Spread fortified with vitamins and minerals induces catch-up growth and eradicates severe anemia in stunted refugee children aged 3–6 y[1–3]

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ABSTRACT

Background: Multiple micronutrient deficiencies are often the basic causative factor in stunting and anemia, 2 conditions that affect entire generations of children in deprived populations. No generally accepted recommendations for micronutrient intakes for recovery from stunting are available.

Objective: The objective was to assess the effect of a highly nutrient-dense spread fortified with vitamins and minerals, with or without antiparasitic metronidazole treatment, in correcting retarded linear growth and reducing anemia in stunted children.

Design: Saharawi refugee children ($n = 374$) aged 3–6 y with initial height-for-age *z* scores < -2 were assigned to 1 of 5 groups: fortified spread (FS), fortified spread plus metronidazole (FS+M), unfortified spread (US), unfortified spread plus metronidazole (US+M), or control. Supervised supplementation was given daily for 6 mo. Weight, height, knee-heel length, hematologic indexes, parasitic infections, and morbidity were assessed at 0, 3, and 6 mo.

Results: Linear growth of children fed FS was 30% faster at 3 mo than in US and control groups, after which height-for-age *z* scores increased only slightly in the FS group and remained unchanged in the other groups. No additional benefits from metronidazole were observed. Increase in hemoglobin concentrations in the FS group at 6 mo was twofold that in the US and control groups (37 ± 40, 19 ± 15, and 16 ± 17 g/L, respectively; $P < 0.0001$), and anemia was reduced by nearly 90%.

Conclusions: FS, and not US, induces catch-up growth in stunted children whose diets are poor in micronutrients. Our trial provides support for delivering multiple micronutrients to reverse stunting and reduce anemia in children up to age 6 y. *Am J Clin Nutr* 2004;80:973–81.

KEY WORDS Catch-up growth, stunting, anemia, micronutrient deficiencies, small bowel bacterial overgrowth, fat spreads, refugees, children, Algeria

INTRODUCTION

The optimal growth and development of children is a basic human right and a clear objective of social security and health systems. In developing countries, >200 million children aged <5 y are affected by retarded linear growth, or stunting, and >40% are estimated to have iron deficiency and anemia (1, 2). The functional consequences of becoming and remaining stunted include increased risk of infection and mortality, delays in motor and mental development, and decreased work capacity (3); iron deficiency anemia can lead to several health consequences, including impaired cognitive and physical development (4). Often the 2 conditions coincide in the same person (5), with concurrent impairment of key body functions such as overall growth, immune response, and psychomotor development. Together these symptoms are newly regarded as a syndrome in which stunting is the main feature, which is called the "stunting syndrome" (6). Taken together, stunting and iron deficiency anemia impose massive economic costs on societies in the developing world (7).

The etiology of stunting is thought to be multifactorial but to include inadequate nutrition, sustained infections, and poor mother-child interaction (8–10). Another issue is chronic parasitic infection, which is common in impoverished areas and is associated with appetite loss and nutrient malabsorption (11–13). It is not well understood which is the relative weight of nutrition and nonnutritional factors (14, 15) and to what extent macronutrients such as energy and protein or instead micronutrients are involved. Supplementation with zinc, and possibly iron and vitamin B-12, was shown to improve linear growth in infants and children in deficient populations (16–18). The community-based supplementation trials reviewed by Rivera et al (19) suggest different growth-limiting potentials of iron, zinc, and vitamin A, depending on the severity of deficiencies of these nutrients in populations with poor dietary quality. Randomized trials with multiple micronutrients produced mixed results, possibly because the trials varied in terms of both the initial age of the children and the extent to which the growth insult was already present at the time the intervention occurred, which made it hard for the investigators to distinguish between the prevention of retardation and the induction of catch-up growth (20–22). The potential for catch-up growth among stunted children is thought to be limited after age 2 y (23, 24); therefore, little attention was

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given to the micronutrient requirements for catch-up growth in older children.

Research is warranted to objectively identify the primary growth-limiting macronutrient and micronutrients and to identify suitable technological approaches for providing a safe and adequate nutrient supply to high-risk groups (25). Thus, the current study was conducted to assess the effect of a highly nutrient-dense spread fortified with vitamins and minerals, with or without antiparasitic metronidazole treatment, in correcting retarded linear growth and in reducing anemia in stunted refugee children.

SUBJECTS AND METHODS

Study location

Research was conducted between May 1998 and January 1999 at Saharawi refugee camps near the town of Tindouf in southwest Algeria. After political changes during the 1970s, the Saharawi people fled their homeland in the western Sahara Desert, and, for more than 25 y, they have lived in one of the most inhospitable desert regions of the world, in what can be defined as a permanent state of emergency. Water and food must be provided by external sources of aid, and the sanitary conditions are extremely poor. The basic food basket commonly consists of wheat flour, rice, lentils, sugar, oil, canned fish, canned meat, dried skimmed milk, tea, and yeast. Access to additional food items is limited, and few families can afford to supplement their rations with fresh produce. Although the theoretical nutritional value of the general ration covers basic energy requirements, it remains deficient in several micronutrients, particularly iron, vitamin A, and zinc. Furthermore, the supply of individual commodities is not always ensured on a regular basis because of an erratic food supply.

