Multiple micronutrient supplementation increases the growth of Mexican infants[1–4]

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ABSTRACT

Background: The role of single micronutrient deficiencies in the etiology of growth retardation has recently gained attention. However, because multiple micronutrient deficiencies are common in children in developing countries, it is possible that more than one micronutrient may limit growth and, hence, the correction of a single deficiency may not be enough to improve growth substantially.

Objective: The objective was to evaluate the effect of multiple micronutrient supplementation on the growth of children aged 8–14 mo whose diets were poor in several micronutrients.

Design: Children were randomly assigned to 1 of 2 groups. One group received a multiple micronutrient supplement containing the recommended dietary allowance (RDA) or 1.5 times the RDA of vitamins A, D, E, K, C, B-1, B-6, B-12, riboflavin, niacin, biotin, folic acid, and pantothenic acid, and iron, zinc, iodine, copper, manganese, and selenium. The other group received a placebo. Supplements were administered 6 d/wk for an average of 12.2 mo. Body length was measured at baseline and monthly thereafter until the end of supplementation.

Results: Supplemented infants initially aged < 12 mo had significantly greater length gains than did the placebo group, with a difference of 8.2 mm (length-for-age *z* score: 0.3) at the end of supplementation. In contrast, differences in length gains between the supplemented and placebo groups initially aged ≥ 12 mo were not significant.

Conclusions: Micronutrient deficiencies limited the growth of the Mexican infants studied. Improving micronutrient intakes should be a component of interventions to promote growth in infants living in settings where micronutrient intakes are inadequate. *Am J Clin Nutr* 2001;74:657–63.

KEY WORDS Multiple micronutrient supplementation, growth, growth retardation, micronutrient deficiencies, Mexico, infants, children

INTRODUCTION

Growth retardation is highly prevalent among children in low-income countries (1). Infections and inadequate food intake are well-established causes of growth retardation; however, the possible specific role of micronutrient deficiencies in the etiology of growth retardation and other developmental and health outcomes has gained attention recently. As a result, many studies about the effect of individual micronutrients on growth have been published (2).

Supplementation trials using single micronutrients show positive but small effects of zinc supplementation on growth. The effects are greater in stunted children and in children with low serum zinc concentrations (3). The results of iron supplementation studies indicate positive effects in anemic children but not in nonanemic children (4–7); there appear to be few or no effects of vitamin A on growth (8–10), except in children with severe deficiency (11).

Multiple micronutrient deficiencies are common among children living in poverty. It is possible that more than one micronutrient deficiency is responsible for limiting growth; therefore, the correction of a single deficiency may not be enough to improve growth substantially. In experimental animals, an imbalance of essential nutrients in the diet (12) or micronutrient deficiencies (13) produce anorexia, which may affect growth. It has been suggested that latent deficiencies of other micronutrients besides zinc can suppress growth after zinc repletion (14, 15).

A multiple micronutrient supplementation trial conducted in Chinese children aged 6–9 y found positive effects of supplementation on growth (16). Children received multiple micronutrients, including zinc; multiple micronutrients without zinc; or zinc only. The greatest effects occurred after treatment with the multiple micronutrient mixture that included zinc. Notably, the group that received multiple micronutrients without zinc had a greater growth response than did the group that received zinc

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[2] Preliminary results presented as an abstract at Experimental Biology 1996 (FASEB J 1996;10:A290) and in tabular form at Experimental Biology 1998.

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only. The results suggest that deficiencies in micronutrients other than just zinc were suppressing growth.

The dietary intake of children in rural areas in Mexico is deficient in several micronutrients. A national probabilistic survey conducted in 1999 found that children aged <5 y in rural Mexico had low dietary intakes of iron, vitamin A, vitamin C, and zinc relative to requirements (17). The same survey reported a national prevalence of anemia of 27.2% in children aged <5 y and almost 50% in children aged 12–23 mo. Other dietary information suggests low intakes of vitamin B-6 and riboflavin, and community based studies in rural areas have found biochemical evidence of iron, zinc, vitamin A, vitamin C, and vitamin B-12 deficiencies (18).

We conducted a study to evaluate the effect of multiple micronutrient supplementation on the growth of children aged 8–14 mo living in a setting where the diet is poor in several micronutrients.

SUBJECTS AND METHODS

Study sample

The present study was conducted in Xoxocotla, State of Morelos, a semirural setting located 90 km south of Mexico City, at an altitude of 930 m above sea level, with an estimated population of 16 800 inhabitants. Agriculture is the principal occupation here and the general social and economic conditions are poor. Most streets are unpaved and there is no sewage system, although a water supply system is available. A study conducted in a random sample of 366 families in this community showed that 62% of the houses had dirt floors, 31% had no latrines or toilets, and 21% had no water supply into the house. Twenty-three percent of children aged <5 y of age were stunted [length-for-age or height-for-age z score < −2 of the reference data of the World Health Organization/National Center for Health Statistics/Centers for Disease Control and Prevention (WHO/NCHS/CDC; 19)]. Most of the men in this region are either agricultural laborers or construction workers, whereas most of the women sell agricultural products in local markets or work as domestic employees in nearby cities.

