical gastric and colorectal cancer patients, finding higher levels of IL-6, TNF-α and CRP in the MCT/LCT group at every study time, although without statistically significant differences between both groups, as in our study. Additionally, Chen et al. [17] found that the expression of mRNA encoding pro-inflammatory cytokines was higher in the MCT/LCT group and, similarly to our study, IL-1β was increased in the MCT/LCT group and reduced in the n-3 PUFA group. In addition, Demirer et al. [16], evaluated the effect of the three lipid emulsions on inflammatory response after abdominal surgery, reporting that TNF-α and IL-6 concentrations were lower in patients receiving olive oil-based PN after 4 days of PN. However, they did not study the other proinflammatory cytokines that were reduced in the n-3 PUFA group of our sample, nor FGF23, that has been pointed out as a stimulus of systemic inflammation given that increases hepatic secretion of IL-6 and CRP [22]. Unfortunately, these authors did not study anti-inflammatory cytokines either, some of which were significantly reduced over time in our study in the olive oil group (IL-1RA) or in the MCT/LCT group (IL-13).

Of note, recent studies have shown that the anti-inflammatory profile of n-3 PUFA PN observed in our study may promote better clinical recovery in a wide range of conditions, such as Crohn's disease or severe burns, and in hospitalized patients, with fewer infections or other complications, in addition to the mentioned reduction in inflammatory cytokines [23–25]. The reduction of pro-inflammatory factors with n-3 PUFA PN could play a major role in patients with T2DM, as they present a dramatical elevation of IL-6, TNF-α, IL-1β and CRP [26,27].

In our study, MCT/LCT PN also presented the most unfavourable characteristics regarding intestinal permeability markers, with a significant increase over time of indoxylsulfate, a toxin produced by intestinal bacteria, and zonulin, a protein that induces disruption of intestinal epithelial cell tight junctions. In line with this, in the study of Chen et al. there were no differences in the mRNA levels of several tight junction proteins, including zonulin, despite finding that fish oil led to reduced LPS diffusion to the blood circulation compared to MCT/LCT [17]. Indoxyl sulphate primarily originates from the metabolism of dietary tryptophan by the gut microbiota, a process that is not significantly influenced by the tryptophan supplied via PN, as PN bypasses the intestinal tract. However, PN can indirectly affect indoxyl sulphate levels by altering the gut microbiota leading to shifts in bacterial populations [28].

The underlying mechanisms by which MCT/LCT lipid emulsion promotes inflammation, oxidative stress and intestinal permeability in patients with T2DM, who already present a pro-inflammatory environment, may include its higher n-6 fatty acid content, associated with increased synthesis of proinflammatory metabolites and intestinal villous atrophy. Additionally, the different composition of lipid emulsions alters gut microbiota composition. Some changes in gut microbiota, such as the enrichment of *Proteobacteria* observed after administering MCT/LCT, are suspected to cause local inflammation in the intestinal mucosa [17], which could contribute to increased production of zonulin and bacterial metabolites such as indoxylsulfate. However, the specific mechanisms need further study.

Our study has certain limitations but also some important strengths. The limitations include a short follow-up (5 days), and therefore our results cannot be extrapolated to patients who are under treatment with long-term PN. However, although a longer evaluation period could have helped to elucidate the long-term impact of different lipid formulas in patients with T2DM who received PN, the 5-day time frame allowed us to minimize potential confounding effects of other variables, such as variations in enteral feeding. Besides, the percentage of people maintaining PN for periods longer than 5 days steadily decreases, thus increasing drop-outs from the study, and reducing statistical power.

On the other hand, it is important to highlight that, instead of evaluating baseline parameters at day 0, we collected them at day 1. This is related to the pragmatic design of the study, an independent trial conducted in routine clinical practice. As the clinical evaluation to consider inclusion of the patients in the study were done in the morning, PN was to be started in the afternoon (but without a baseline blood test), or be delayed until next day (with the possibility of collecting a new blood test). Despite the second option would have been ideal from an academic point of view, when the study was designed and approved it was deemed unethically to delay PN in patients who required it, just in order to collect a baseline blood test the next day. In summary, we believe that the chosen baseline of day 1, while not ideal in a purely experimental setting, provides a practical approach for evaluating the effects of PN in this study.

Additionally, despite we did not analyse all existing biomarkers of oxidative status, inflammation and intestinal permeability, we analysed a wide representation of many of these parameters. On the other hand, the strengths of our study lie in the prospective design, and the inclusion of sufficient sample size to ensure an adequate statistical power. Moreover, it was a multicentric study, so more generalizable findings are provided. Besides, it was a substudy of a randomized clinical trial, with no significant differences between our cohort and the rest of the trial cohort, which reduces risk of selection bias.

5. Conclusion

In patients with T2DM that received PN, formulas with MCT/LCT lipid emulsions were associated with an increment of proinflammatory, prooxidative and intestinal permeability biomarkers compared to formulas enriched with n-3 PUFA and based on olive oil, while formulas enriched with n-3 PUFA showed the more favourable effects on these parameters.

