Separate and Joint Effects of Micronutrient Deficiencies on Linear Growth[1]

Jorge L. Rosado

Department of Nutritional Physiology, National Institute of Nutrition, Vasco de Quiroga No 15, Tlalpan, Mexico D.F. 14000, Mexico

ABSTRACT Recent studies have investigated the effect of micronutrient deficiencies on growth stunting, with special attention toward the effect of zinc, iron, vitamin A and iodine deficiencies. In Mexico, the prevalence of growth stunting in children <5 y old is ~24%; it is higher in rural areas and lower in urban areas. In an initial study, the effect of zinc and/or iron supplementation on linear growth was investigated in a longitudinal, placebo-controlled design. After 12 mo of supplementation, there was no difference between the groups supplemented with zinc, iron or zinc plus iron and the placebo group. At baseline, 82% of the children in this study were deficient in at least two out of the five micronutrients that were determined, and 73% were anemic. In another study, a mixture of those micronutrients that were documented to be lacking in Mexican children was formulated in a supplement and given to Mexican children over a period of 12 mo in a longitudinal, placebo-controlled, supplementation design. Children in the low and medium socioeconomic status grew about 1 cm more than similar children in the placebo group. This difference was not found in children of high socioeconomic status. It is suggested that, in most cases, growth stunting is associated with marginal deficiencies of several micronutrients and that in populations with multiple micronutrient deficiencies, the effect on linear growth of supplementation with single nutrients will not be significant. Supplementation with multiple micronutrients is expected to be more effective, but even in that case the actual increment in height was less than the expected potential increment. J. Nutr. 129: 531S–533S, 1999.

KEY WORDS: • *growth stunting* • *micronutrient deficiency* • *iron* • *zinc* • *growth*

Growth stunting constitutes the most common evidence of marginal malnutrition throughout the world. Protein and energy deficiency were initially evaluated as major causes of stunting (Beaton and Ghassemi 1982, Brooke and Wheeler 1976, Hansen-Smith et al. 1979, Lampl et al. 1978; Malcolm 1970, Sepúlveda-Amor et al. 1995); some supplementation studies that have used milk or soybeans have reported a height gain with supplementation (Lampl et al. 1978, Malcolm 1970). In those studies, it is not possible to be certain whether this was an effect of protein per se or whether other nutrients added to the diet such as phosphorus, calcium, zinc or potassium had a causal role. It is also clear that the supplementation studies that have used milk or soybeans have produced increments in height that have been much smaller than the potential increment expected (Golden 1988), demonstrating that other nutrients or other factors might also be involved. In some populations, it has been demonstrated that delayed growth is not associated with low protein intakes (Allen 1994).

Observational studies that showed a widespread existence of marginal deficiency of some micronutrients and its association with growth stunting prompted the realization of intervention studies (mainly with zinc, iron, iodine and vitamin A) (Allen 1994) to investigate whether such deficiency was the cause of growth stunting. Supplementation studies with these micronutrients have also led to conflicting results. In this paper, we present the results of studies conducted in rural areas of Mexico to demonstrate the notion that growth stunting occurs in association with marginal deficiencies of several micronutrients; consequently, supplementation with single nutrients will produce in most instances little or no beneficial effect on linear growth.

GROWTH STUNTING IN MEXICO

In Mexico, according to the National Nutrition Survey of 1988, the prevalence of linear growth deficit in children <5 y of age is 24% (Rivera-Dommarco et al. 1995). Growth deficiency was considered as height for age >2 SD below the median given by NCHS/WHO. In some of the poorest rural areas, these figures can be as high as 50% of preschool children. Decreased growth rate in children has been associated with increased morbidity and reduced scholastic achievement (Martorell et al. 1992a); it also has long-term negative effects on physical work capacity and reproduction performance (Martorell et al. 1992a and 1992b).

Effect of zinc and iron supplementation. Considering the high prevalence of growth stunting in Mexican children and the potential role of zinc and iron deficiencies in reducing growth rate, zinc and/or iron supplementation was investigated to determine whether this would improve significantly the

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TABLE 1

Proportion of children with deficient micronutrient status during the 1-y follow-up[1]

	Baseline	6 mo	12 mo
Retinol	29	5	10
Tocopherol	68	53	53
Hemoglobin	73	45	43
Ferritin	51	27	12
Vitamin B-12	10	3	7
Holo TCII	26	1	7
Zinc	25	—	17

[1] Deficient values: retinol < 20 ug/dL; tocopherol < 500 ug/dL; hemoglobin < 11.7 g/dL; ferritin < 12 ng/mL; vitamin B-12 < 200 pg/mL; holo TCII < 20 pg/mL; zinc < 70 mg/dL.

nutritional status and growth of Mexican preschoolers (Rosado et al. 1997).