The research team completed a census of Xoxocotla to identify children aged 8–14 mo. A total of 337 children in this age group were enrolled after written consent was obtained from their parents. The study protocol was explained in detail to each family and was approved by the Committee on the Use of Human Subjects in Research of the National Institute of Public Health.

Study design

The Moses-Oakford method (20) was used to randomly assign children to 1 of 2 groups in this double-blind, placebo-controlled, supplementation trial. One group received 30 mL of a beverage containing multiple micronutrients (micronutrient group) and the other received 30 mL of a placebo (placebo group). The 2 beverages were indistinguishable, both of which contained sugar and artificial flavors but no protein or fat, and provided 126 kJ (30 kcal).

The supplement contained the recommended dietary allowance (RDA; 21) for children aged 1–3 y of the vitamins D_3 (as cholecalciferol), E (as tocopheryl acetate), K_1, niacin (as nicotinamide), thiamine (as thiamine mononitrate), B-6 (as pyridoxine hydrochloride), D-biotin, folic acid, and pantothenic acid (as D-calcium pantothenate) and of the minerals iodine (as potassium iodide), copper (as copper gluconate), manganese (as manganese sulfate), and selenium (as selenium sulfate). The supplement also contained 1.2 times the RDA for children aged 1–3 y of vitamin A (as retinyl palmitate) and 1.5 times the RDA of ascorbic acid (extra fine), riboflavin, vitamin B-12, iron (as ferric orthophosphate), and zinc (as zinc sulfate).

The beverages were provided to the children 6 d/wk for an average of 12.2 mo under supervision of the study personnel, who recorded whether the supplement was consumed.

Data collection

At baseline, anthropometric measures were made, morbidity and socioeconomic (eg, education level of the parents and housing quality) data were collected, intakes of breast milk and complementary foods were obtained by direct weighing, and information about the children's appetites was ascertained. Biochemical data on the micronutrient status of the children were unavailable because most of the families considered it unacceptable to draw blood from infants. After the baseline data were collected, all participating children (n = 337) were followed for an average of 12.2 ± 1.8 mo. During this time, anthropometric measures were made and dietary intakes were ascertained.

Anthropometric measures

Anthropometric measures were made approximately every month until the end of supplementation. Weight was measured to the nearest 10 g with an electronic scale (model 1583; Tanita, Tokyo) and length was measured to the nearest millimeter with a locally made wooden measuring board by 2 anthropometrists who were trained to take all measurements using standard techniques (22, 23). Technical errors of measurement (TEMs) at the end of the standardization period were within values reported for carefully conducted studies such as the Fels Longitudinal Study (22). For example, the intrameasurer TEMs for the 2 anthropometrists were 0.4 and 1.1 mm for length and 90 and 110 g for weight. The corresponding intermeasurer TEMs were 3.6 mm for length and 136 g for weight. An experienced anthropometrist visited the field every other week to supervise the measuring techniques. Length and weight data were transformed to z scores by using the WHO/NCHS/CDC reference data (19).

Morbidity data

Morbidity data were collected daily at the time the supplement was distributed. A checklist was used to record symptoms of diarrhea and acute respiratory infection observed by the mothers or caretakers during the previous 24 h. The morbidity data are presented separately.

Dietary intakes

In a subsample of 163 children (87 in the micronutrient group and 76 in the placebo group), dietary intakes were evaluated at baseline and 2–3 mo after the initial measurement. Dietary evaluations included direct weighing of all foods and beverages consumed during ≈12 h and a 24-h dietary recall questionnaire concerning dietary intakes during the 24 h before the direct weighing began. Data obtained from the use of both methods were combined to give complete 24-h dietary intakes of the children. A test-weighing technique was used to measure breast-milk consumption during the same ≈12-h period of direct weighing. Breast-milk consumption during the day was extrapolated to 24 h, assuming that children were breast-fed during the night, by using

a prediction equation derived from a study of Peruvian infants (24). The test-weighing data were not corrected for insensible water loss, which amounts to 0.03–0.05 $g \cdot kg^{-1} \cdot min^{-1}$ (25, 26). Therefore, our values for breast-milk intake were underestimated by 1–5% (27). Energy and nutrient intakes were derived by using a food-composition database compiled by our group that used 3 different data sources. The main source was the food-composition database of the Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán" (the Mexican database).

This database was complemented with data from the US Department of Agriculture (28) and from the Institute of Nutrition of Central America and Panama (Guatemala City, Guatemala) for nutrients or foods not available in the Mexican database. The composition of breast milk from healthy US women (29) was used to derive energy and nutrient intakes from the breast milk consumed in the present study.