A 1997 survey among Saharawi children aged <5 y indicated that 46% were stunted, 10% were wasted, and 70% were anemic (defined as hemoglobin concentrations <110 g/L) (F Branca, personal communication, 1997). Anemia was likely due to poor dietary intake, a theory supported by the fact that it was primarily women and children, rather than adult men, who were affected (26). Most mothers reported at baseline that their children would frequently eat soil (geophagia), a behavior indicative of severe iron and zinc deficiencies (27). Saharawi children presented with signs of wariness, hesitancy, tiredness, depressed mood, and general lack of involvement, as was previously described in persons with iron deficiency anemia (IDA; 4).

Study subjects

To select subjects for the study, a census was conducted in the refugee camp between May and June 1998, and a database of all children aged <6 y was created. Because stunting was the target of the trial, children were assessed for height and weight. Children's birth dates were ascertained by cross-checking vaccination registers with immunization cards. Of 1144 children identified in the census, a total of 374 children aged 3–6 y with height-for-age *z* scores (HAZ) <−2.0 with use of World Health Organization and National Center for Health Statistics (WHO/NCHS) reference median were eligible to enter the trial. Exclusion criteria were severe or chronic illness, severe clinical malnutrition, or congenital abnormalities.

The study design was explained to the Saharawi health authorities, the Saharawi Ministry of Co-operation, community and religious leaders, and the women's association leaders. The objectives and procedures were also fully explained to mothers. The study was conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983, and oral informed consent was obtained from all mothers before inclusion of their children in the trial; each mother had the option to withdraw her child at any stage (28). Mothers of children in the control group were informed that their children would receive the supplement at the end of the trial. The study was approved by the ethical review committees of the Ministry of Health and the Saharawi Arab Democratic Republic, granted on the basis that all children would be treated at the end of the study with the most effective food supplement.

Study design

The study was designed as a randomized, double-blind, placebo-controlled supplementation trial in stunted children aged 3–6 y, with or without antiparasitic treatment. Eligible children were randomly assigned to 1 of 5 groups. The first group received a highly nutrient-dense spread fortified with multiple vitamins and minerals (fortified spread; FS), and the second group received the identical high-energy spread without micronutrient fortification (unfortified spread; US). The children receiving supplements were further randomly assigned to receive a full-course treatment of metronidazole (also mebendazole to children positive for helminth) or a placebo tablet. The fifth group functioned as a control subjects and did not receive any intervention. Subjects were eventually assigned to each of the 5 groups: FS + placebo (FS), FS + metronidazole (FS+M), US + placebo (US), US + metronidazole (US+M), and control with use of a simple computer-generated randomization method.

Supplementation was double-blind. The supplements were color coded at production, and the key revealing the code was kept by the manufacturer in France. Neither the field assistants nor the investigator was aware of group assignment. The codes were revealed only after all subjects had completed the trial.

Interventions

Micronutrient-fortified supplements

The supplementation consisted of 50 g/d of a fat spread that was high in energy and proteins. Depending on the group, a vitamin-mineral mix was added (Nutriset, Malaunay, France). Ingredients used in the spread were peanut, whey powder, soybean flour, vegetable fat, and sugar (**Table 1**). Because micronutrient requirements for catch-up growth are not yet established, a customized vitamin-mineral mix was formulated specifically for the study. Formulating the rationale of the fortification was the first step in choosing the correct concentrations of vitamins and minerals. We determined that, for catch-up growth to occur, the incremental rate of height increases should be doubled compared with that of normal growth, as shown in studies on nutritional rehabilitation of malnourished children (29). On the basis of this assumption, we designed our vitamin-mineral supplement by first doubling the vitamin and mineral amounts that are recommended by Italian Nutrition Society for a normal growing child of the same age (30). Micronutrient amounts hereby obtained were then compared with those used in other supplementation studies that showed a benefit to growth. For most vitamins and minerals, fortification amounts were 1.5–3 times the Dietary Reference Intakes (31). Ratios were then

TABLE 1
Energy and nutrient contents of supplements and daily coverage of vitamin mineral requirements[1]

	Fortified spread		Unfortified spread	
	Content	Percentage of DRIs	Content	Percentage of DRIs
	per 100 g	%	*per 100 g*	%
Energy (kcal)	637.5	NA	637.5	NA
Protein (g)	11.5	NA	11.5	NA
Lipids (g)	54.8	NA	54.8	NA
Calcium (mg)	1000	62.5	95	5.9
Potassium (mg)	1134	75.6	730	48.7
Phosphorus (mg)	635	63.5	208	20.8
Magnesium (mg)	156	60.0	85	32.7
Iron (mg)	42	210.0	2	10.0
Zinc (mg)	41	410.0	1	10.0
Copper (mg)	2	227.3	0	0
Vitamin A (μg)	2000	250.0	0	0
Vitamin D (μg)	50	500.0	0	0
Vitamin E (mg)	20	142.9	0	0
Vitamin C (mg)	125	250.0	0	0
Vitamin B-1 (mg)	4	291.7	0	0
Vitamin B-2 (mg)	4	333.3	0	0
Vitamin B-6 (mg)	4	291.7	0	0
Vitamin B-12 (μg)	4	145.8	0	0
Folate (μg)	500	125.0	0	0
Pantothenic acid (mg)	25	416.7	0	0
Niacin (mg)	50	312.5	0	0

[1] DRIs, US dietary reference intakes for children aged 4–8 y (31). NA, not available

adjusted for known interactions between micronutrients. For example, zinc, which has no identified storage compartment in the body but which has been shown to affect linear growth when deficient in the diet (32), was supplemented at 43 mg/d, an amount >3 times the Dietary Reference Intakes, to adjust for the zinc-to-iron ratio. Micronutrient adjustments were also made to prevent any potential absorption issues and to avoid toxic concentrations. Inclusion of electrolytes such as potassium, phosphorus, and magnesium was regarded as important, given their central role in diarrhea management. No micronutrients were added to the spread used in the US group. The spreads used in the FS and US groups were identical in their energy, protein, and lipid contents. They were indistinguishable in color and appearance, and the slight metallic taste of the spread used in the FS group was acceptable to the children.