The study was conducted in five rural communities in the central highland plateau of Mexico, located in the State of Mexico, ~150 kilometers northwest of Mexico City. A total of 219 children between 18 and 36 mo of age were randomly assigned to one of four groups according to age, sex and height-for-age deficit. Each of the four groups received a daily supplement consisting of a 20 mL fluid that contained 20 mg of elemental iron as ferrous sulfate, 20 mg of elemental zinc as zinc methionine, 20 mg of elemental zinc plus 20 mg of elemental iron and a placebo, respectively. Supplements were formulated in a flavored beverage, which was given under direct supervision from Monday to Friday for 12 mo. Compliance was excellent; children consumed the supplements 97% of the days and only 25 children dropped from the study before the 12 mo of supplementation were completed.

Anthropometry measurements were collected at baseline before supplementation and at 6 and 12 mo afterwards. Venous blood was collected from every preschooler at baseline before supplementation and at 6 and 12 mo after supplementation for analysis of hemoglobin, hematocrit, ferritin, zinc, retinol, C-reactive protein, α-tocopherol, vitamin B-12 and riboflavin.

After 12 mo of supplementation, linear growth varied from 8.9 to 9.3 cm/y in the different groups and no difference among them was detected. There was a lack of effect of iron and/or zinc supplementation on growth even though plasma zinc and zinc in red blood cells increased in the zinc-supplemented groups and ferritin increased in the iron-supplemented groups.

Although it is well recognized that zinc deficiency produces delayed growth and development, the benefits of zinc supplementation on incremental growth is more controversial. Some studies have found a positive effect of zinc supplementation on linear growth (Gibson et al. 1992, Walravens and Hambidge 1976, Walravens et al. 1983, Xue-Cun et al. 1985), whereas others did not find that effect (Carter et al. 1969, Cavan et al. 1993). In a recent meta-analysis in which 25 zinc supplementation studies were reviewed, Brown (1995) found a pooled effect of 0.2 SD on height and 0.26 SD on weight. Both effects were positive and small but nevertheless significant.

The effect of iron nutritional status on growth is even more controversial. Angeles et al. (1993) demonstrated a positive effect of iron and ascorbic acid on linear growth compared with a supplement of ascorbic acid alone. The effect was attributed to a reduction in morbidity observed with iron supplementation. Other studies have not found an effect of iron supplementation on growth (Gershoff et al. 1988, Migasena et al. 1972).

The proportion of children with deficient nutritional status of the micronutrients analyzed in the study is shown in **Table 1**. At the beginning of the 1-y supplementation, there was a high incidence of anemia and low ferritin, tocopherol, retinol, vitamin B-12, holo TC11 and zinc. Of the total group of children, <7% had no deficiency, 11% had deficiency of one nutrient, 18% had deficiencies of two nutrients and 64% had deficiency of more than two nutrients. The high proportion of some of these deficiencies was present during the 12 mo of observation. The lack of effect on linear growth observed with zinc and iron supplementation could be due to the fact that the children in this study were deficient in several other nutrients, which may in itself have impaired growth or impaired the potential positive effect of zinc and/or iron. Our study suggests that, for interventions directed to reduce retarded growth in populations in which multiple micronutrient deficiencies are suspected, attention to one single nutrient will have little, if any effect.

Table 2 compares the incidence of some of the micronutrient deficiencies between rural and urban children; the urban children included a sample of 264 children (12–43 mo) of low socioeconomic status. The urban children had less anemia and lower incidence of deficient values of retinol and tocopherol, which is associated with the inclusion of some animal products and more fat in the diet (Madrigal et al. 1986) and a lower incidence of growth stunting (Rivera-Dommarco et al. 1995).

