HHS Public Access

Author manuscript

J Pediatr Gastroenterol Nutr. Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2015 July ; 61(1): 138–143. doi:10.1097/MPG.0000000000000741.

High oleic ready-to-use therapeutic food maintains docosahexaenoic acid status in severe malnutrition: a randomized, blinded trial

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Abstract

Objective—Ready-to-use therapeutic food (RUTF) is the preferred treatment for uncomplicated severe acute malnutrition. RUTF contains large amounts of linoleic acid and very little α-linolenic acid, which may reduce the availability of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) to the recovering child. A novel high oleic RUTF (HO-RUTF) was developed with less linoleic acid to determine its effect on DHA and EPA status.

Methods—We conducted a prospective, randomized, double-blinded, clinical effectiveness trial treating rural Malawian children with severe acute malnutrition. Children were treated with either HO-RUTF or standard RUTF. Plasma phospholipid (PL) fatty acid status was measured upon enrollment and after 4 weeks and compared between the two intervention groups.

Results—Among the 141 children enrolled, 48/71 receiving HO-RUTF and 50/70 receiving RUTF recovered. Plasma PL samples were analyzed from 43 children consuming HO-RUTF and 35 children consuming RUTF. The change in DHA content during the first 4 weeks was +4% and −25% in the HO-RUTF and RUTF groups, respectively ($P = 0.04$). For EPA, the change in

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Conflicts of interest: The authors have no conflicts of interest to declare.

Author Contributions

MZ, SI, JTB, KM and MJM conceived and planned the study. MZ, JTB and MJM identified funding sources for the study. MZ and MJM oversaw the production of the study foods. CC, CT, KM. SI and IT obtained ethical approval. CC, CT, KM, MJM and IT identified the study sites, enrolled the participants and collected the clinical data. LL and JTB processed the fatty acids samples, analyzed the samples and interpreted the plasma PL fatty acid results. JCH, IT, LS and MJM analyzed the clinical data. JCH, LL, JTB and MJM wrote the first draft of the manuscript. All authors read the final version of the manuscript and approve of its content. All authors meet the ICMJE criteria for authorship.

content was 63% and −24% in the HO-RUTF and RUTF groups ($P < 0.001$). For arachidonic acid, the change in content was −3% and 13% in the HO-RUTF and RUTF groups ($P < 0.009$).

Conclusions—The changes in DHA and EPA seen in the children treated with HO-RUTF warrant further investigation as they suggest HO-RUTF support improved PUFA status, necessary for neural development and recovery.

Keywords

Severe acute malnutrition; Ready to use therapeutic food; Docosahexaenoic Acid; Eicosapentaenoic Acid; Linolenic Acid

Introduction

Ready to use therapeutic food (RUTF) is the standard home-based treatment and has greatly improved the recovery rate of children with severe acute malnutrition (SAM) in sub-Saharan Africa (1). Conventional RUTF formulations appropriately focus on delivery of macronutrients and essential micronutrients with long shelf life to restore health and restart growth and development. RUTF is a peanut paste-based food, which is very rich in ω-6 linoleic acid (LA), with negligible amounts of all other polyunsaturated fatty acids (PUFAs), including the ω3 α-linolenic acid (ALA) (2).

LA and ALA are substrates that are elongated and desaturated by the same enzymes (3). An excess of LA is antagonistic to the endogenous biosynthesis and incorporation into cell membranes of ω3 long chain PUFAs, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Tissue accumulation of DHA is essential for normal neural development, and EPA deposition in membranes is similarly important as a balance to n-6 arachidonic acid. Over 60 animal studies show that a dietary deficiency of ω3 PUFAs during neural development leads to neurocognitive abnormalities despite normal weight and length-based growth (4). These studies were based on a standard model of ω3 deficiency in which rodents are fed high ω6 (LA) with ω3 (ALA) not dissimilar to PUFA in contemporary RUTF. Additional evidence suggests that excess LA and low ALA in protein deficient, malnourished animals compromises neural development (5).

Recently, traditional plant breeding methods have been applied to commodity oil-bearing crops to yield an extensive variety of fatty acid compositions (6). A major commercial effort has been the development of oils that have mostly replaced LA with oleic acid. High oleic peanuts are commercially available and their use in RUTF allows for large reductions of LA in RUTF.

