nWhole blood long-chain n-3 fatty acids as a measure of fish oil compliance in children with acute lymphoblastic leukemia: a pilot study

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Highlights

- Fish oil supplementation is feasible in children with acute lymphoblastic leukemia.
- Absolute intake of n-3 LCPUFA reflects the relative content in whole blood.
- Intake-biomarker correlations were disrupted when expressed in absolute concentrations and intake per kg bodyweight.
- Whole blood n-3 LCPUFA response did not appear to be affected by blood transfusions and differences in bodyweight.

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Author Contributions

Conception and design; TLF, CM, LL, RDL and TI; Data collection and analysis; RDL and TI; Interpretation; RDL, TI, KS, KDS and LL; Laboratory analyses; KDS; First draft; RDL and LL; Final approval of manuscript; All authors

Abstract

Long-chain n-3 fatty acids (n-3 LCPUFA) may prevent chemotherapy-induced hyperlipidemia in children with acute lymphoblastic leukemia (ALL). However, compliance could be a problem and intake-biomarker correlations may be affected by bodyweight and blood transfusions. We assessed whole blood n-3 LCPUFA three times during the first 83 days of treatment in six 1-17-year-old children with ALL, who received 2.4-4.9 g/d n-3 LCPUFA depending on bodyweight. Mean compliance was 73%, which resulted in a 2.5-fold increase in blood n-3 LCPUFA irrespective of blood transfusions. The correlation between relative blood content of n-3 LCPUFA and intake in g/d across the study period was strong ($r=0.76$, $p=0.001$). When n-3 LCPUFA was expressed in absolute concentrations and intake per kg bodyweight the correlation decreased ($r=0.39$, $p=0.164$) and was driven by baseline values. Thus, relative content of n-3 LCPUFA in blood reflects fish oil compliance in children with ALL despite blood transfusions and differences in bodyweight.

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer in children and although treatment has improved, almost 50% of patients experience severe non-infectious side effects [1,2]. Hyperlipidemia is common during concomitant therapy with dexamethasone and pegylated-asparaginase (PEG-ASP) [3–5] with triglyceride (TG) levels up to 200 times the upper normal limit [6]. Plasma TG can be reduced by supplementation with n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [7–9]. However, fish oil compliance can be a problem in cancer patients, due to nausea and loss of appetite [10]. Many trials in cancer patients have assessed intake of fish oil by dietary records, which are imprecise and prone to bias, or capsule counts, which may not be reliable. The level of EPA and DHA in red blood cells (RBC) is the most well established and reliable biomarker of n-3 LCPUFA intake [11–13], but it may be affected by RBC transfusions, which most children with ALL receive during treatment [14]. The EPA+DHA concentration in plasma varies from day to day. Whole blood is better in terms of fluctuations [12,15], but it is potentially vulnerable to blood transfusions and has not been validated as a biomarker of intake in children with cancer. Furthermore, it is debated whether fish oil should be given at a fixed dose or dosed depending on bodyweight in order to achieve similar tissue levels in children across a broad age range.

This paper presents data from a pilot study investigating compliance and potential effects of fish oil on hyperlipidemia during intensive chemotherapy in children with ALL. The aim of the paper is to examine the use of EPA and DHA in whole blood as a biomarker for compliance and evaluate if this might be disrupted by blood transfusions and if the association with dietary intake depends on bodyweight.

2. Materials and methods

The study was conducted at Rigshospitalet, Copenhagen, Denmark from December 2017–June 2018 in children (1−17.9 years) with ALL, who were treated according to the Nordic Society of Pediatric Hematology and Oncology ALL2008 protocol. Children were eligible, if they were stratified to standard-risk and intermediate-risk after induction therapy. The study was approved by the Danish Ethical Committee (H-17030827) and the Danish Data Protection Authorities (RH-2018-67). Informed consent was obtained before inclusion in accordance with the Helsinki Declaration.

Fish oil supplementation started at treatment day 30, when therapy with PEG-ASP (1,000 IU/m^2 intramuscularly) was initiated, and lasted until end of therapy with PEG-ASP and dexamethasone (day 113) [16]. The children were provided with fish oil that contained 0.244 g n-3 LCPUFA per mL (61% EPA and 40% DHA) (supplied in kind by Lýsi, Reykjavik, Iceland), which was dosed depending on their bodyweight: 1) 5-29 kg: 10 mL/d, 2) 30-39 kg: 12.5 mL/d, 3) 40-49 kg: 15 mL/d, 4) 50-59 kg: 17.5 mL/d, and 5) > 60 kg: 20 mL/d.