The supplement was packaged in 50-g single-serving sachets. The supplement did not require any special preparation and was eaten alone as a snack. The fortification content of the supplement was monitored by the manufacturer, and it was found to retain about one-half of the vitamin A content after being stored for 6 mo at high temperature. Some vitamin C was lost because of oxidation. No other changes in the nutritional profile of the spread were noted as a result of storage.

Antiparasitic and antibiotic treatment

The drug treatment aimed to enhance nutrient absorption and to improve appetite by reducing parasitic infestation and bacterial overgrowth of the small bowel. Treatment for intestinal parasites was given, at baseline and at 3 mo, only to children receiving supplements. Treatment was single-blinded and consisted of 250 mg metronidazole (International Dispensary Association, Amsterdam) given twice a day for 5 d, with or without 200 mg mebendazole (International Dispensary Association) given twice a day for 3 d to children positive for helminth, or an identical placebo tablet given with equal frequency.

Supplementation procedures

Supplements were provided to the children between 0700 and 1000 every day except Friday. On Thursdays, an extra take-home ration of the spread would be given to the mother to feed her child at home. Supplementation was given for a total of 6 mo. Distribution took place from 1 of 6 secure dispensaries located in supplementary feeding centers run by local health staff members. Mothers were asked to bring their children to these feeding centers, where supplements were consumed on site under the direct supervision of study personnel. Daily attendance at supplementary feeding centers was monitored, and reasons for absence were recorded. Each child wore a colored bracelet that matched the color coding on the boxes that contained the supplements, both to facilitate the daily distribution and to ensure that each subject received the proper supplement for his or her group.

Sample size

The sample size was computed before the study, based on an estimated effect on the primary outcome measure, ie, linear growth performance (HAZ), to test the null hypothesis of "no difference" in average growth or mean hemoglobin concentrations between groups receiving fortified supplement and the control group, at 0.05 level of significance and 80% power. A minimum required sample size of 68 children was calculated to detect a mean ($\pm$SD) difference in HAZ of 0.3 $\pm$0.5, with the same confidence level and power. Allowing for a 10% dropout rate, a total of 75 children was recruited for each group.

Data collection

Anthropometric measures

Anthropometric status was taken for all groups at baseline and at 3 and 6 mo. Additionally, knee-heel length (KHL) was measured monthly in children receiving supplements. All measures were taken by the same investigator with use of standard techniques. Weight was measured with minimal clothing to the nearest 0.1 kg with use of a digital scale (Soehnle, Murrhardt, Germany), and height was measured in duplicate to the nearest 0.1 cm with a metallic portable measuring board (PROMES, Wageningen, Netherlands). Age was corroborated with immunization cards or, for the 37 (10%) subjects without cards, by parent's report. Height and weight data were transformed into *z* scores with use of the WHO/NCHS 1977 Reference Data (EPI-INFO 2000; version 1.0). Stunting, underweight, and wasting are defined as HAZ <-2.0, weight-for-age *z* score (WAZ) <-2.0, and weight-for-height *z* score (WHZ) < -2.0, respectively, as compared with the WHO/NCHS reference standards. KHL was measured to the nearest 0.1 mm with use of an electronic portable infant knemometer (Force Institute, Copenhagen). The right leg was always measured, with the mean of 5 independent knemometric estimations used as the actual measurement. An SD limit of 0.8 mm was established, above which the whole series of 5 readings was repeated.

Hemoglobin and hematocrit concentrations

Hemoglobin and hematocrit concentrations were measured from capillary blood samples. For collection, the participant's fingertip was warmed, cleaned with alcohol, and punctured with a needle with use of a sterile Hemolance lancet (HaeMedic AB, Munka Ljungby, Sweden). The first drop of blood was discarded. One drop of blood was then collected in a microcuvette, and the hemoglobin concentration was read directly in the field with the use of a hemoglobin spectrophotometer (HemoCue, Angelhom, Sweden). All measurements were performed in duplicate, and results were retained only when <3 g/L apart. Field spectrophotometers were monitored daily by measuring the control cuvette, ensuring that equipment was calibrated correctly. The HemoCue method was shown to be comparable in both accuracy and precision with the standard cyanmethemoglobin method (33). WHO guidelines were used to define anemia as hemoglobin concentrations <110 g/L and a hematocrit <33%. Anemia severity was classified with the following hemoglobin concentrations: mild anemia, hemoglobin 90–109 g/L; moderate anemia, hemoglobin 70–89 g/L; and severe anemia, hemoglobin <70 g/L (34).

Morbidity data

Morbidity data were collected every 2 wk at the supplementary feeding centers from children receiving supplements, and at baseline, 3 mo, and 6 mo from children in the control group. Information was obtained from the child's mother or primary caretaker about the presence or absence of symptoms of illness on the day of the interview and during the 6 preceding days. The checklist included symptoms of diarrhea (defined as >3 liquid stools/d), fever (high temperature and transpiration for >12 h), and respiratory infections (runny nose, cough, wheezing, difficulty breathing). Other disease symptoms freely reported by caretakers were also recorded. Morbidity rates were calculated as follows, using diarrhea as an example: the number of episodes of diarrhea was divided by the total number of days at risk for an episode of diarrhea, ie, diarrhea-free days (excluding days with missing data or when diarrhea was already present).