In this prospective, randomized, double-blind clinical effectiveness trial, we compared standard RUTF to a high oleic acid RUTF (HO-RUTF) in the treatment of SAM. We tested the hypothesis that treatment with HO-RUTF results in greater plasma phospholipid (PL) DHA and EPA levels than standard RUTF.

Methods

Subjects

Malawian children with SAM aged 6-59 mo were recruited from six clinics in rural southern Malawi from January to May 2014. Inclusion criteria were having a mid-upper arm circumference <11.5 cm and/or bilateral pitting edema, who qualify for community-based management of SAM. Appetite was assessed by giving the child 30g of RUTF and requiring him/her to consume it within 20 min. Exclusion criteria were treatment for SAM in the previous 6 months, the presence of a chronic, debilitating condition such as cerebral palsy or congenital heart disease, or peanut allergy. HIV infection was not an exclusion criterion.

Ethical approval was obtained from the University of Malawi, the College of William and Mary, and Washington University in St. Louis. The study was registered at ClinicalTrials.gov as NCT02053857.

Study Design

Children with SAM were recruited to this prospective, randomized, double-blind clinical effectiveness trial comparing RUTF and HO-RUTF. The primary outcome was the change in plasma DHA and EPA content after 4 wk. Secondary outcomes were rates of recovery from SAM, length and weight gain, and the change in plasma content of arachidonic acid. Recovery from SAM was defined as having a mid-upper arm circumference > 12.4 cm without edema within 12 wk of enrollment.

The planned sample size for the study was 55 participants in each study arm. This sample size allows for detection of 20% increase in DHA and EPA in the children receiving HO-RUTF when compared to children receiving RUTF with 95% sensitivity and 80% power. This sample size estimate assumed that the SD would be 30% of the mean and 10% of the participants would be lost to follow up.

Subjects were randomized to either RUTF or HO-RUTF by choosing a treatment designation in a sealed envelope, prepared by a study assistant who did not participate in the data collection or analysis. The children, caretakers, and clinic workers were blinded to the assigned intervention.

Participation

Given that the population is primarily communitarian and illiterate, informed consent was obtained through a verbal, staged process. Initially village leaders and health advocates were informed about the study through a discussion and their permission was requested for the research team to proceed. When permission was granted, the village health aids raised community awareness about the study through regularly scheduled health talks, so mothers would know this new activity was taking place in the clinic setting. Then, among the caretakers of eligible children, experienced pediatric nutrition nurses explained the study participation and purpose of the study in the local language and invited the caretakers to participate in the study. Finally, a document was ‘signed’ with a fingerprint as an official record that consent was obtained.

Initial demographic and health information was collected, mid-upper arm circumference, length, and height were measured, and the presence of edema was assessed on the dorsum of the feet. A 1 mL blood sample was drawn and placed in a tube with calcium EDTA. Randomization then occurred and focused nutritional counselling and instructions on therapeutic feeding were provided by the nurses.

Children returned every 2 wk for a follow-up visit until either the child recovered or 12 wk had passed from the time of enrollment. Anthropomorphic measurements were taken at each visit, and caretakers were asked about their child's health status and feeding habits. When a child recovered, no more RUTF was given and the child deemed to be free of acute malnutrition. At 4 wk after enrollment a second blood sample was collected.

Foods

Each subject was given a quantity of RUTF that provided about 175 kcal/kg/d (735 kJ/kg/d). Standard RUTF was made with peanuts, palm oil and soy oil, while HO-RUTF was made with high oleic peanut, palm oil and linseed oil (Table 1). The fatty acid content of the HO-RUTF contained more ALA and less LA than RUTF (Table 1). Other than the fatty acid content, the nutrient content of the study foods was very similar (Table S1). Each subject was given a ration sufficient for 2 weeks.

RUTF was produced by Project Peanut Butter in Blantyre, Malawi, and the HO-RUTF was produced by Nutriset (Malaunay, France). Both RUTF products passed safety testing for aflatoxin and microbial contamination (Malawi Bureau of Standards and Eurofins Scientific Inc., Des Moines, Iowa, USA).

Caretakers were instructed to feed their children the entire ration of RUTF over the 2 wk period. Well-nourished twins were given a RUTF ration to limit sharing of RUTF within households. Participants who lived in the same household received the same food to prevent confounding.

Acceptability Trial

Prior to the trial, a double-blind acceptability trial of HO-RUTF with 148 Malawian children from 6 months to 5 years of age with SAM was conducted June-August 2013. Each child was randomly assigned to receive either the standard RUTF or HO-RUTF.