At baseline, at midpoint and at the end of the study period (treatment days 30, 71 and 113), venous blood was collected in 2 mL tubes with lithium heparin from the antecubital vein or central vein catheter. Within 30 minutes, 0.1% butylated hydroxytoluene (Sigma-Aldrich) was added and the samples were stored at –80°C for up to 6 months before analysis.

The parents were asked to record the child's fish oil intake and intake was also estimated from oil remaining in the bottles returned at the end of the study period. The participants completed an online 3-day dietary record in "Madlog" (https://www.madlog.dk) at baseline, at midpoint and at the end of the study period (day 30-32, 57-59, and 99-101). The dietary records were analyzed using "Food data" (frida.fooddata.dk, version 4, 2019) to estimate intake of energy (EI), macronutrients and EPA+DHA. We had to exclude one of the participants from the analysis of compliance, as we did not receive the self-registration form and dietary records and a family member had taken oil from the bottles.

Whole blood fatty acid composition was determined by high-throughput gas chromatography as previously described [17]. Briefly, 22:3n-3 ethyl ester (Nu-Check Prep) was added as internal standard and fatty acids were directly transesterified with 14% boron trifluoride in methanol and hexane containing BHT by convectional heating for 60 min at 90°C. The fatty acid methyl esters in hexane were then collected and analyzed on a Varian 3900 gas chromatograph. The n-3 LCPUFA status is expressed as absolute concentrations of EPA+DHA, relative percentage of total fatty acids (weight%) or percentage of n-3 LCPUFA (≥20 carbons and ≥3 double bonds) in total LCPUFA (n-3 LCPUFA%).

Timepoint of blood transfusions during the study period were collected retrospectively from the patients' medical records. RBC transfusions were indicated if hemoglobin ≤ 5.00 mmol/L or presence of clinical symptoms of anemia, and the volume given were calculated based on bodyweight (15 ml/kg).

Statistical analyses were performed with IBM SPSS Statistics version 25. Self-registered compliance and returned fish oil was compared by Mann-Whitney U-test. Wilcoxon Signed Rank-test was used to test differences in whole blood EPA+DHA at day 30, 71, and 113. Linear regression was used to examine the relationship between the absolute concentration or relative percentage EPA+DHA in whole blood and the estimated reported intake of EPA+DHA expressed in g/d, per kg bodyweight, or relative to EI.

3. Results

Six boys with ALL was included in the study (**Table 1**), one in dosage category 5 and five in category 1. The mean reported EI of the children was around 135% of their estimated requirement when PEG-ASP therapy was initiated at baseline (day 30) and at the end of the treatment period (day 99-101), but it was only 64% in mid-chemotherapy (day 57-59). The mean reported intake of EPA+DHA from the diet was 0.09±0.10 g/d (range 0-0.3 g/d, n=5) and did not change over the course of the study.

Based on the self-registration forms, we estimated that compliance with the fish oil supplement was 73% (range 52-92%) and it was 69% (range 48-89%) if assessed by the remains in the bottles at day 113 (p=0.76 for difference). The fish oil was estimated to contribute with an average of 9% of the total EI (range 6-13%) at day 57-59 and 5% (range 4-5%) at day 99-101 and with an average of approximately 1.7 g/d of EPA+DHA during the intervention (Table 1).

The relative content of EPA+DHA and n-3 LCUFA% in whole blood increased and n-6 PUFA and the n-6 to n-3 PUFA ratio decreased during fish oil supplementation, while there were no changes in total PUFA, saturated, or monounsaturated fatty acids (**Table 2**). The absolute concentration of EPA+DHA also increased and this appeared to be unaffected by blood transfusions in the individual children **(Fig. 1)**.