Fecal microscopy and egg counts

Stool examinations were performed at baseline and after 3 mo of supplementation. Parents were asked to collect a stool sample from their children early in the morning of the assessment day. Quantitative fecal microscopy was conducted with use of the standard concentration for the formol-ether method to screen for intestinal protozoan and helminth infections. The laboratory technician conducting the microscopic analysis was blinded to the study design and the treatment or placebo status of stool specimens. The number of eggs was counted, and the number of eggs per gram of feces was calculated from the volume of fluid examined and the weight of the stool specimen. Samples were transported to Rome, where further analyses were performed to assay for the presence of *Cryptosporidium parvum* infection.

Data analysis

The primary response variable was linear growth. Linear growth outcomes were converted to effect sizes, which were calculated as the mean change in height (or HAZ) of the FS and FS+M groups, minus the mean change in the US, US+M, and control groups, respectively, divided by the pooled SD of change for all groups (18).

Statistical analyses were by intention-to-treat and included participants who completed the entire study protocol. Data were checked for normal distribution by using the Kolmogorov-Smirnov test of normality. Descriptive data are expressed as mean (±SD). Statistical significance was set at $P < 0.05$. Differences in prevalence were tested with Pearson's chi-square test; differences in baseline characteristics between children who did not complete the study and those who did were tested with Student's *t* test; differences in characteristics at baseline among groups were tested with analysis of variance (ANOVA).

Variations among the supplementation groups for anthropometry and hematologic indexes at recruitment and after 3 and 6 mo of supplementation were analyzed by using multivariate ANOVA (MANOVA) for repeated measurements. When the overall *F* test was significant, differences among the groups were further investigated with post hoc multiple comparisons for ANOVA (Bonferroni multiple-comparison *t* test for comparison among the groups, $P < 0.01$). The effects of age at baseline and initial HAZ on change in height were tested with multiple regression analysis. Statistical analyses were performed with EPI-INFO 2000 software (version 6.04b; Centers for Disease Control and Prevention, Atlanta) and SPSS software (version 8; SPSS Inc, Chicago).

RESULTS

A total of 374 stunted children entered into the supplementation trial; of these participants, 254 completed the study protocol with follow-up measurements at both 3 and 6 mo (**Figure 1**). One severely anemic child in the control group was removed from the study for ethical reasons after the 3-mo follow-up. Dropout rates were similar between intervention groups. The children who dropped out did not differ in their baseline characteristics from those who completed the trial. The dropout rate during the study turned out to be larger than expected; however, it did not affect the power of the study because 2 groups could be combined to test the main effects of the 2 spreads.

No differences were seen between the groups with respect to the main characteristics at recruitment (**Table 2**). On average, the subjects were in their midchildhood ($\bar{x}$ ± SD age: 49.3 ± 11.5 mo) and were severely stunted (HAZ: −2.87 ± 0.67), mildly wasted (WHZ: −0.77 ± 0.74), and moderately anemic (hemoglobin: 91 ± 22 g/L; hematocrit: 31.5 ± 4.9%). Most children had received partial breastfeeding until age 2 y (duration: 22.8 ± 11.8 mo). Groups were also similar in terms of their socioeconomic and demographic variables.

Mean (±SD) overall compliance was calculated as the total number of days that the supplement was consumed expressed as a percentage of the total intended dose (ie, 180 snacks in 6 mo). Among all the children who received the snacks, compliance was 80 ± 16%, and 70% of them completed at least three-quarters of the total intended supplementation dosage. Compliance rates dropped by ≈20% in the second trimester of supplementation ($P < 0.001$). There were no differences in compliance rates among the supplemented groups (ANOVA) (**Table 3**).

Change in height indexes

To determine whether metronidazole treatment and supplement intake had an independent effect on linear growth, we carried out a two-way ANOVA by using 2 factors: drug (metronidazole or placebo) and spread (none, US, or FS). There was no