The acceptability trial involved two components. All 148 children were given 30 g of the assigned food and the time to consume all the food was measured. If all of the food was not consumed after 40 min or the child stopped eating, the remaining food was weighed and time recorded. Caretakers then completed a survey that assessed each child's appetite and likeability of the food.

The second stage of the acceptability trial was conducted with a subset of 57 children from the first stage, 29 children receiving HO-RUTF and 28 children receiving RUTF. These children were provided with 90 g of the assigned food for each day for 3 d and consumption was monitored by their caretaker. On the 4th day, participants returned and caretakers completed a final likeability survey.

Fatty Acid Analysis

Plasma from blood samples drawn into EDTA tubes was separated, frozen and maintained below −20 °C for transport to the Brenna laboratory in Ithaca, NY, USA. All samples that were received intact were analyzed in a blinded fashion and no data were excluded from the statistical analyses. Plasma phospholipids (PL) were separated by thin layer chromatography and fatty acid profiles were measured by gas chromatography after derivation to fatty acid methyl esters with BF_3 in methanol (7-9). Capillary gas chromatography with flame ionization detection was used to detect the esters, with calibration based on an equal weight standard run daily to establish response factors, as well as heptadecanoic acid internal standard for quality control. Fatty acid identities were periodically checked by GC-covalent adduct chemical ionization mass spectrometry.

Data Analysis

Clinical data were entered into a Microsoft Access database, cleaned, and kept blinded throughout the analyses. Summary statistics were calculated for each dietary group, including plasma PL fatty acid content. Fatty acid content was expressed as g/100g lipid. The difference in fatty acid content for the two dietary groups was calculated from enrollment to 4 wk. Student's t-test was used to compare continuous outcomes after passing a test of normality (Shapiro-Wilks test with $P > 0.1$) and Fisher's exact test was used to compare categorical outcomes (SPSS 22.0, IBM, Chicago, IL). Differences were considered significant if $P < 0.05$.

Binary logistic regression modeling was used to predict recovery. The type of RUTF was the primary independent variable; other covariates included whether the mother was the child's primary caretaker, baseline anthropometric measurements and HIV status of the mother and child. Covariates were considered significant if $P < 0.05$.

Results

Study Subjects

A total of 141 children were enrolled from January to May 2014 (Table 2, Figure S1). No adverse reactions to any of the study foods were reported. After randomization, 70 children were assigned to RUTF and 71 children were assigned to HO-RUTF. Both initial and 4-week blood samples were analyzed from 78 children, 35 receiving RUTF and 43 receiving HO-RUTF. No differences were detected in any plasma PL fatty acids between the two dietary groups at enrollment ($P > 0.15$, Table S2).

Acceptability Trial

Likeability on the first day for both the first and second components showed a score of 5, highest on the scale, for 64/74 participants receiving RUTF and 59/74 receiving HO-RUTF ($P = 0.38$). On day 4 of the acceptability survey in the second component of the trial, all participants reported a likeability score of 5. During the first activity of the acceptability trial, children consumed 30g of standard RUTF in 9.3 min and 30 g of HO-RUTF in 12.3 min. In the second activity, standard RUTF and HO-RUTF consumption took 10.4 and 12.8 minutes, respectively. The amount of food remaining at the end of the taste test was greater

among the HO-RUTF food taste testers than standard RUTF tasters in both components (3.7 ± 8.0 vs 1.3 ± 4.6 g, $P = 0.03$).

Clinical outcomes

The overall recovery rate for children receiving RUTF was 71% and 68% for children receiving HO-RUTF ($P = 0.72$, Table 3). Binary logistic regression modeling also confirmed that the type of RUTF administered did not predict recovery. Children receiving HO-RUTF had a greater weight-for-height z-score upon completion of therapy ($P = 0.02$).

Plasma PL fatty acids

Plasma PL EPA levels were higher, while arachidonic acid was lower in children who received HO-RUTF, compared to children who received RUTF (Table 3). DHA levels decreased by 25% after 4 weeks from enrollment in the standard RUTF group, but did not change significantly in the HO-RUTF group, while opposite changes were seen in arachidonic acid and DPAn-6 (Figure 1). EPA and DPAn-3 increased over 4 weeks in the HO-RUTF group, while DHA did not change (Table S2).