Author contributions

VS-U, JA-H CVS, SYR-Z and JCF-G contributed to the acquisition, analysis, and interpretation of the data; statistical analysis; revised the article for important intellectual content and drafting of the manuscript. GO substantially contributed to the conception and design of the study, acquisition, analysis, and interpretation of the data; statistical analysis; drafting of the manuscript and obtained funding. CVS and SYR-Z processed samples. AA-C, RL-U, SH-A, JMG-A, KG-M, MF-G, AM-B, LML-P, CA-V, MJO-B, AG-M, IB-L, PS-A, NP-F, JJL-G, JO-A, MM-M, CT-P, SG-A, ALA-G, MRA-E, AZ-M, JP-B, ST-J and JA contributed to the data acquisition and critical review of the manuscript. VS-U, JCF-G and GO are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest

The authors have declared that no competing interests exist.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.11.044.

References

[1] Lappas BM, Patel D, Kumpf V, Adams DW, Seidner DL. Parenteral nutrition: indications, access, and complications. Gastroenterol Clin N Am 2018 Mar;47(1):39–59. https://doi.org/10.1016/j.gtc.2017.10.001.
[2] Moron R, Galvez J, Colmenero M, Anderson P, Cabeza J, Rodriguez-Cabezas ME. The importance of the microbiome in critically ill patients: role of nutrition. Nutrients 2019 Dec 7;11(12):3002. https://doi.org/10.3390/nu11123002.
[3] Abuín-Fernández J, Tapia-Guerrero MJ, López-Urdiales R, Herranz-Antolín S, García-Almeida JM, García-Malpartida K, et al. Fish oil enriched intravenous lipid emulsions reduce triglyceride levels in non-critically ill patients with TPN and type 2 diabetes. A post-hoc analysis of the INSUPAR study. Nutrients 2020 May 27;12(6):1566. https://doi.org/10.3390/nu12061566.
[4] Martindale RG, Berlana D, Boullata JI, Cai W, Calder PC, Deshpande GH, et al. Summary of proceedings and expert consensus statements from the international summit "lipids in parenteral nutrition". J Parenter Enter Nutr 2020 Feb;44(Suppl 1):S7–20. https://doi.org/10.1002/jpen.1746.
[5] Honeywell S, Zelig R, Rigassio Radler D. Impact of intravenous lipid emulsions containing fish oil on clinical outcomes in critically ill surgical patients: a literature review. Nutr Clin Pract 2019 Feb;34(1):112–22. https://doi.org/10.1002/ncp.10224.
[6] Zhao Y, Wang C. Effect of ω-3 polyunsaturated fatty acid-supplemented parenteral nutrition on inflammatory and immune function in postoperative patients with gastrointestinal malignancy: a meta-analysis of randomized control trials in China. Medicine (Baltim) 2018 Apr;97(16):e0472. https://doi.org/10.1097/MD.0000000000010472.
[7] Pradelli L, Mayer K, Klek S, Omar Alsaleh AJ, Clark RAC, Rosenthal MD, et al. ω-3 fatty-acid enriched parenteral nutrition in hospitalized patients: systematic review with meta-analysis and trial sequential analysis. J Parenter Enter Nutr 2020 Jan;44(1):44–57. https://doi.org/10.1002/jpen.1672.
[8] Ocón Bretón MJ, Ilundain Gonzalez AI, Altemir Trallero J, Agudo Tabuenca A, Gimeno Orna JA. Predictive factors of hypertriglyceridemia in inhospital patients during total parenteral nutrition. Nutr Hosp 2017 Jun 5;34(3):505–11. https://doi.org/10.20960/nh.485.
[9] Cai W, Calder PC, Cury-Boaventura MF, De Waele E, Jakubowski J, Zaloga G. Biological and clinical aspects of an olive oil-based lipid emulsion - a review. Nutrients 2018 Jun 15;10(6):776. https://doi.org/10.3390/nu10060776.
[10] Luc K, Schramm-Luc A, Guzik TJ, Mikolajczyk TP. Oxidative stress and inflammatory markers in prediabetes and diabetes. J Physiol Pharmacol 2019 Dec;70(6). https://doi.org/10.26402/jpp.2019.6.01.
[11] Ye J, Wu Z, Zhao Y, Zhang S, Liu W, Su Y. Role of gut microbiota in the pathogenesis and treatment of diabetes mellitus: advanced research-based review. Front Microbiol 2022 Oct 19;13:1029890. https://doi.org/10.3389/fmicb.2022.1029890.
[12] Olveira G, Abuín J, López R, Herranz S, García-Almeida JM, García-Malpartida K, et al. Regular insulin added to total parenteral nutrition vs subcutaneous glargine in non-critically ill diabetic inpatients, a multicenter randomized clinical trial: INSUPAR trial. Clin Nutr 2020 Feb;39(2):388–94. https://doi.org/10.1016/j.clnu.2019.02.036.
[13] Olveira G, Abuín J, López R, Herranz S, García-Almeida JM, García-Malpartida K, et al. Risk factors for hypoglycemia in inpatients with total parenteral nutrition and type 2 diabetes: a post hoc analysis of the INSUPAR study. Endocr Pract 2020 Jun 2;26(6):604–11. https://doi.org/10.4158/EP-2019-0482.
[14] Ma CJ, Wu JM, Tsai HL, Huang CW, Lu CY, Sun LC, et al. Prospective double-blind randomized study on the efficacy and safety of an n-3 fatty acid enriched intravenous fat emulsion in postsurgical gastric and colorectal cancer patients. Nutr J 2015 Jan 21;14:9. https://doi.org/10.1186/1475-2891-14-9.
[15] Gervasio JM. Controversies in the use of lipid injectable emulsion in hospitalized patients. Nutr Clin Pract 2018 Jun;33(3):370–5. https://doi.org/10.1002/ncp.10099.
[16] Demirer S, Sapmaz A, Karaca AS, Kepenekci I, Aydintug S, Balci D, et al. Effects of postoperative parenteral nutrition with different lipid emulsions in patients undergoing major abdominal surgery. Ann Surg Treat Res 2016 Dec;91(6):309–15. https://doi.org/10.4174/astr.2016.91.6.309.
[17] Chen S, Xiao Y, Liu Y, Tian X, Wang W, Jiang L, et al. Fish oil-based lipid emulsion alleviates parenteral nutrition-associated liver diseases and intestinal injury in piglets. J Parenter Enter Nutr 2022 Mar;46(3):709–20. https://doi.org/10.1002/jpen.2229.
[18] Roggero P, Mosca F, Giannì ML, Orsi A, Amato O, Migliorisi E, et al. F2-isoprostanes and total radical-trapping antioxidant potential in preterm infants receiving parenteral lipid emulsions. Nutrition 2010 May;26(5):551–5. https://doi.org/10.1016/j.nut.2009.06.018.
[19] Wang Y, Feng Y, Lu LN, Wang WP, He ZJ, Xie LJ, et al. The effects of different lipid emulsions on the lipid profile, fatty acid composition, and antioxidant capacity of preterm infants: a double-blind, randomized clinical trial. Clin Nutr 2016 Oct;35(5):1023–31. https://doi.org/10.1016/j.clnu.2015.10.011.
[20] Deshpande G, Simmer K, Deshmukh M, Mori TA, Croft KD, Kristensen J. Fish Oil (SMOFlipid) and olive oil lipid (Clinoleic) in very preterm neonates. J Pediatr Gastroenterol Nutr 2014 Feb;58(2):177–82. https://doi.org/10.1097/MPG.0000000000000174.
[21] Suárez-Lledó Grande A, Llop Talaveron JM, Leiva Badosa E, Farran Teixido L, Miró Martín M, Bas Minguet J, et al. Effect of fish oil parenteral emulsion supplementation on inflammatory parameters after esophagectomy. Nutrients 2023 Dec 21;16(1):40. https://doi.org/10.3390/nu16010040.
[22] Sharaf El Din UAA, Salem MM, Abdulazim DO. FGF23 and inflammation. World J Nephrol 2017 Jan 6;6(1):57–8. https://doi.org/10.5527/wjn.v6.i1.57.
[23] Ge X, Liu H, Wu Y, Liu W, Qi W, Ye L, et al. Parenteral n−3 polyunsaturated fatty acids supplementation improves postoperative recovery for patients with Crohn's disease after bowel resection: a randomized, unblinded controlled clinical trial. Am J Clin Nutr 2024 Apr 19;119(4):1027–35. https://doi.org/10.1016/j.ajcnut.2023.12.022.