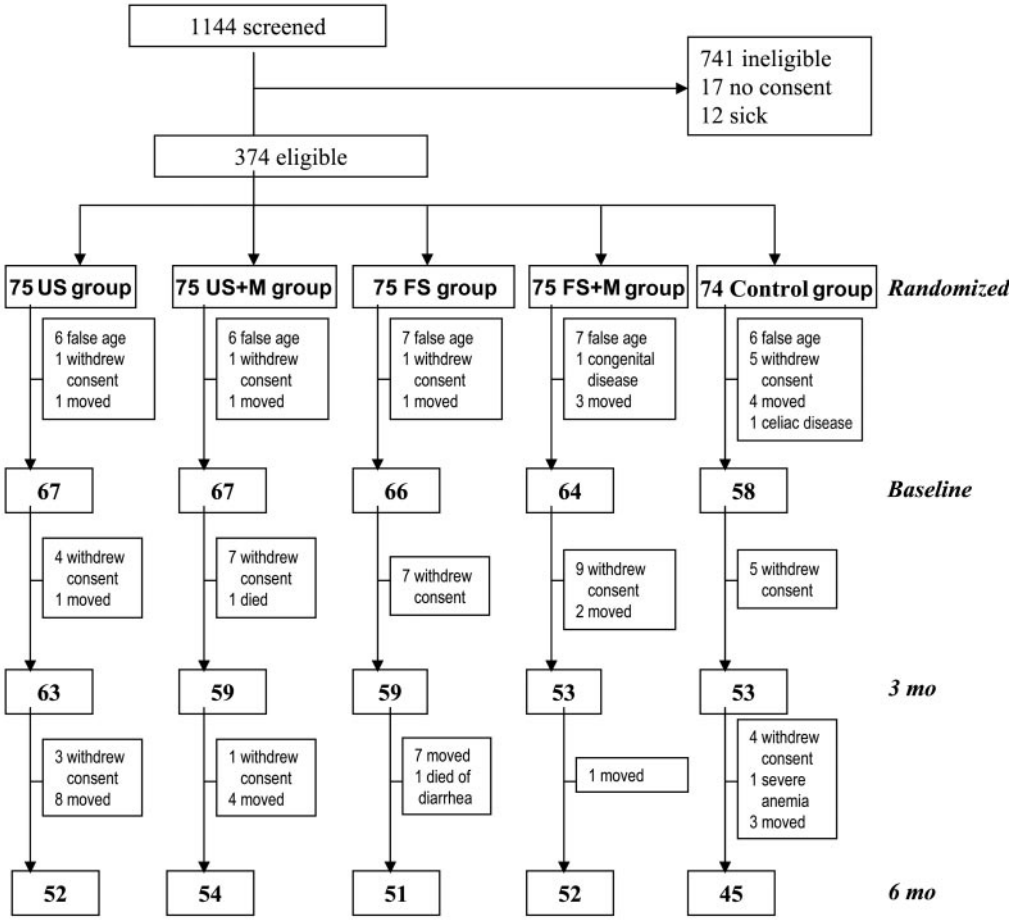

FIGURE 1. Trial profile.

effect of the drug treatment or any interaction between the 2 main effects. On the basis of this analysis, we went on with the analysis by combining the drug groups to assess the main effects of the spread fortification. Linear growth, reflected by height and KHL velocities, was significantly greater (20–30%) in the FS groups than in the US and control groups over the entire trial period ($P < 0.0001$, ANOVA). Children receiving the FS supplement grew an overall average of 1 mm/mo faster than did children in the other groups throughout the study, but the most rapid growth occurred in the first trimester, when the former group grew 2 mm/mo faster. The mean height growth increments exhibited by children receiving the FS supplement were 9 ± 3 mm/mo in the first trimester and 6 ± 2 mm/mo in the second trimester, compared with 7 ± 3 in the US group and 6 ± 3 mm/mo in the control group in the first trimester and 5 ± 2 mm/mo in the second trimester for both of these same groups (MANOVA, $P < 0.001$).

TABLE 2
Characteristics at baseline of children who completed the study[1]

	US group	US+M group	FS group	FS+M group	Control group
No. (boys/girls)	52 (26/26)	54 (25/29)	51 (28/23)	52 (27/25)	45 (24/21)
Age (mo)	49.7 ± 11.2[2]	50.0 ± 10.6	50.0 ± 11.7	49.0 ± 12.2	47.4 ± 11.8
Height (cm)	91.4 ± 6.0	90.6 ± 6.3	91.1 ± 6.7	90.7 ± 6.7	89.2 ± 7.1
Weight (kg)	12.5 ± 1.5	12.3 ± 1.7	12.8 ± 1.6	12.5 ± 2.1	11.9 ± 2.0
Knee-heel length (mm)	255.1 ± 22.0	251.8 ± 23.3	254.7 ± 23.8	251.2 ± 23.5	246.1 ± 24.2
Height-for-age *z* score	−2.73 ± 0.55	−2.97 ± 0.84	−2.87 ± 0.56	−2.80 ± 0.62	−3.00 ± 0.71
Weight-for-age *z* score	−2.19 ± 0.56	−2.33 ± 0.68	−2.11 ± 0.56	−2.23 ± 0.69	−2.42 ± 0.75
Weight-for-height *z* score	−0.79 ± 0.67	−0.81 ± 0.65	−0.55 ± 0.69	−0.77 ± 0.77	−0.96 ± 0.87
Hemoglobin (g/L)	91 ± 19	89 ± 22	92 ± 23	90 ± 22	91 ± 23
Hematocrit (%)	31.2 ± 4.9	31.0 ± 5.1	32.0 ± 4.8	31.6 ± 5.4	32.0 ± 4.3
Percentage with anemia[3] (%)	82.7	83.3	70.6	80.8	82.2

[1] US, unfortified spread; FS, fortified spread; M, metronidazole treatment. There was no significant difference among the groups (ANOVA).
[2] $\bar{x}$ ± SD (all such values).
[3] Anemia, hemoglobin < 100 g/L.

TABLE 3
Compliance and changes in anthropometric variables after 3 and 6 mo of intervention[1]