Socioeconomic status

Information about the participants household characteristics (eg, type of floor, presence of toilet, and kitchen in a bedroom), the possession of selected household goods (eg, radio, television, blender, and refrigerator), and the education level of the parents was obtained by interviewing the mothers of the participating children. An indicator of housing conditions was derived by the first component obtained by principal components analysis (30). Only variables with factor loadings >0.5 were maintained in the model (ie, house and floor material and availability of piped water and a sewer system). The component explained 51.3% of the total variance. The resulting factor scores, which have a mean of 0 and an SD of 1, were used as a continuous variable [the socioeconomic status (SES) score]. In addition, the factor scores were divided into tertiles, which were further used to construct a categorical variable.

Data analysis

Baseline characteristics of the study children, their mothers, and their families were compared between treatment groups by using Student's *t* tests for continuous variables and chi-square tests for categorical variables to identify potential confounding factors.

Taking advantage of the repeated-measures design of the study, we analyzed the data by using generalized estimating equations (GEEs). This technique is used for the analysis of longitudinal data that are an extension of the generalized linear models, which were specially developed to account for the autocorrelation due to serial measurements (31), and allows the use of time-dependent covariates, giving the regression coefficients the usual interpretation. The assumption of Gaussian distribution of the outcome variables (length and length-for-age *z* score) were supported by an exploratory analysis of the empirical distribution of the variables. An exchangeable correlation structure that was robustly estimated was used.

Two sets of GEE models were used to test the effect of treatment on length. The first set used the dependent variable length, which was measured monthly from the first to the last month of supplementation, and the independent variables treatment (micronutrients or placebo), baseline length, SES score, and sex, which were fixed; weight-for-length *z* score, age, and breast-feeding status, which were measured monthly from the first to the last month of supplementation; and an indicator variable for the first to the fourth 3-mo periods of supplementation. The second set of GEE models used the dependent variable length-for-age *z* score, which was determined monthly during supplementation, and the same independent variables used in the first set, except that the baseline length-for-age *z* score was used instead of baseline length. GEE models were also used to test for two-way interactions between treatment and sex, treatment and age at baseline, and treatment and period of supplementation.

Probability values <0.05 were considered statistically significant for main effects and <0.10 for interactions (32, 33). All statistical analyses were performed by using STATA (release 6.0, Stata Statistical Software, Stata Corporation, College Station, TX).

RESULTS

Compliance rates relative to the total projected days of supplementation were 80.5% in the placebo group and 91% in the supplemented group ($P < 0.05$). Of the 337 children originally recruited ($n = 169$ in the micronutrient group and 168 in the placebo group), 18 ($n = 8$ in the micronutrient group and 10 in the placebo group) had missing anthropometric information; therefore, 319 children ($n = 161$ in the micronutrient group and 158 in the placebo group) were included in the analysis. Baseline characteristics of the children, their parents, and their households by treatment group are presented in **Table 1** according to the age of the children at baseline: <12 mo (infants) and ≥12 mo. In the children aged ≥12 mo, there were no significant differences in any of the variables between treatment groups. In the infants, the average weight of children in the placebo group was 260 g less than that of children in the micronutrient group ($P < 0.05$). However, all other variables, including baseline length, age, and anthropometric indexes, were not significantly different between treatment groups.

In the children aged ≥12 mo, the proportion of households with the kitchen in a bedroom was significantly greater in the placebo than in the micronutrient group. No other variables were significantly different between treatment groups.

The mean dietary intake of iron ranged from 2.12 to 2.85 mg, of zinc ranged from 2.63 to 3.13 mg, and of vitamin A from 506 to 660 μg retinol equivalents in the total population. Protein intakes were >20 g in all groups and energy intakes were between 2804 and 3210 kJ/d. Differences between treatment groups were not significant.

Changes in anthropometric measurements from baseline to the end of supplementation are presented in **Table 2** by treatment group according to the age of the children at baseline. In the children aged ≥12 mo, there were no significant differences in age or in the anthropometric variables between treatment groups. Infants in the micronutrient group were an average of 0.7 cm taller ($P < 0.05$) and had a length-for-age *z* score 0.33 units higher ($P < 0.05$) than children in the placebo group. None of the other variables differed significantly by treatment group between baseline and the end of supplementation.

A GEE model for the assessment of effects of multiple micronutrient supplementation on linear growth was first tested for all ages combined (data not shown). An interaction term between treatment and age was significant ($P < 0.10$), indicating that the effect of treatment was greater in the younger than in the older age group. Therefore, results are presented separately for the children aged <12 mo and for those aged ≥12 mo.