The relative content of EPA+DHA in whole blood was strongly correlated with the reported intake of EPA+DHA from diet and fish oil across the entire course of the study period (**Fig. 2)**. Although, no longer significant after exclusion of baseline, this had little effect on the slope and the correlations at day 71 and day 113 appear to be in parallel (Fig 2). Correlations were equally strong when the intake was expressed as percent compliance (r=0.80, p<0.001; without baseline: r=0.43, p=0.22) and with total n-3 LCPUFA% in whole blood instead of EPA+DHA (data not shown). Correlation was also observed with the absolute concentration of EPA+DHA versus the reported intake in g/d (r=0.60, p=0.024), but this was much reduced by exclusion of baseline (r=0.13, p=0.73). The correlation was also weaker if intake of EPA+DHA was replaced by intake expressed per kg bodyweight versus the relative content of EPA+DHA in whole blood (r=0.62, p=0.017) and there was absolutely no signs of correlation after exclusion of baseline (r=0.02, p=0.95) or within day 71 and 113 separately. The same pattern was observed for the correlation between intake per kg bodyweight and absolute concentration of EPA+DHA, which showed general increases in both intake and blood levels over time, but there were no trends within the individual days of assessment and even signs of a weak correlation in the inverse direction at day 113 **(Fig. 3)**.

4. Discussion and Conclusion

The children with ALL had a high fish oil compliance assessed by both fish oil remaining in the bottles and self-registered logs. The observed correlation between whole blood EPA+DHA and the reported intake from fish oil and diet is similar to previously reported relationships [18–23]. Conversely, we did not find any correlation when the reported intake of EPA+DHA was expressed per kg bodyweight. This is supported by results in adult athletes that tested if bodyweight could explain variability in the RBC EPA+DHA response to n-3 LCPUFA intake [24]. However, two other studies, one of them in children in remission from cancer, reported equally good correlations between RBC EPA+DHA and intake of EPA+DHA from supplements in g/d and relative to weight [25,26].

Although correlations with EPA+DHA intake have been shown to be good in all blood fractions [23], it could influence the result that we used whole blood and not RBC. Changes in the intake of n-3 LCPUFA is reflected faster in whole blood than in RBC [12], but we observed a continuous increase over 12 weeks with no signs of steady state or saturation. We used whole blood to minimize the effect of RBC transfusions, which could introduce variability and weakened intake-biomarker correlations. All the children received blood transfusions during the study, presumably from donors with a lower n-3 LCPUFA intake, but the courses of the curves did not indicate reductions in whole blood EPA+DHA after transfusions. Blood levels of EPA+DHA would also be affected by chemotherapy-induced hyperlipidemia [27–29], which would likely dilute the n-3 LCPUFA. However, plasma TG did not increase in most of the children and in the few instances where TG was high this did not affect the correlations with relative concentrations of EPA+DHA, as the concentrations of EPA+DHA was also increased and disproportionally high relative to the intake.

The observed correlations are limited by the pilot nature of the study and its open label non-randomized design and small sample size. The children are therefore not representative for the general population of children with ALL, but there was an almost two-fold range in bodyweight. Furthermore, we only had two blood samples during the chemotherapy period, which restrained our ability to detect effects of blood transfusion unless they occurred close to the time of blood sampling. We assessed intake of n-3 LCPUFA from diet and supplement and used both self-registered logs and fish oil returned, which showed good agreement. We find that the observed differences in intake-biomarker correlations for absolute and bodyweight-adjusted intakes warrant larger studies in children with cancer across a broad age range and more blood fractions as well as blood samples enough to examine the influence of blood transfusions.

In conclusion, our results showed good compliance with fish oil supplementation in pediatric ALL patients. Furthermore, intake of n-3 LCPUFA was reflected in the relative content in whole blood, which did not appear to be affected by blood transfusions and differences in bodyweight.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables and figure captions

Table 1. Patient characteristics and reported intakes of n-3 LCPUFA from diet and supplement during the study

Table 2. Whole blood fatty acid composition

Fig. 1. Whole blood concentration of EPA+DHA over the course of the intervention with indicated times for blood transfusions (↓) in the individual children. Plasma triglyceride concentrations were all <2.5 mmol/L with an intra-individual variation of 50±17%, except in patient 4 at day 71 (3.8 mmol/L) and 113 (6.4 mmol/L) and patient 5 at day 71 (5.9 mmol/L).

Fig. 2. Whole blood EPA+DHA in response to reported intake of EPA+DHA from diet and supplement during the intervention. Each point represents an individual at baseline (small symbols), day 71 (medium-sized symbols) and day 113 (big symbols). Correlations are shown both with baseline (solid line; r=0.76, p=0.001) and without baseline (dashed line; r=0.43, p=0.22).

Fig. 3. EPA+DHA concentration in whole blood versus reported intake of EPA+DHA from diet and supplement relative to bodyweight. The children had a bodyweight of 11-19 kg. Each point represents an individual at baseline (small symbols), day 71 (medium-sized symbols) and day 113 (big symbols).