Discussion

Children with SAM treated with conventional RUTF, demonstrated a relative reduction in ω3 long chain PUFA status, compared to children treated with HO-RUTF after 4 wk of treatment. HO-RUTF led to relative increases of +29% and +87% for DHA and EPA, respectively. Anthropometric recovery and growth rates were similar between the two groups, and thus shows that the HO-RUTF does not compromise physical recovery. Importantly, the effectiveness of high LA/low ALA in supporting growth and recovery is consistent with much animal data showing normal growth but severe neurological abnormalities in similarly LA-dominant diets (4).

The small sample size limited our ability to detect differences in recovery of < 10% and the study design did not assess developmental outcomes. The participants were rural African children consuming a plant-based diet and the findings cannot necessarily be generalized to urban settings, outside of Africa and to other populations with greater breast milk DHA content and other dietary differences. Our findings may also not be generalizable to populations with considerable fish consumption, especially salmonids and other fatty fish, which are known to increase breast milk EPA and DHA. Another limitation of the study was that the 4 week period between the first and second blood sampling was not enough time to change erythrocyte fatty acid content, thus only the short term plasma PL content was measured.

The clinical importance of these results as related to neurodevelopmental function are uncertain because of the paucity of research on DHA in malnutrition. A recent study in rats showed that protein malnutrition compromises brain DHA, and that brain DHA can be improved by increasing DHA in rat milk (5). If these results apply to humans the importance of nutritional DHA support via reduced LA and/or supplemental DHA are all the more critical.

DHA and EPA status have known and emerging neurophysiological implications. Development of neural tissue requires a steady supply of DHA during the brain growth spurt, which in well-nourished children, starts at about week 27 of gestation and continues through two years of age (10). Compromise of plasma PL DHA is particularly worrisome in light of data indicating that a major route of entry of DHA to the brain is as lysophosphatidylcholine mediated by a recently identified protein transporter (11-12). A plausible interpretation of our results is that the dramatic drop in plasma PL DHA is caused in part by central nervous system DHA demand outpacing hepatic DHA synthesis as SAM subsides and growth and development restart. DHA and EPA metabolites are well known to have anti-inflammatory effects via signaling eicosanoids and docosanoids (13). The increase in circulating EPA induced by the HO-RUTF compared to the standard RUTF would be expected to be especially significant as a balance to arachidonic acid, which was increased in the standard RUTF, but decreased in HO-RUTF. Emerging data show that DHA and EPA are anti-nociceptic signaling epoxides, and our previous data show that circulating vicinal diols, the excreted forms of these metabolites, are higher in developing animals that have better DHA status (14-15).

Endogenous DHA synthesis needed for neurodevelopment is particularly vulnerable to excess LA. Two dozen studies in adult humans now show that raising dietary ALA, or indeed any precursor including EPA, does not increase circulating levels of DHA (16). The rate-limiting desaturase coded by the FADS2 gene has numerous substrates all competing with one another for Δ6- and Δ8-desaturation. Endogenous synthesis of DHA uses the FADS2 desaturase twice, once for insertion of the double bond at eventual position 10 via Δ6-desaturation of 18:3n- 3 →18:4n-3 (ALA → 18:4n-3), and once for insertion of the double bond at position 4 by Δ6-desaturation of 24:5n-3 → 24:6n-3 or direct Δ4-desaturation 22:5n-3 → 22:6n-3 (DPAn-3 → DHA), as is the case in some vertebrates and as we have recently presented for human cells (17-18). As a result, excess LA inhibits endogenous synthesis of DHA, as well as its incorporation into membranes.

The HO-RUTF studied here was formulated to provide a similar quantity of nutrients as are included in standard RUTF and to test the hypothesis that large excesses of LA alter DHA status. The precise composition of HO-RUTF was not optimized for endogenous DHA synthesis because the amounts of LA and ALA remain high. Both LA and ALA are substrates for the FADS2 desaturase, antagonizing the insertion of the last double bond into DHA. This leads to the superficially counterintuitive, but mechanistically well understood, result that high LA or high ALA or both reduce endogenous DHA synthesis (19). In mice, plasma PL DHA is maximal when dietary ALA and LA account for about 2% of fatty acids (20). At any particular proportion (or ratio) of ALA and LA, ALA levels much above 2% cause a decrease in plasma DHA; this phenomenon is independent of total fat as a percent of energy and depends only on the relative amounts of ALA and LA in fat. In HO-RUTF they are about 13%, suggesting that lower amounts of ALA and LA will boost endogenous DHA synthesis. This quantity and proportion of ALA and LA would be obtained in a diet where the majority of fat is obtained from edible leaves, such as spinach and cabbage, in which ALA predominates over LA, but where both provide only a small fraction of total energy intake. This pattern of fatty acid consumption was seen in the preindustrial diet.