Results of the use of GEEs to determine the effects of micronutrient supplementation on length are shown in **Table 3** and **Figure 1** and on length-for-age *z* scores in **Figure 2**. The main

TABLE 1
Baseline characteristics of the children, their parents, and their households by age[1]

	Infants (<12 mo)		Children ≥12 mo	
	Micronutrient group	Placebo group	Micronutrient group	Placebo group
Categorical variable (%)				
Females	45.7 [105]	47.8 [115]	62.5 [56]	48.8 [43]
Breast-fed	84.8 [105]	82.6 [115]	76.8 [56]	79.1 [43]
Illiterate mother	13.3 [105]	8.7 [115]	10.7 [56]	18.6 [43]
Illiterate father	13.6 [103]	8.9 [112]	9.4 [53]	4.9 [41]
Continuous variable				
Child's age (mo)	10.3 ± 1.2[2] [105]	10.2 ± 1.1 [115]	13.2 ± 0.9 [56]	13.0 ± 0.9 [43]
Length (cm)	69.6 ± 2.5 [105]	69.1 ± 3.0 [115]	71.9 ± 2.8 [56]	71.6 ± 3.2 [43]
Weight (kg)	8.08 ± 1.01 [105]	7.82 ± 0.91[3] [115]	8.39 ± 0.88 [56]	8.28 ± 0.99 [43]
Length-for-age *z* score	−1.24 ± 0.76 [105]	−1.36 ± 1.10 [115]	−1.54 ± 0.93 [56]	−1.64 ± 1.01 [43]
Weight-for-age *z* score	−1.20 ± 1.03 [105]	−1.43 ± 0.93 [115]	−1.55 ± 0.88 [56]	−1.69 ± 0.88 [43]
Weight-for-length *z* score	−0.34 ± 1.00 [105]	−0.49 ± 0.78 [115]	−0.63 ± 0.80 [56]	−0.74 ± 0.83 [43]
SES score	0.07 ± 1.00 [105]	−0.06 ± 1.00 [115]	−0.13 ± 1.10 [56]	0.16 ± 1.10 [43]
Duration of supplementation (y)	12.0 ± 2.0 [105]	12.1 ± 1.6 [115]	12.3 ± 1.9 [56]	12.7 ± 0.7 [43]
Mother's age (y)	25.4 ± 6.0 [105]	25.5 ± 6.1 [115]	24.4 ± 5.6 [56]	24.9 ± 5.5 [43]
Energy intake (kJ)[4]	2804 ± 1113 [40][5]	3076 ± 1327 [41]	3210 ± 1302 [47]	3013 ± 1481 [35]
Protein intake (g)[4]	20.1 ± 13.2 [40]	21.3 ± 16.4 [41]	20.9 ± 15.0 [47]	20.1 ± 13.7 [35]
Iron intake (mg)[4]	2.85 ± 4.01 [40]	2.12 ± 3.33 [41]	2.23 ± 2.23 [47]	2.46 ± 2.65 [35]
Zinc intake (mg)[4]	2.63 ± 1.81 [40]	2.86 ± 2.40 [41]	2.74 ± 2.56 [47]	3.13 ± 4.45 [35]
Retinol intake (μg RE)[4,6]	660 ± 909 [40]	506 ± 316 [41]	576 ± 372 [47]	508 ± 393 [35]

[1] *n* in brackets.
[2] $\bar{x}$ ± SD.
[3] Significantly different from the micronutrient group, $P < 0.05$ (two-tailed *t* test).
[4] Daily intake, including breast milk.
[5] Subsample for dietary study.
[6] Retinol equivalents.

effect of treatment and the interaction between treatment and period of supplementation were significant in the children aged <12 y for both length and length-for-age *z* score, indicating that the effect of supplementation on linear growth increased as the duration of supplementation increased in this group. In contrast, the main effect of treatment and the interaction between treatment and the indicator variables were not significant for length in any of the 3-mo periods of supplementation in the children aged ≥12 mo; however, the interaction between treatment and period of supplementation was significant for length-for-age *z* score only in the second and third periods of supplementation.

During data analysis, a differential response between sexes emerged; therefore, an interaction between sex and treatment was formally tested and it was significant ($P < 0.10$) in both the model that had length as the dependant variable and in the model that had length-for-age *z* score as the dependent variable (data not shown). Results indicate that girls benefited more from supplementation than did boys.

The magnitude of the differences in attained length between the micronutrient and placebo groups by period of supplementation, after adjustment for potential confounders, are presented separately for the 2 age subgroups in Figure 1. In the infants, micronutrient supplementation had a positive effect on length gain, which increased from 2.6 mm at the end of the first 3-mo period to 8.3 mm at the end of the fourth 3-mo period of supplementation. Most of the length gain (7.9 mm) occurred during the first 3 periods of supplementation. In children aged ≥12 mo, differences between the micronutrient and placebo groups were smaller and were not significant. At the end of supplementation, children aged ≥12 mo in the micronutrient group were on average only 2.0 mm taller than the children in the placebo group.

