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Ji-Cheng Hsieh

Indi Trehan

Christina Craig

Scott Ickes
College of William and Mary

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High-Oleic Ready-to-Use Therapeutic Food Maintains Docosahexaenoic Acid Status in Severe Malnutrition

*Ji-Cheng Hsieh, †Lei Liu, ‡Mamane Zeilani, §Scott Ickes, *Indi Trehan, ||Ken Maleta, *Christina Craig, ||Chrissie Thakwalakwa, *Lauren Singh, †J. Thomas Brenna, and *Mark J. Manary

ABSTRACT

Objectives: Ready-to-use therapeutic food (RUTF) is the preferred treatment for uncomplicated severe acute malnutrition. It contains large amounts of linoleic acid and 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-blind clinical effectiveness trial treating rural Malawian children with severe acute malnutrition. Children were treated with either HO-RUTF or standard RUTF. Plasma phospholipid fatty acid status was measured on enrollment and after 4 weeks and compared between the 2 intervention groups.

Results: Among the 141 children enrolled, 48 of 71 receiving HO-RUTF and 50 of 70 receiving RUTF recovered. Plasma phospholipid 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 content was 63% and −24% in the HO-RUTF and RUTF groups, respectively ($P < 0.001$). For arachidonic acid, the change in content was −3% and 13% in the HO-RUTF and RUTF groups, respectively ($P < 0.009$).

Conclusions: The changes in DHA and EPA seen in the children treated with HO-RUTF warrant further investigation because they suggest that HO-RUTF support improved polyunsaturated fatty acid status, necessary for neural development and recovery.

Key Words: docosahexaenoic acid, eicosapentaenoic acid, linolenic acid, ready-to-use therapeutic food, severe acute malnutrition

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What Is Known

- Conventional ready-to-use therapeutic food (RUTF) contains high omega-6 linoleic acid and 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 with conventional RUTF.
- RUTF versus 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 while supporting recovery.

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 rich in ω-6 linoleic acid (LA), with negligible amounts of all of the other polyunsaturated fatty acids (PUFAs), including the ω-3 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 ω-3 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. More than 60 animal studies show that a dietary deficiency of

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From the *Department of Pediatrics, Washington University, St. Louis, MO, the †Division of Nutritional Sciences, Cornell University, Ithaca, NY, the ‡Nutriset, Malaunay, France, the §Department of Kinesiology and Health Sciences, College of William and Mary, Williamsburg, VA, and the ||College of Medicine, University of Malawi, Blantyre, Malawi, Africa.

Address correspondence and reprint requests to Mark J. Manary, MD, Department of Pediatrics, St Louis Children's Hospital, One Children's Place, St Louis, MO 63110 (e-mail: manary@kids.wustl.edu); J. Thomas Brenna, Division of Nutritional Sciences, Cornell University, Ithaca, NY 14853 (e-mail: jtb4@cornell.edu).

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ω-3 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 ω-3 deficiency in which rodents were fed high ω-6 (LA) with ω-3 (ALA) not dissimilar to PUFA in contemporary RUTF. Additional evidence suggests that excess LA and low ALA in protein-deficient, malnourished animals compromise 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 the present prospective, randomized, double-blind clinical effectiveness trial, we compared standard RUTF with a high-oleic 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 that with standard RUTF.

METHODS

Patients

Malawian children with SAM aged 6 to 59 months were recruited from 6 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 30 g of RUTF and requiring him/her to consume it within 20 minutes. 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. human immunodeficiency virus 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.

Study Design

Children with SAM were recruited to the present 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 weeks. 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 weeks 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 with that in children receiving RUTF, with 95% sensitivity and 80% power. This sample size estimate assumed that the standard deviation would be 30% of the mean and 10% of the participants would be lost to follow-up.

Patients 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 increased community awareness about the study through regularly scheduled health talks, so mothers would know that 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 ethylenediaminetetraacetic acid. Randomization then occurred and focused nutritional counseling and instructions on therapeutic feeding were provided by the nurses.

Children returned every 2 weeks for a follow-up visit until either the child recovered or 12 weeks 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 weeks after enrollment, a second blood sample was collected.

Foods

Each patient was given a quantity of RUTF that provided approximately 175 kcal/kg/day (735 kJ/kg/day). Standard RUTF was made with peanuts, palm oil, and soy oil, whereas 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 that of the RUTF (Table 1). Other than the fatty acid content, the nutrient content of the study foods was similar (Table S1, *http://links.lww.com/MPG/A432*). Each patient 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, IA).

Caretakers were instructed to feed their children the entire ration of RUTF during the 2-week 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

Before 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 during June to August 2013. Each child was randomly assigned to receive either the standard RUTF or HO-RUTF.