Future research to confirm and extend these preliminary results should include a larger clinical trial investigating HO-RUTF with measures of cognitive outcome. An alternative strategy to improve long chain PUFA status is to supplement EPA and DHA directly. However, EPA-DHA containing oils are the most labile of food ingredients, and care is necessary to avoid introducing off-flavors during formulation and storage, thus increasing production cost and reducing shelf-life. In contrast, high oleic oils are no more expensive to produce and are more shelf stable than conventional commodity counterparts. It is for this reason that industrial production of high oleic edible oils has increased dramatically in recent years; for instance, most U.S. sunflower oil is high oleic, and soy oil, presently supplying greater than 15% of calories in the U.S., is projected to be about 40% high oleic by 2020 (21). High oleic peanuts are widely available in food products in Australia and production in the U.S. is expanding. Finally, no inherent incompatibility exists in supplementing HO-RUTF with EPA and DHA oils, should that step be desirable on a commercial scale.

In conclusion, the effectiveness of HO-RUTF was similar to that of standard RUTF in achieving anthropometric recovery in SAM. Children who consumed HO-RUTF better maintained their DHA and EPA content in plasma PL when compared to those children consuming standard RUTF. This observation, in conjunction with what is known about DHA and EPA biosynthesis, questions whether PUFAs in RUTF are optimized for neurocognitive recovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Karl Seydel and the laboratory staff at the Blantyre Malaria Project for their technical assistance with preparation and storage of blood specimens.

Sources of funding: This study was supported by NIH grant R01 AT007003 from the National Center for Complementary and Integrative Health (NCCIH) and the Office of Dietary Supplements (ODS). The therapeutic foods were donated by Nutriset and Project Peanut Butter. The sponsors played no role in the study design, data collection, data analyses, interpretation or decision to submit for publication.

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What is known

- Conventional ready-to-use therapeutic food (RUTF) contains high omega-6 linoleic acid and very little omega-3 α-linolenic acid.
- Animal studies suggest that this composition reduces neuroactive docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) status while supporting growth.

What is new

- A novel high oleic RUTF (HO-RUTF) with less linoleic acid showed that clinical recovery rates were similar compared to conventional RUTF.
- RUTF vs HO-RUTF caused different changes in DHA (−25% vs +4%) and EPA (−24% vs +63%) status.
- HO-RUTF avoided precipitous reductions in DHA and EPA and while supporting recovery.

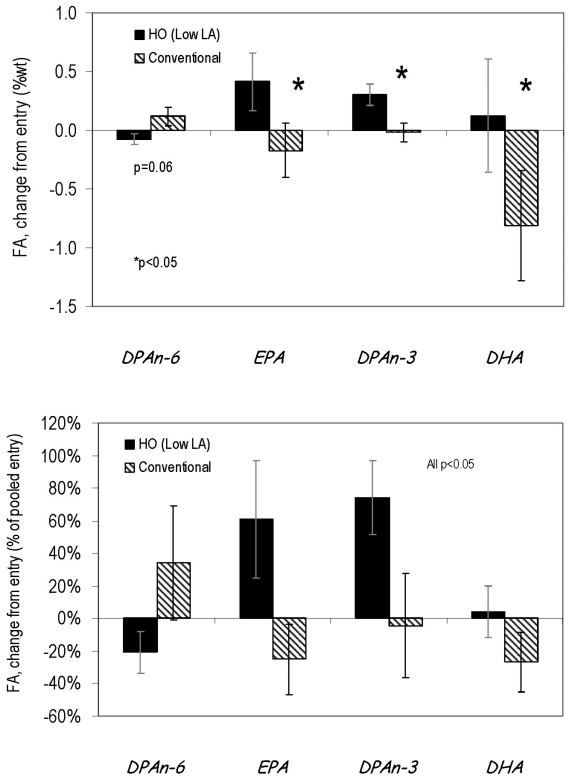

Figure 1.