	FS and FS+M groups	US and US+M groups	Control group
No. (boys/girls)			
Baseline	103 (55/48)	106 (51/55)	45 (24/21)
3 mo	103 (55/48)	106 (51/55)	45 (24/21)
6 mo	103 (55/48)	106 (51/55)	45 (24/21)
Compliance (%)			
3 mo	89.6 ± 13.2[a,2]	89.1 ± 15.5[a]	—
6 mo	69.2 ± 22.7[b]	72.9 ± 23.4[b]	—
Height (cm)[3,4]			
Baseline	90.9 ± 6.6[a]	91.0 ± 6.2[a]	89.2 ± 7.1[b]
3 mo	93.5 ± 6.4[c]	93.0 ± 6.1[d]	91.1 ± 6.8[a]
6 mo	95.1 ± 6.3[e]	94.5 ± 6.0[f]	92.7 ± 6.7[d]
Weight (kg)[3,4]			
Baseline	12.6 ± 1.9[a]	12.4 ± 1.6[a]	11.9 ± 2.0[b]
3 mo	13.5 ± 1.8[c]	13.1 ± 1.6[d]	12.5 ± 2.0[a]
6 mo	14.3 ± 1.8[e]	13.9 ± 1.6[f]	13.4 ± 1.9[c]
Knee-heel length (mm)[4,5]			
Baseline	253.2 ± 23.5[a]	253.2 ± 21.8[a]	246.1 ± 24.2[b]
3 mo	262.1 ± 23.0[c]	260.7 ± 20.9[c]	252.7 ± 23.1[a]
6 mo	268.2 ± 23.0[d]	266.0 ± 21.2[e]	258.4 ± 23.1[f]
Height-for-age *z* score[3,4]			
Baseline	−2.84 ± 0.59[a]	−2.86 ± 0.72[a]	−3.01 ± 0.71[b]
3 mo	−2.70 ± 0.59[c]	−2.85 ± 0.72[a]	−3.00 ± 0.68[b]
6 mo	−2.68 ± 0.59[c]	−2.84 ± 0.71[a]	−3.00 ± 0.68[b]
Weight-for-age *z* score[3]			
Baseline	−2.17 ± 0.63[a]	−2.26 ± 0.62[a]	−2.42 ± 0.75[b]
3 mo	−1.95 ± 0.64[c]	−2.15 ± 0.62[a]	−2.30 ± 0.77[a]
6 mo	−1.71 ± 0.63[d]	−1.90 ± 0.65[c]	−2.05 ± 0.70[c]
Weight-for-height *z* score[3]			
Baseline	−0.66 ± 0.74[a,c]	−0.80 ± 0.66[a]	−0.96 ± 0.87[a]
3 mo	−0.46 ± 0.74[b]	−0.65 ± 0.70[c]	−0.77 ± 0.94[a,c]
6 mo	−0.11 ± 0.72[d]	−0.28 ± 0.66[e]	−0.41 ± 0.88[b,e]

[1] US, unfortified spread; FS, fortified spread; M, metronidazole treatment. All variables were analyzed by using two-way repeated-measures ANOVA. Values in the same row with different superscript letters are significantly different, $P < 0.01$.
[2] $\bar{x}$ ± SD (all such values).
[3] Significant treatment effect at 3 and 6 mo, $P < 0.001$.
[4] Significant time-by-treatment interaction, $P < 0.001$.
[5] Significant treatment effect at 6 mo, $P < 0.001$.

Overall growth performance in the FS group was significantly better during the first trimester than in the second trimester (MANOVA, $P < 0.001$). At the 3-mo follow-up, the HAZ in the FS group increased significantly (0.14 ± 0.19), but at 6 mo the HAZ did not further increase (MANOVA, $P < 0.001$). No difference was found in linear growth between boys and girls in the intervention groups (data not shown).

The use of FS produced highly significant, positive incremental height increases among subjects, reaching 2.6 ± 0.8 cm after 3 mo, compared with 2.0 ± 0.8 cm in the US group and 1.9 ± 0.9 cm in the control group and, at 6 mo, reaching 4.2 ± 1.1 cm in the FS group compared with 3.6 ± 1.1 cm in both the US and control groups. No improvement in height was observed in the US and control groups, in which subjects showed similar growth performances throughout the intervention period (Table 3).

At 6 mo, HAZ was significantly increased in the FS-supplemented groups (0.15 ± 0.22), whereas it remained unchanged in the other groups (MANOVA, $P < 0.0001$). The magnitude of the catch-up growth response was negatively associated with the age at baseline ($\beta = -0.034$; 95% CI: −0.045, −0.022); hence, the younger the age, the greater the growth increase. This effect remained after correcting for differences in treatment between groups, initial hemoglobin concentrations, and baseline HAZ ($\beta = -0.0315$; 95% CI: −0.043, −0.020). Baseline HAZ was negatively associated with growth increase, but the effect was not significant ($\beta = -0.097$; 95% CI = −0.289, 0.096).

Changes in weight indexes

Weight indexes improved overall across all groups. At 3 mo, changes in WAZ were not significant when comparing the 5 intervention groups against each other, but became so when looking at the FS groups together against non-FS groups. WAZ was greater in children receiving FS supplement (0.21 ± 0.26 for both FS groups) than in the other study groups at the 3-mo assessment (0.11 ± 0.29 in the US group and 0.12 ± 0.36 in the control group; MANOVA, $P < 0.01$; Table 3). However, these differences disappeared after 6 mo. Over the entire study period, significant improvement in WHZ was found across all groups (0.54 ± 0.45). No differences were found between groups, and no sex-based variations were observed (data not shown).

Changes in hematologic indexes and anemia

FS had a highly significant effect on hemoglobin concentration and hematocrit (**Table 4**), as well as on anemia distribution over the 6-mo period. This finding confirmed that the anemia was caused by a dietary deficiency. Increases in hematologic indicators were, on average, twice as high in FS groups than in the US and control groups. After 6 mo of supplementation, hemoglobin concentrations rose by 37 ± 40 g/L in FS groups, in contrast to 19 ± 15 g/L in the US group and 16 ± 17 g/L in the control group (MANOVA, $P < 0.0001$). No significant changes were observed in the control group, and there was only a marginally significant increase in the US groups ($P = 0.03$). The antiparasitic treatment did not produce any significant differences among groups. Total anemia dropped by nearly 90% among children in the FS group—compared with decreases of 40% in children in the US group and 27% in children in the control group—which represents a complete eradication of the severe and moderate forms of anemia (Table 4).