TABLE 2
Changes in anthropometric measurements and indexes from baseline to the end of supplementation in the micronutrient and placebo groups by age categories at baseline[1]

	Infants (<12 mo)		Children ≥ 12 mo	
Variable	Micronutrient group	Placebo group	Micronutrient group	Placebo group
Age (mo)	12.0 ± 2.0	12.1 ± 1.6	12.3 ± 1.9	12.7 ± 0.7
Length (cm)	11.0 ± 2.4	10.3 ± 2.3[2]	10.3 ± 2.4	10.4 ± 2.0
Weight (kg)	2.0 ± 0.82	2.1 ± 0.84	2.09 ± 0.77	2.23 ± 0.71
Length-for-age *z* score	−0.13 ± 0.61	−0.46 ± 0.64[2]	0.31 ± 0.58	0.31 ± 0.60
Weight-for-age *z* score	−0.22 ± 0.70	−0.15 ± 0.74	0.06 ± 0.53	0.15 ± 0.64
Weight-for-length *z* score	−0.53 ± 0.78	−0.31 ± 0.84	−0.20 ± 0.57	−0.05 ± 0.66

[1] $\bar{x}$ ± SD.
[2] Significantly different from the micronutrient group, $P < 0.05$ (one-tailed *t* test).

TABLE 3
Results of the use of generalized estimation equations to determine the effect of multiple micronutrient supplementation on length by 3-mo periods of supplementation, adjusted for covariates

	Infants (<12 mo) (n = 220)		Children ≥ 12 mo (n = 99)	
	β	P	β	P
Intercept	72.99	0.001	73.24	0.001
Treatment[1]	0.26	0.017	−0.27	0.135
Initial length	0.99	0.001	0.95	0.001
Weight-for-length z score	0.12	0.046	0.23	0.017
Breast-fed[2]	−1.07	0.001	−0.61	0.024
Sex[3]	0.07	0.626	−0.39	0.116
Socioeconomic tertile[4]	−0.27	0.108	−0.57	0.021
Period 2[5]	2.77	0.001	2.43	0.001
Period 3[5]	5.31	0.001	4.92	0.001
Period 4[5]	7.73	0.001	7.19	0.001
Treatment × period 2	0.26	0.001	0.34	0.068
Treatment × period 3	0.53	0.003	0.45	0.092
Treatment × period 4	0.56	0.001	0.47	0.153

[1] Micronutrient = 1, placebo = 0.
[2] Yes = 1, no = 0.
[3] Boys = 1, girls = 0.
[4] Low tertile = 1, medium and high tertiles = 0.
[5] Three-month periods of supplementation.

The magnitude of the differences in length-for-age z scores between the micronutrient and placebo groups by period of supplementation, after adjustment for potential confounders, are presented separately for the 2 age subgroups in Figure 2. Length-for-age z scores increased from 0.12 to 0.30 units from the first to the fourth 3-mo periods of supplementation in the infants. As was the case for length, most of the effect (0.29 units) was achieved during the first 3 periods of supplementation. In children aged ≥12 mo, adjusted differences between treatment groups were smaller than those for the children aged <12 mo. At the end of the fourth 3-mo period of supplementation, the adjusted differences between treatment groups were 0.10 z score units ($P < 0.10$).

DISCUSSION

Administration of a multiple micronutrient supplement 6 d/wk for ≈12 mo to children aged 8–14 mo at baseline resulted in an overall length gain that was almost 5 mm (length-for-age z score: 0.19) greater than the gain in the placebo group. The effect of supplementation was greater in infants than in the children aged ≥12 mo. In the younger age group, supplementation resulted in an increase in length of 8.3 mm and in the length-for-age z score of 0.3 units. In the infants, the length-for-age z score decreased during follow-up by ≈0.1 units in the micronutrient group and by ≈0.4 units in the placebo group. In contrast, in the children aged ≥12 mo, the micronutrient group gained only 2.0 mm more in length (a greater length-for-age z score of ≈0.1) than did the placebo group after 12 mo of supplementation.

Compared with other supplementation trials, the observed effect on the infants in the present study was not only significant but was interpreted as biologically important given that the mean baseline length-for-age z score of the study children was −1.3, that macronutrients were not administered, and that the study lasted only 1 y. For example, a well-controlled supplementary feeding trial that provided a beverage with both macronutrients and micronutrients to Guatemalan children for almost 3 y (from 3 to 36 mo of age) resulted in a cumulative effect of 2.5 cm in length (34), ≈3 times the size of the effect observed in the present trial; however, most of the effect of supplementary feeding occurred during the first 2 y of life (35). In addition, the median length-for-age z scores in the Guatemalan infants was less than −2 before supplementation (36), a value that is well below the median values in the present study. It is well known that the closer the z score is to 0, the less likely it is to detect any effect on linear growth.