[24] Zhou YY, Wang Y, Wang L, Jiang H. The efficacy of Omega-3 polyunsaturated fatty acids for severe burn patients: a systematic review and trial sequential meta-analysis of randomized controlled trials. Clin Nutr ESPEN 2024 Feb;59:126–34. https://doi.org/10.1016/j.clnesp.2023.11.019.
[25] Pradelli L, Mayer K, Klek S, Rosenthal MD, Povero M, Heller AR, et al. Omega-3 fatty acids in parenteral nutrition - a systematic review with network meta-analysis on clinical outcomes. Clin Nutr 2023 Apr;42(4):590–9. https://doi.org/10.1016/j.clnu.2023.02.008.
[26] Huang K, Liang Y, Ma Y, Wu J, Luo H, Yi B. The variation and correlation of serum adiponectin, nesfatin-1, IL-6, and TNF-α levels in prediabetes. Front Endocrinol 2022 Mar 3;13:774272. https://doi.org/10.3389/fendo.2022.774272.
[27] Liu C, Feng X, Li Q, Wang Y, Li Q, Hua M. Adiponectin, TNF-α and inflammatory cytokines and risk of type 2 diabetes: a systematic review and meta-analysis. Cytokine 2016 Oct;86:100–9. https://doi.org/10.1016/j.cyto.2016.06.028.
[28] Hou Y, Li J, Ying S. Tryptophan metabolism and gut microbiota: a novel regulatory axis integrating the microbiome, immunity, and cancer. Metabolites 2023 Nov 20;13(11):1166. https://doi.org/10.3390/metabo13111166. PMID: 37999261; PMCID: PMC10673612.