FIGUR1

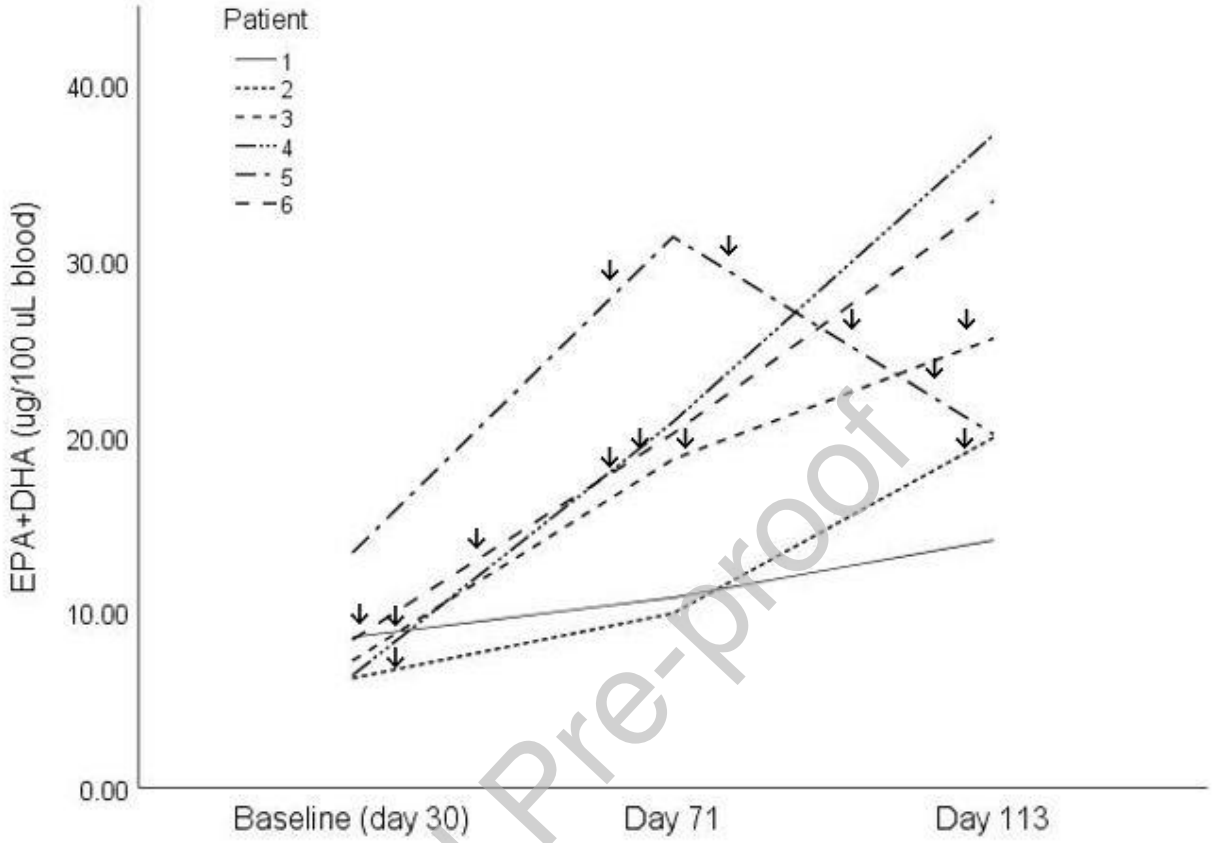

Figure 2

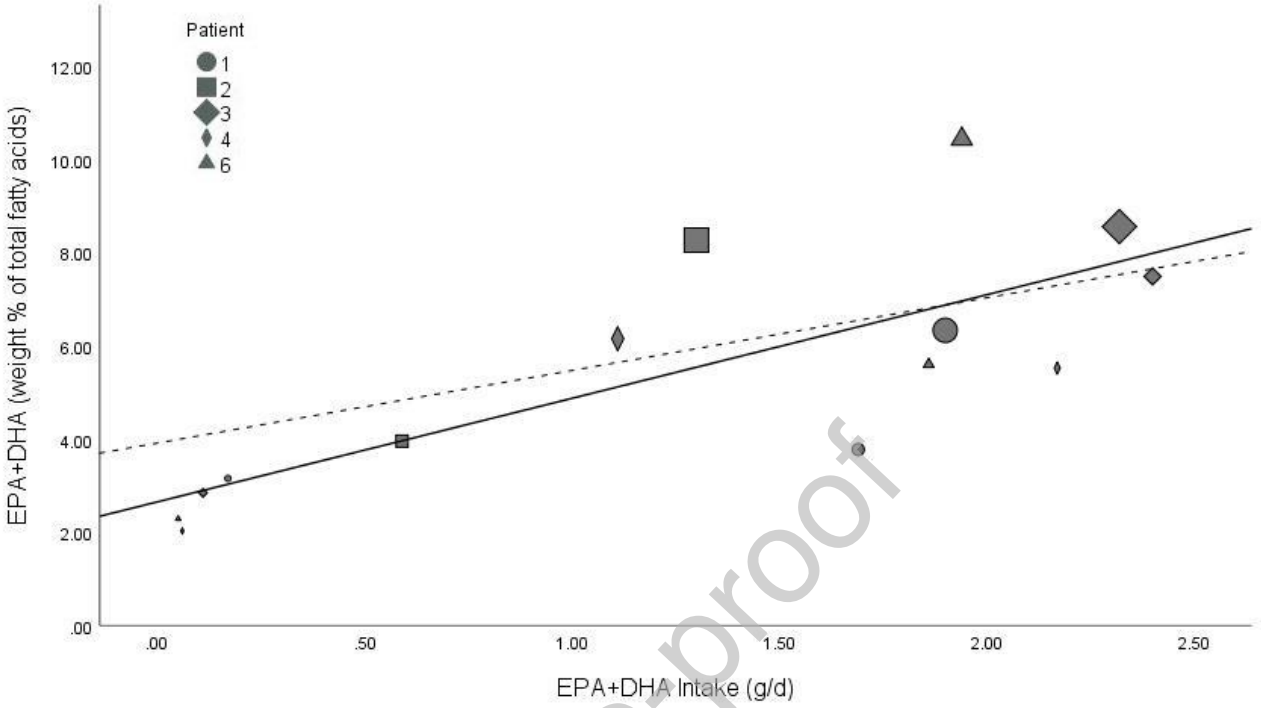

Figure 3