The effects of micronutrient supplementation on length in the infants in the present study were greater than those shown in a meta-analysis of zinc supplementation trials (3). In contrast, the effects on older children, although statistically significant for some 3-mo periods of supplementation, were small compared with the effects of other interventions involving supplementary feeding or zinc supplementation. The finding of greater effects in infants than in older children is biologically plausible. Infants grow at faster rates than do older children, their micronutrient needs to sustain this accelerated growth are greater, and their diets are often more restricted than those of older children. As mentioned previously, most of the effect of supplementary feeding occurs during the first year of life (35); therefore, we had expected larger effects on younger children at the time the study was designed.

Moreover, it is possible that the effects of supplementation would have been greater if the infants had been admitted to the

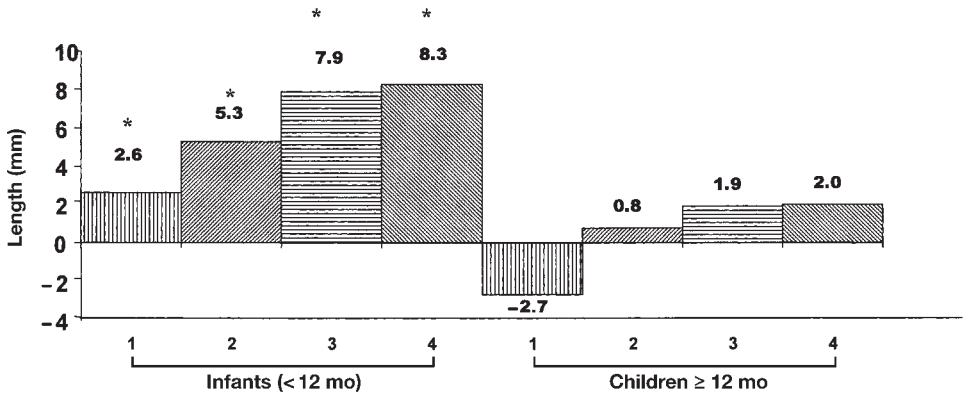

FIGURE 1. Differences in length between the micronutrient and placebo groups (micronutrient − placebo) adjusted for length at baseline, weight-for-length z score at baseline, monthly breast-feeding status, sex, and socioeconomic status. *Significantly different from 0, $P < 0.05$.

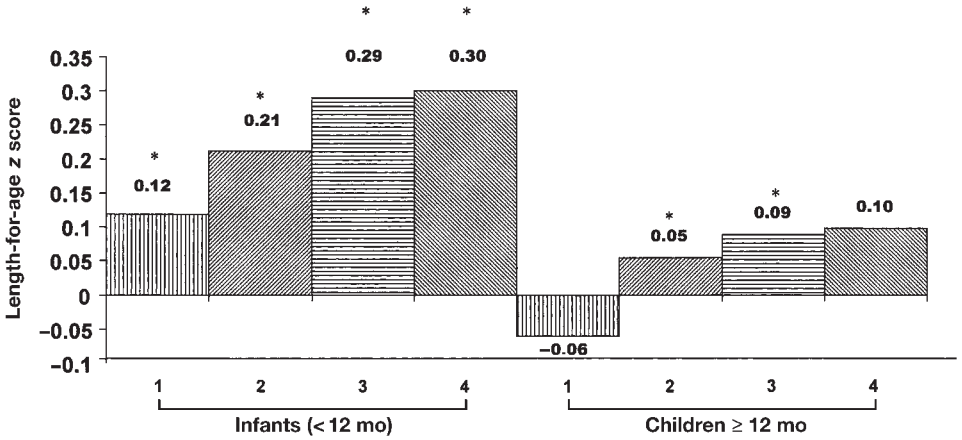

FIGURE 2. Differences in length-for-age *z* scores between the micronutrient and placebo groups (micronutrient − placebo) adjusted for length-for-age *z* score at baseline, weight-for-length *z* score at baseline, monthly breast-feeding status, sex, and socioeconomic status. *Significantly different from 0, $P < 0.05$.

study at a younger age. The mean length of our study children at baseline was already 1.3 SDs below the reference mean. The mean length in the placebo group 1 y later was 0.25 SDs lower. Therefore, potentially, a greater effect could have been achieved in younger children. We did not include children aged <8 mo because we were also interested in evaluating the effects of supplementation on appetite and behavior, which were considered easier to evaluate at older ages. Future studies should start supplementation at younger ages.

It is highly likely that the differences in linear growth between the micronutrient and the placebo groups was due to supplementation because our study was randomized and double-blind, the supplements were administered to all children 6 d/wk under supervision, and the supplements were well accepted as reflected by the high compliance rate; on average, the supplements were consumed on 86% of the scheduled days. Because the anthropometric indexes at baseline, most of the anthropometric measures made during the study period, and other characteristics of the children and their families at baseline were similar between treatment groups, we considered randomization to have been effective (Table 1).