Morbidity

Overall, the mean assessment period (defined as the number of days with information about morbidity) was 66.7 d, with no differences among groups. The incidence of diarrhea, fever, and cough in the children receiving the FS supplement was slightly less or comparable to that in the children fed the unfortified spread (**Table 5**). No differences were seen in the duration of disease episodes between groups. The data from children in the control group were not reported, because they would only cover 2 wk before the visits at month 3 and 6, whereas in the intervention groups recalls were performed twice monthly.

TABLE 4
Hemoglobin and hematocrit at baseline and after 3 and 6 mo of intervention[1]

	FS and FS+M groups	US and US+M groups	Control group
No. (boys/girls)			
Baseline	82 (44/38)	93(46/47)	40(20/20)
3 mo	82 (44/38)	93(46/47)	40 (20/20)
6 mo	82 (44/38)	93(46/47)	40 (20/20)
Hemoglobin (g/L)[2]			
Baseline	$90 \pm 23^{a,3}$	90 ± 21^{a}	$93 \pm 23^{a,e,h}$
3 mo	115 ± 16^{b}	$101 \pm 22^{c,e,f,g}$	$107 \pm 23^{b,f,h}$
6 mo	127 ± 14^{d}	$109 \pm 19^{b,c}$	$109 \pm 19^{b,g}$
Hematocrit (%)[2]			
Baseline	31.6 ± 4.9^{a}	31.0 ± 5.0^{a}	$32.2 \pm 4.4^{a,b}$
3 mo	35.9 ± 4.2^{b}	$33.5 \pm 4.6^{a,b}$	$34.6 \pm 5.9^{a,b,d}$
6 mo	37.3 ± 3.3^{d}	$34.3 \pm 4.0^{b,c}$	$34.8 \pm 3.0^{b,c,d}$
Percentage with anemia[4] (%)			
Baseline	78.0	82.8	80.0
3 mo	32.9	59.1	42.5
6 mo	9.8	48.4	60.0

[1] US, unfortified spread; FS, fortified spread; M, metronidazole treatment. All variables were analyzed by using two-way repeated-measures ANOVA. Values in the same row with different superscript letters are significantly different, $P < 0.01$.
[2] Significant treatment effect at 3 and 6 mo, $P < 0.001$.
[3] $\bar{x} \pm$ SD (all such values).
[4] Anemia, hemoglobin <110 g/L.

Parasitic infections

Of 248 stool samples screened at baseline, 149 (60%) were positive for protozoan infections (mostly *Giardia lamblia* and *Escherichia coli* with a few cases of *Entamoeba histolytica* and *Hymenolepis nana*). Additionally, 37 (15%) stool samples were positive for helminth infections of low intensity (mostly *Enterobius vermicularis*, commonly known as pinworm). Most mothers reported the presence of mucus in feces. At 3 mo, after the second treatment cycle, the proportion of protozoan infections had dropped to 44%, with no effect on helminths. We found no presence of *C. parvum* infections.

DISCUSSION

This study demonstrates that supplementation with use of a novel food highly fortified with multiple micronutrients was successful, at least in part, in reversing the stunting process in Saharawi refugee children. It is important that only a micronutrient-fortified supplement—and not a supplement with identical macronutrient composition but devoid of micronutrients—was effective in inducing accelerated catch-up linear growth. A second important finding was that this catch-up growth was achieved in children up to age 6 y. These findings have great positive potential, given that catch-up growth after the age of 3 y was so far considered unlikely for children with a history of height faltering (23). Finally, severe and moderate forms of anemia were successfully eradicated among children who received the fortified supplement.

TABLE 5
Incidence of diarrhea, cough, fever, and all illnesses in supplemented children during the 6-mo intervention period[1]

	US group	US + M group	FS group	FS + M group
Diarrhea	2.4	2.2	1.7	1.9
Fever	2.1	3.0	2.0	1.8
Cough	1.4	1.6	1.9	1.7
All illnesses	7.3	10.8	7.3	8.3

[1] US, unfortified spread; FS, fortified spread; M, metronidazole treatment. There were no significant differences between groups.

The most innovative aspect of this study lay in the use of energy-dense high-fat spread that allows delivery of high amounts of multiple micronutrients to high-risk groups. This fortified spread is far more appealing to subjects than are the pharmaceutical preparations commonly distributed in most supplementation trials. It presents several advantages such as palatability, bacteriologic safety, protection against vitamin oxidation, and prolonged shelf-life (25). Convenience is perhaps the greatest advantage offered by this new method, because FS comes in the form of a ready-to-eat snack food with no preparation required. This convenience resulted in high compliance. Furthermore, the fat matrix allowed micronutrient supplementation to reach much higher amounts than those reported in other trials (18).

Because the children were initially severely stunted, moderately anemic, and in all likelihood deficient in multiple micronutrients, consumption of this nutrient-dense food product was an important intervention. During the 6 mo of supplementation, increase in HAZ was 0.15 SD greater (equivalent to 5% catch-up growth in respect to the initial −2.79 deficit) in children receiving FS supplement than in the other groups. In fact, none of the other groups could achieve catch-up growth, as shown in Table 3. Highest mean effect sizes, achieved at 3 mo, reached 0.73 SD units in the US group and 0.79 SD units in the control group, indicating a larger magnitude of effect compared with other micronutrient supplementation trials conducted in deficient populations (17, 18). The physiologic significance of a 0.2-point change in height-for-age is not dramatic at an individual level but might be significant at the population level. The significant positive effect on HAZ likewise registered in Vietnamese children stunted at baseline provides further support for the role of multiple-micronutrient supplementation in the recovery of initially stunted persons (20).