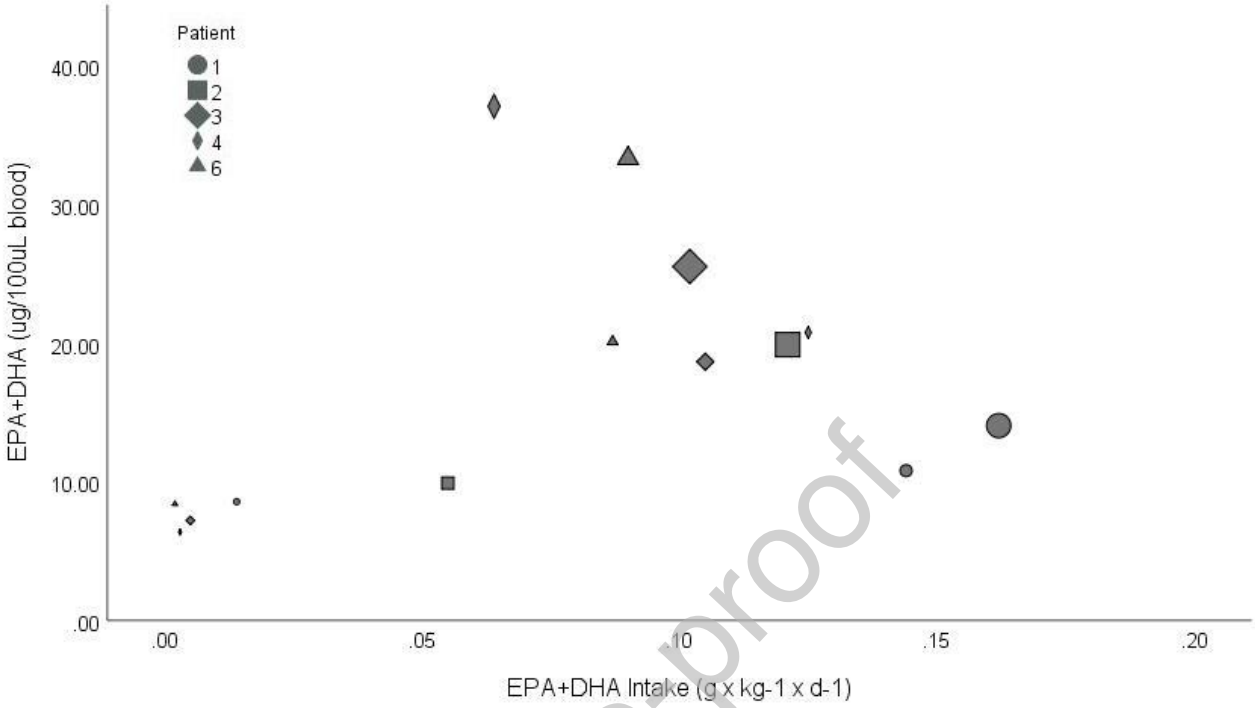

Table 1. Patient characteristics and reported intakes of n-3 LCPUFA from diet and supplement during the study