Our results indicate that growth was stimulated in the infants in the first 3 mo of supplementation and continuation of supplementation yielded ongoing positive effects on growth for at least 9 mo. Additional studies are needed to measure growth responses when supplementation is begun at younger ages and continued for a longer time.

We had hypothesized that children who were more stunted at baseline would benefit more from supplementation than would less-stunted children, as was observed in a zinc supplementation trial in Guatemalan children (37). However, the interaction between degree of initial stunting and treatment was not significant. It is possible that the lack of an interaction between treatment and the degree of stunting was because the degree of stunting in the group studied was not as severe as in other studies. For example, the average baseline length-for-age *z* score in our zinc supplementation trial in Guatemala was −2.11 compared with −1.3 in the present study, despite the fact that the Guatemalan children were younger (average age at baseline: 7.5 mo) than the children in the present study (11.2 mo).

The energy intakes of the micronutrient and placebo groups were well within the requirements (38, 39) for the age groups of the children in the present study. However, the mean total protein intake was 30–40% greater than recommended amounts (21) and human and cow milk were the main protein sources, indicating that the protein consumed was generally of high quality. In contrast, iron and zinc intakes were well below recommendations (21). Our results corroborate that micronutrients were a limiting dietary factor in the population studied.

The finding that girls benefited more from supplementation than did boys, based on the effects of the interaction between sex and treatment on length, should be interpreted with caution because sex was an unplanned comparison. Moreover, many variables, including length-for-age *z* score, were significantly different between treatment groups within sexes at baseline because randomization was not stratified by sex. We recommend that future studies investigate this association.

Breast-feeding was negatively associated with linear growth in this analysis, however, this finding may have been due to negative confounding. In poor rural and semirural settings in Mexico, such as the site in the present study, more educated women and those who work out of home tend to breast-feed less but live in better conditions, which in turn is associated with better growth. In addition, anthropometric measures tend to be smaller in breast-fed than in bottle-fed infants (40).

The results of our study show that micronutrients are a limiting factor for the growth of infants in Mexico and that public health interventions aimed at improving the nutritional status and growth of infants and young children should consider improvements in micronutrient intakes as an essential component. In addition, infants should be targeted in interventions aimed at promoting growth through improvements in micronutrient status.

REFERENCES

1. Administrative Committee on Coordination/Sub-committee on Nutrition. Fourth Report on the world nutrition situation. Geneva: ACC/SCN in collaboration with IFPRI, 2000.
2. Allen LH. Nutritional influences on linear growth: a general review. Eur J Clin Nutr 1994;48:S75–89.
3. Brown KH, Peerson JM, Allen LH. Effect of zinc supplementation on children's growth: a meta-analysis of intervention trials. Bibl Nutr Dieta 1998;54:76–83.