Effect of multiple micronutrient supplementation. The objective of the study was to evaluate the effect of a mixture of multiple micronutrient supplementation on growth of children living in a rural Mexican community (Rivera et al., unpublished data). The study was a randomized, double-blind, community intervention conducted in a rural community in Xoxocotla in the state of Morelos. A total of 337 children between 8 and 14 mo of age were randomly assigned into two groups. One group received a supplement (n = 168) and the other received a placebo (n = 169). Both treatments were administered 6 d/wk over a period of 12 mo and were ingested under supervision. The supplement was formulated to contain the nutrients that are known or expected to be deficient in Mexican children or for which there is some evidence of low intake (Rosado et al. 1995a and 1995b). The supplement contained 1 Recommended Dietary Allowance (RDA) of vitamins D, E, K, niacin, B-1, B-6, folic acid, pantothenic acid, iodine copper, manganese fluoride and selenium; 1.2 RDA of vitamin A; and 1.5 RDA of ascorbic acid, riboflavin, vitamin B-12, iron and zinc. The supplement was formulated into a

TABLE 2

Comparison of deficiency of some micronutrients between rural and urban Mexican preschoolers of low socioeconomic status[1]

	Rural	Urban
	% deficient	
Retinol	29	5
Tocopherol	64	23
Hemoglobin	73	35
Hematocrit	61	20
Ferritin	51	68

[1] Deficient values: retinol < 20 ug/dL; tocopherol < 500 ug/dL; hemoglobin < 11.7 g/dL; hematocrit < 30%; ferritin < 12 ng/mL.

TABLE 3

Anthropometry results after 12 mo of supplementation with multiple micronutrients or placebo

Variable	Micronutrients $n = 168$	Placebo $n = 167$
Age, *mo*	22.9 ± 3.1	22.9 ± 2.8
Length in total sample,[1] *cm*	79.5 ± 3.7	78.9 ± 4.7
Length in low/medium SES,[1] *cm*	79.2 ± 3.1	78.3 ± 4.2
Length in high SES, *cm*	79.4 ± 3.2	79.6 ± 3.8
Weight, *kg*	10.2 ± 1.2	10.1 ± 1.2
Height-for-age Z-score[1]	−1.36 ± 1.0	−1.68 ± 1.1
Weight-for-age Z-score	−1.48 ± 0.9	−1.58 ± 0.9
Weight-for-height Z-score	−0.87 ± 0.8	−0.78 ± 0.7

[1] The difference between the groups is significant $P < 0.05$. Results are adjusted for age, initial length, sex and socioeconomic status (SES).

flavored beverage that contained 30 kcal and no fat or protein. The placebo consisted of a 30-kcal flavored beverage with no micronutrients added. Both supplements were developed into a 25-mL flavored beverage. Anthropometry was measured every month by trained personnel during the observation period; Z-scores were calculated for weight for age, weight for height and height for age. At the beginning of the study, information on characteristics of the house, possession of selected household goods and parental education was obtained by direct interviewing of the mothers.

Anthropometry results are shown in **Table 3**. Final length was 0.9 cm higher for the group supplemented with multiple micronutrients compared with the placebo group. This difference decreased to 0.6 when adjusting for age, initial length, sex and socioeconomic status. Both values are significant compared with the placebo group ($P < 0.05$). The difference between the placebo group and the group supplemented with multiple micronutrients is higher when the groups are divided according to socioeconomic status; children of low and medium socioeconomic status of the micronutrient-supplemented group grew ~1 cm more than the same group of children in the placebo group. In this study, we found a positive highly significant effect on linear growth of supplementation with a preparation containing multiple micronutrients. The effect, however, was lower than expected for catch-up growth, suggesting that a full correction of growth stunting requires more than supplementation with the apparently deficient nutrients.

CONCLUSIONS

Growth stunting could be the consequence of deficiency of one or several nutrients. In communities in which stunting is prevalent, it is highly likely that several nutrient deficiencies occur simultaneously in the stunted children. In a study in a rural community in Mexico, 82% of children 18–36 mo of age were deficient in at least two micronutrients out of five that were determined. Results of studies with single nutrient supplementation are conflicting; thus that there is no consistent evidence for any nutrient that its use for supplementation will promote linear growth. In the case of Mexican preschoolers in whom deficiencies of multiple micronutrients were demonstrated, we did not find any effect on linear growth after 1 y of supplementation with zinc and/or iron.

Supplementation with multiple micronutrients produced a significant increment in linear growth. However, even in children supplemented with multiple micronutrients, the actual increment in height was much less than the potential increment expected.

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