Changes in plasma fatty acids after receiving 4 wk of HO-RUTF or RUTF. (A) Change expressed in percent by weight of fatty acid, showing HO-RUTF induces a slight reduction in DPAn-6 and increases in the ω3 long chain PUFAs EPA and DHA. In contrast, treatment with conventional RUTF led to an increase in DPAn-6 and a decrease in DHA. (B) Changes expressed as percent of the pooled means demonstrate the most significant percent change was in EPA. * indicates the difference beween the RUTFs was $P < 0.05$ (using Excel 2003, build 11.5612.5606). Means ± 95%CI. EPA, DPAn-3, and DHA changes are normally distributed by Shapiro-Wilks test ($P > 0.1$); DPAn-6 evaluated by t test ($P = 0.0002$).

TABLE 1

Ingredient composition and fatty acid content of ready-to use study foods

Ingredient	Ready-to-use therapeutic food	High oleic ready to use therapeutic food
Dry skimmed milk	25%	17.2%
Sweet whey	0	14.5%
Peanuts	27%	24.6%
Linseed oil	0	8.2%
Palm oil	15.8%	13.0%
Soy oil	2.9%	0
Sugar and maltodextrin	26%	19.0%
Micronutrients and mono– & diglyceride emulsifier	3.2%	3.3%

Fatty acid content	Fraction	Amount g/ 100 g	Fraction	Amount, g/ 100 g
Saturated fat	37.2%	15.7	28.7%	10.1
Monounsaturated fat	41.1%	17.4	44.7%	15.8
Linoleic acid (LA)	21.3%	8.9	13.1%	4.4
α-linolenic acid (ALA)	0.4%	0.17	13.1%	4.4
LA:ALA ratio	53:1		1:1	

TABLE 2

Characteristics of children upon enrollment[‡]

	Ready-to-use therapeutic food N = 70	High oleic ready-to-use therapeutic food N = 71
Age, mo	19 ± 9.7	20 ± 13
Males	25 (36)	27 (38)
Currently breastfeeding	33 (47)	33 (46)
Primary caregiver was mother	66 (94)	66 (93)
Mother was HIV positive	8 (11)	2 (3)
Edemamatous malnutrition	44 (63)	41 (58)
Mid upper arm circumference, cm	12.0 ± 1.2	11.8 ± 1.3
Weight-for-height, z-score	−1.8 ± 1.1	−1.9 ± 1.0
Height-for-age, z-score	−2.9 ± 1.4	−3.3 ± 1.7
Plasma phospholipid content	N = 40	N=41
Docosahexaenoic acid, % weight of lipid	3.2 ± 1.6	2.8 ± 1.4
Eicosapentaenoic acid, % weight of lipid	0.7 ± 0.7	0.7 ± 0.7
α-linolenic acid, % w of lipid	0.4 ± 0.3	0.3 ± 0.3
Linoleic acid, % w of lipid	15.6 ± 3.5	14.7 ± 4.3

[‡]Values are means ± SD or n (%)

TABLE 3

Clinical outcomes[‡]

	Ready-to-use therapeutic food N = 70	High oleic ready-to-use therapeutic food N = 71	*P*
Clinical outcomes, n (%)			
Recovered	50 (71)	48 (68)	0.72
Remained malnourished	9 (13)	19 (27)	
Lost to follow-up	6 (9)	3 (4)	
Died	5 (7)	1 (1)	
MUAC gain after 4 wk, mm/d[#]	0.15 ± 0.28	0.22 ± 0.31	0.20
Weight gain after 4 wk, g/kg/d	2.0 ± 2.6	2.8 ± 3.1	0.41
Length gain at study completion, mm/d	0.13 ± 0.36	0.22 ± 0.34	0.22
Weight-for-height at recovery, z-score	−0.60 ± 1.0	−0.15 ± 1.3	0.02
Plasma PL fatty acid (%,w/w) after 4 wk	N=35	N=43	
Docosahexaenoic acid (DHA)	2.4 ± 1.1	3.0 ± 1.5	0.04
Eicosapentaenoic acid (EPA)	0.5 ± 0.6	1.1 ± 0.8	< 0.001
α-linolenic acid (ALA)	0.7 ± 1.1	0.8 ± 0.8	0.53
Linoleic acid (LA)	17.3 ± 6.5	16.3 ± 5.7	0.43
Arachidonic acid	7.6 ± 3.7	5.6 ± 3.2	< 0.01

[‡]Values are means ± SD or n (%)

[#]MUAC, mid-upper arm circumference