The acceptability trial involved 2 components. All of the 148 children were given 30 g of the assigned food, and the time to consume all of the food was measured. If all of the food was not consumed after 40 minutes 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.

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 monoglyceride and diglyceride emulsifier	3.2	3.3

Fatty acid content	Ready-to-use therapeutic food		High-oleic ready-to-use therapeutic food	
	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
LA	21.3%	8.9	13.1%	4.4
ALA	0.4%	0.17	13.1%	4.4
LA:ALA ratio	53:1		1:1	

ALA = α-linolenic acid; LA = linoleic acid.

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 days, and consumption was monitored by their caretaker. On the fourth day, participants returned and caretakers completed a final likeability survey.

Fatty Acid Analysis

Plasma from blood samples drawn into ethylenediaminetetraacetic acid tubes was separated, frozen, and maintained at $<-20^{\circ}C$ for transport to the Brenna laboratory (Ithaca, NY). All of the samples that were received intact were analyzed in a blinded fashion, and no data were excluded from the statistical analyses. Plasma PLs were separated by thin layer chromatography, and fatty acid profiles were measured by gas chromatography (GC) after derivation to fatty acid methyl esters with BF_3 in methanol (7–9). Capillary GC 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 grams per 100 g lipid. The difference in fatty acid content for the 2 dietary groups was calculated from enrollment to 4 weeks. Student *t* test was used to compare continuous outcomes after passing a test of normality (Shapiro-Wilk test with $P > 0.1$), and Fisher 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 human immunodeficiency virus status of the mother and the child. Covariates were considered significant if $P < 0.05$.

RESULTS

Study Patients

A total of 141 children were enrolled from January to May 2014 (Table 2; Fig. S1, *http://links.lww.com/MPG/A433*). 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 2 dietary groups at enrollment ($P > 0.15$; Table S2, *http://links.lww.com/MPG/A434*).

Acceptability Trial

Likeability on the first day for both the first and the second components showed a score of 5, highest on the scale, for 64 of 74 participants receiving RUTF and 59 of 74 receiving HO-RUTF ($P = 0.38$). On day 4 of the acceptability survey in the second component of the trial, all of the participants reported a likeability score of 5. During the first activity of the acceptability trial, children consumed 30 g of standard RUTF in 9.3 minutes and 30 g of HO-RUTF in 12.3 minutes. 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 that among the 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

TABLE 2. Characteristics of children on 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)
Presently breast-feeding	33 (47)	33 (46)
Primary caregiver was mother	66 (94)	66 (93)
Mother was HIV positive	8 (11)	2 (3)
Edematous 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, % weight of lipid	0.4 ± 0.3	0.3 ± 0.3
Linoleic acid, % weight of lipid	15.6 ± 3.5	14.7 ± 4.3

HIV = human immunodeficiency virus; SD = standard deviation.
* Values are means ± SD or n (%).

RUTF administered did not predict recovery. Children receiving HO-RUTF had a greater weight-for-height *z* score on completion of therapy ($P = 0.02$).

Plasma PL Fatty Acids

Plasma PL EPA levels were higher and arachidonic acid was lower in children who received HO-RUTF, compared with those in 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, whereas opposite changes were seen in arachidonic acid and docosapentaenoic acid n-6 (DPAn-6; Fig. 1). EPA and docosapentaenoic acid n-3 (DPAn-3) increased during 4 weeks in the HO-RUTF group, whereas DHA did not change (Table S2, *http://links.lww.com/MPG/A434*).

DISCUSSION

Children with SAM treated with conventional RUTF demonstrated a relative reduction in ω-3 long-chain PUFA status, compared with children treated with HO-RUTF after 4 weeks 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 2 groups, and thus this shows that the HO-RUTF does not compromise physical recovery. More important, 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

TABLE 3. Clinical outcomes*

	Ready-to-use therapeutic food N = 70	High-oleic ready-to-use therapeutic food N = 71	*P*
Clinical outcomes, n (%)			0.72
Recovered	50 (71)	48 (68)	
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/day	0.15 ± 0.28	0.22 ± 0.31	0.20
Weight gain after 4 wk, g/kg/day	2.0 ± 2.6	2.8 ± 3.1	0.41
Length gain at study completion, mm/day	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	
DHA	2.4 ± 1.1	3.0 ± 1.5	0.04
EPA	0.5 ± 0.6	1.1 ± 0.8	<0.001
ALA	0.7 ± 1.1	0.8 ± 0.8	0.53
LA	17.3 ± 6.5	16.3 ± 5.7	0.43
Arachidonic acid	7.6 ± 3.7	5.6 ± 3.2	<0.01

ALA = α-linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; LA = linoleic acid; MUAC = mid-upper arm circumference; PL = phospholipid; SD = standard deviation.
* Values are means ± SD or n (%).