Growth rates were not constant over the 6-mo intervention period. In the first trimester of supplementation, the mean rate of incremental height increases among children in the FS group was >40% higher than was exhibited in the second trimester, although it eventually leveled off to a velocity rate similar to that observed in the US and control groups and was also close to the median height increment increase documented by WHO/NCHS, ie, 6.0 mm/mo (35). The drop in compliance between the first and second trimesters cannot explain this phenomenon, as the 10% drop was consistent across all groups. Possible reasons for this phenomenon might include other environmental factors, such as fluctuations in normal child growth patterns and seasonality in diarrheal disease. The growth deceleration observed during the second trimester of supplementation might suggest that complete catch-up from stunting cannot be corrected by simply extending the period of supplementation. Furthermore, this finding indicates that a 3-mo cycle could be sufficient to achieve the best

possible growth improvement. However, longer supplementation might be necessary to maintain growth. Walker et al (36) report sustained growth trajectories only when supplementation of children is continued. Follow-up anthropometric data on this cohort of children, collected 2.5 years after the original study, are currently being evaluated. Further research must be done in this area to determine how long treatment cycles should last, how many should be given, and exactly what the best combination of supplemented micronutrients is to effectively treat stunting.

Other studies reported associations between early infant growth and increased risk of adult chronic diseases (37–39), casting doubts as to the desirability of inducing catch-up growth. This might be an important issue in this population, because diabetes and obesity among adults, especially women, are a problem among Saharawi refugees. Further follow-up is necessary to investigate some of these issues, which will help to evaluate potential benefits and risks of intervention.

The successful eradication of severe and moderate forms of anemia that was achieved through the fortified supplementation is an important result from a public health point of view. Hemoglobin concentrations also improved in the US and control groups, although to a lesser extent. It must be noted that the general diet of the Saharawi refugees improved overall during the course of the study, which coincided with the introduction of iron-fortified flour and vitamin A–and vitamin C–fortified powdered skim milk, although these foods were insufficient to correct preexisting anemia in high-risk groups.

We did not find any additional benefit of the antiparasitic treatment on growth. It would, thus, appear that stunting is not primarily determined by parasitic infestations in these Saharawi refugee children. The only helminthic parasite found in these children was *E. vermicularis*, usually asymptomatic. No presence of *C. parvum* infection, a pathogen associated with long-term effect on childhood growth and development in impoverished areas, was detected (20).

Contrary to our expectations, but in line with other studies (40), we did not find an association between nutritional status and morbidity. Other studies indeed indicated that supplementation with 10 mg elemental zinc has produced a significant reduction in morbidity of diarrheal diseases, particularly in children deficient in zinc. Sazawal et al (41) found that overall zinc supplementation resulted in a 17% lower diarrheal incidence in children with plasma zinc concentrations <9.18 μmol/L at enrollment and a 33% lower incidence in children with concentrations <50 μmol/L. Zinc supplementation was also shown to reduce the duration and severity of acute and persistent diarrhea (42). Our sample size was inadequate to identify a difference because sample size calculations were done on the primary variable of interest in this study, ie, linear growth and not on morbidity. However, inaccuracies of the recall technique might also be important, because the interview was referred to the week before assessment, whereas the previous 24−48 h would have been more accurate.

Delaying the distribution of food to the control group was agreed with the local health authorities and was explained to the population. Practical considerations often prevent interventions from simultaneously addressing the entire population and were, therefore, considered acceptable. Furthermore, having a no-intervention group allowed us to assess the relevance of a supplementary feeding program in this population. At the end of this pilot randomized control trial, supplementary feeding program was extended to all the camps, covering almost 4000 children.

Clearly, more studies are needed to confirm the efficacy of multiple micronutrient-fortified foods, including fat-based spread and other novel approaches, in fighting the stunting syndrome among refugee populations before public health and nutrition policies about micronutrient supplementation among refugees are revised. Availability of a convenient and palatable supplement that contains high-dose multiple micronutrients allows a quick solution of the anemia problem as well as a moderate effect on growth retardation. For the purpose of reduction of stunting rates it is probably more efficient to act on prevention that would take care of several causative prenatal and postnatal factors: poor maternal micronutrient status, a low educational level, lack of hygiene, overcrowding, a high disease load, and inadequate breastfeeding and complementary feeding modalities. Still, a 5% reduction of stunting induced by an intervention on stunted children in midchildhood and late childhood would cumulate with the advantages of prevention and would deal with the ethical issue of not discriminating a generation of children. However, the formidable health advantage constituted by anemia eradication at all ages indicates that supplementation with multiple micronutrients throughout childhood is warranted. Furthermore, even a 3-mo supplementation course could produce a sizable health effect, and this is a public health measure that can be sustained in most situations. An ideal public health strategy should thus include a combination of early and late type interventions targeted at different life cycle stages, including infants and young children, pregnant and lactating women, and any woman of childbearing age.

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This study was designed by CL and FB, with key input from AB in formulating the fortified supplement and in discussing the rationale and design of the trial. The fieldwork was executed under the supervision of CL and YG, who gathered and entered data, organized field logistics, and trained and managed local teams. Statistical analyses were performed by CL (with the assistance of Paola D'Errigo and Lorenza Mistura). All authors contributed to writing the manuscript. AB was consultant for Nutriset, a company that produces fortified spreads. Other authors had no conflict of interest to declare.

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