4. Auckett MA, Parks YA, Scott PH, Wharton BA. Treatment with iron increases weight gain and psychomotor development. Arch Dis Child 1986;61:849–57.
5. Bhatia D, Seshadri S. Growth performance in anemia and following iron supplementation. Indian Pediatr 1993;30:195–200.
6. Chwang LC, Soemantri AG, Pollitt E. Iron supplementation and physical growth of rural Indonesian children. Am J Clin Nutr 1988; 47:496–501.
7. Lawless JW, Latham MC, Stephenson LS, Kinoti SN, Pertet AM. Iron supplementation improves appetite and growth in anemic Kenyan primary school children. J Nutr 1994;124:645–54.
8. Ramakrishnan U, Martorell R. The role of vitamin A in reducing child mortality and morbidity and improving growth. Salud Publica Mex 1998;40:189–98.
9. West KP Jr, Djunaedi E, Pandji A, et al. Vitamin A supplementation and growth: a randomized community trial. Am J Clin Nutr 1988; 48:1257–64.
10. Muhilal, Permeisih D, Idjradinata YR, Muherdiyantiningsih, Karyadi D. Vitamin A–fortified monosodium glutamate on health, growth, and survival of children: a controlled field trial. Am J Clin Nutr 1988;48:1271–6.
11. Sommer A, West KP Jr. Consequences of vitamin A deficiency: child survival. In: Sommer A, West KP Jr, Olson JA, Ross CA, eds. Health, survival, and vision. New York: Oxford University Press, 1996.
12. Golden BE, Golden MHN. Relationship among dietary quality, children's appetites, growth stunting, and efficiency of growth in poor populations. Food Nutr Bull 1991;3:105–9.
13. Wallwork JC, Fosmire GJ, Sanstead HH. Effect of zinc deficiency on appetite and plasma amino acid concentrations in the rat. Br J Nutr 1981;45:127–36.
14. Carter JP, Grivetti LE, Davis JT, et al. Growth and sexual development of adolescent Egyptian village boys. Effects of zinc, iron, and placebo supplementation. Am J Clin Nutr 1969;22:59–78.
15. Ronaghy HA, Reinhold JG, Mahloudji M, Ghavami P, Fox MR, Halsted JA. Zinc supplementation of malnourished schoolboys in Iran: increased growth and other effects Am J Clin Nutr 1974;27: 112–21.
16. Sandstead HH, Penland JG, Alcock NW, et al. Effects of repletion with zinc and other micronutrients on neuropsychologic performance and growth in Chinese children. Am J Clin Nutr 1998; 68(suppl):470S–5S.
17. Instituto Nacional de Salud Pública. Encuesta Nacional de Nutrición 1999. Tomo I. Niños menores de cinco años. (National nutrition survey 1999. Vol 1. Children under five years of age.) Cuernavaca, México: Instituto Nacional de Salud Pública, 2000 (in Spanish).
18. Rivera J, Bourges H, Arroyo P, et al. Deficiencias de mirconutrimentos. (Micronutrient deficiencies.) In: De la Fuente JR, Sepúlveda J, eds. Diez problemas relevantes de salud pública en México. (Ten relevant public health problems in México.) México DF: Fondo de Cultura Económica, 1999 (in Spanish).
19. World Health Organization. Measurement of nutritional impact. Geneva: WHO, 1979.
20. Meinert CL, Tonascia S. Clinical trials. Design, conduct and analysis. New York: Oxford University Press, 1968:95–112.
21. National Research Council. Recommended dietary allowances. 10th ed. Washington, DC: National Academy Press, 1989.
22. Lohman T, Roche A, Martorell R. Anthropometric standardization reference manual. Chicago: Human Kinetics, 1988.
23. Habicht JP. Estandarización de métodos epidemiológicos cuantitativos sobre el terreno. (Standardization of quantitative epidemiologic methods in the field.) Bol Oficina Sanit Panam 1974;76:375–84 (in Spanish).
24. de Kanashiro HC, Brown KH, López de Romaña G, Lopez T, Black RE. Consumption of food and nutrients by infants in Huascar (Lima), Perú. Am J Clin Nutr 1990;52:995–1004.
25. Dewey KG, Heinig MJ, Nommsen LA, Lonnerdal B. Maternal versus infant factors related to breast milk intake and residual milk volume: the DARLING study. Pediatrics 1991;87:829–37.
26. Hendrikson EC, Seacat JM, Neville MC. Insensible weight loss in children under one year of age. Acta Paediatr 1985;74:678–80.
27. Brown KH, Black RE, Robertson AD, Akhtar NA, Ahmed G, Becker S. Clinical and field studies of human lactation: methodological considerations. Am J Clin Nutr 1982;35:745–56.
28. US Department of Agriculture, Agricultural Research Service. USDA nutrient database for standard reference, release 13. Beltsville, MD: USDA Nutrient Data Laboratory, 1999.
29. National Academy of Sciences. Nutrition during lactation. Washington, DC: Institute of Medicine, National Academy Press, 1991:116.
30. Kleinbaum DG, Kupper LL, Muller KE. Applied regression analysis and other multivariate methods. Boston: PWS-Kent Publishing Co, 1988:595–641.
31. Diggle PJ, Liang KY, Zeger SL. Analysis of longitudinal data. Oxford, United Kingdom: Clarendon Press, 1996. (Oxford Statistical Science series 13.)
32. Cohen J. Statistical power analysis for the behavioral sciences. Rev ed. New York: Academic Press, 1977:1–292.
33. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons, 1989:82–133.
34. Habicht JP, Martorell R, Rivera JA. Nutritional impact of supplementation in the INCAP longitudinal study: analytic strategies and inferences. J Nutr 1995;125:1042S–50S.
35. Schroeder DG, Martorell R, Rivera JA, Ruel MT, Habicht J-P. Age differences in the impact of nutritional supplementation on growth. J Nutr 1995;125:1051S–9S.
36. Rivera JA, Habicht J-P. The recovery of Guatemalan children with mild to moderate wasting: factors enhancing the impact of supplementary feeding. Am J Public Health 1996;86:1430–4.
37. Rivera JA, Ruel MT, Santizo MC, Lönnerdal B, Brown KH. Zinc supplementation improves the growth of stunted rural Guatemalan infants. J Nutr 1998;128:556–62.
38. Bute NF. Energy requirements of infants. Eur J Clin Nutr 1996;50: S24–36.
39. Torún B, Davis PSW, Livingstone MBE, Paolisso M, Sackett R, Spurr GB. Energy requirements and dietary energy requirements for children and adolescents 1 to 18 years old. Eur J Clin Nutr 1996;50:S37–81.
40. World Health Organization. Physical status: the use and interpretation of anthropometry. World Health Organ Tech Rep Ser 1995;845: 227–43.