Patient	Age	Body weight	Transfusions	EI	EPA+DHA intake		Compliance
	(years)	(kg)	(n)	(kJ)	(g/d)	(g/kg*d)	(%)
1	2	12	1	3996	1.80	0.153	83
2	1	11	2		0.95	0.088	58
3	7	24	2	6120	2.36	0.104	92
4	3	16	2	5000	1.64	0.095	52
5	17	74	4	13401			
6	7	19	2	5853	1.90	0.089	78

Intake of energy (EI) and eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) from diet and supplement are given as estimated means across the intervention period. Mean fish oil compliance during the study period is estimated from self-registration logs. No dietary data and compliance registrations were available from patient 2 and 5, respectively.

Table 2. Whole blood fatty acid composition

	Baseline	Day 71	Day 113	p-values		
				t1-t2	t2-t3	t1-t3
Saturated fatty acids	44.1±2.5	44.3±1.8	42.8±1.8	0.80	0.24	0.35
Monounsaturated fatty acids	24.3±2.6	27.5±2.1	22.8±3.5	0.022	0.059	0.40
Polyunsaturated fatty acids	31.1±1.0	27.6±1.4	33.4±2.5	0.016	0.012	0.062
C 18:2n-6	16.1±1.18	13.08±1.88	14.99±1.72	0.043	0.15	0.34
C 18:3n-6	0.35±0.22	0.07±0.05	0.13±0.08	0.031	0.029	0.059
C 20:3n-6	1.82±0.42	0.96±0.21	1.25±0.48	0.006	0.13	0.027
C 20:4n-6	7.17±0.52	5.76±0.49	6.73±1.58	0.004	0.17	0.51

C 22:4n-6	0.73±0.07	0.46±0.12	0.52±0.10	0.010	0.28	0.019
C 22:5n-6	0.14±0.03	0.10±0.04	0.11±0.03	0.062	0.23	0.15
n-6 fatty acids	26.5±1.3	20.6±2.1	23.9±2.9	0.006	0.056	0.141
C 18:3n-3	0.55±0.17	0.58±0.04	0.51±0.19	0.70	0.40	0.70
C 20:5n-3	0.96±0.47	2.29±1.16	3.35±1.43	0.021	0.14	0.014
C 22:5n-3 (EPA)	1.08±0.30	1.05±0.21	1.46±0.39	0.90	0.057	0.16
C 22:6n-3 (DHA)	1.84±0.53	2.99±0.42	4.09±0.69	0.017	0.010	0.003
n-3 fatty acids	4.44±0.92	6.92±1.49	9.42±2.28	0.024	0.050	0.009
n-6/n-3 fatty acid ratio	6.2±1.3	3.1±0.9	2.7±0.9	0.011	0.40	0.012
EPA+DHA	2.80±0.7	5.28±1.3	7.45±2.0	0.011	0.053	0.006
n-3 LCPUFA%	27.7±4.2	45.9±6.7	50.5±9.6	0.004	0.32	0.009
Total fatty acid concentration (ug/100 uL)	99.55±0.26	99.41±0.14	98.97±0.30	0.34	<0.001	0.026
Triglyceride (mmol/L)	1.87±0.50	2.87±1.67	2.15±2.17	0.20	0.50	0.80

The fatty acid composition is presented as weight% of total fatty acids; mean ±SD (n=6) and p-value for change from baseline (day 30) to day 71 (t1-t2), day 71 to 113 (t2-t3), and baseline to day 113 (t1-t3).

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; n-3 LCPUFA%, percentage omega-3 highly unsaturated fatty acids.

Author Statement

Conception and design; TLF, CM, LL, RDL and TI; Data collection and analysis; RDL and TI; Interpretation; RDL, TI, KS, KDS and LL; Laboratory analyses; KDS; First draft; RDL and LL; Final approval of manuscript; All authors