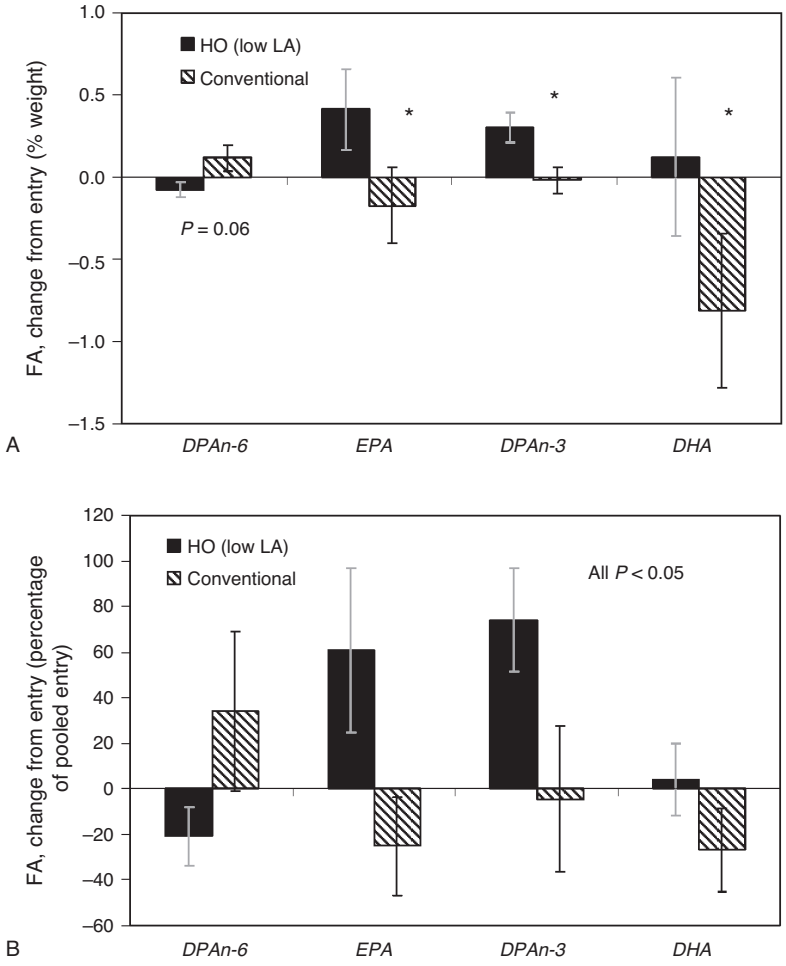

FIGURE 1. Changes in plasma fatty acids after receiving 4 weeks of HO-RUTF or RUTF. (A) Change expressed in percentage by weight of fatty acid, showing HO-RUTF induces a slight reduction in DPAn-6 and increases in the ω-3 long-chain PUFAs EPA and DHA. In contrast, treatment with conventional RUTF led to an increase in DPAn-6 and a decrease in DHA. (B) Changes expressed as percentage of the pooled means demonstrate the most significant percentage change was in EPA. The symbol "*" indicates that the difference between 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-Wilk test ($P > 0.1$); DPAn-6 evaluated by t test ($P = 0.0002$). CI = confidence interval; DHA = docosahexaenoic acid; DPAn-3 = docosapentaenoic acid n-3; DPAn-6 = docosapentaenoic acid n-6; EPA = eicosapentaenoic acid; FA = fatty acid; HO-RUTF = high-oleic RUTF; LA = linoleic acid; PUFA = polyunsatu-polyunsaturated fatty acid; RUTF = ready-to-use therapeutic food.

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 the 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 is 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 is 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 approximately week 27 of gestation and continues through 2 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 with that by 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 antinociceptic 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 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 of 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, high ALA, or both reduce endogenous DHA synthesis (19). In mice, plasma PL DHA is maximal when dietary ALA and LA account for approximately 2% of fatty acids (20). At any particular proportion (or ratio) of ALA and LA, ALA levels >2% cause a decrease in plasma DHA; this phenomenon is independent of total fat as a percentage of energy and depends only on the relative amounts of ALA and LA in fat. In HO-RUTF, they are approximately 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 in which the majority of fat is obtained from edible leaves, such as spinach and cabbage, in which ALA predominates over LA, but which both provide only a small fraction of the total energy intake. This pattern of fatty acid consumption was routine 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. EPA–DHA-containing oils, however, 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 US sunflower oil is high oleic, and soy oil, presently supplying >15% of calories in the United States, is projected to be approximately 40% high oleic by 2020 (21). High-oleic peanuts are widely available in food products in Australia and production in the United States 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 with the 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.

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