Effect of Micronutrient Supplementation on the Growth of Preschool Children in China

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Objective To study the relationship between micronutrient supplementation and children growth. **Methods** A double-blind, placebo-controlled trial was conducted in 156 growth retarded preschool children. They were randomly assigned to five groups: supplemental control (S-control, n=28), zinc supplementation(+Zn, 3.5mg Zn/day, n=34), zinc and calcium supplementation (+ZnCa, 3.5mg Zn+250mg Ca/day, n=37), zinc and calcium and vitamin A supplementation (+ZnCaVA, 3.5mgZn +250mgCa+200gVA/day, n=28), Calcium and vitamin A supplementation (+CaVA, 250mgCa + 200gVA/day, n=29). Another 34 children with normal height were selected as normal control (N-control). Supplementation continued for twelve months. **Results** The height gain in +Zn group (7.84cm per year) and +ZnCa group (7.70 cm per year) was significantly higher than that in S-control group (6.74 cm per year, $P<0.05$); The weight gain in +ZnCaVA group (2.55kg per year) and +CaVA group (2.57 kg per year) was also significantly higher than that in S-control group (2.19kg per year, $P<0.05$); The average days of illness in each supplementation group were lower than that in S-control (13 days per year compared with 23 days per year). No significant difference was observed on bone age. **Conclusion** Zinc and Zinc+Calcium supplementation can improve the height gain, and vitamin A can improve weight gain in growth retarded preschool children, but do not affect the maturity of bone. Micronutrient supplementation can lower the morbidity of these children.

Key words: Zinc; Calcium; Vitamin A; Preschool children; Growth

INTRODUCTION

Growth retardation of children remains a public healthy problem in developing countries. A study on the overall nutrient status of China in 1992 showed that the incidence of growth retardation was more than 35.7% of children under five years old. On the other hand, the study also showed a very low intake of micronutrients, especially zinc, calcium and vitamin A in Chinese children[1].

Zinc plays many potentially important biological roles in the body. First, it is a component of over 200 metabolic enzymes involved in nucleic acid metabolism, genetic expression and maintaining the structure of cell membrane[2]. Calcium is the main structural material of skeleton and is also associated with many metabolic processes inside cells[3]. A number of studies also reported that sub-clinical vitamin A deficiency is associated with reduced immune function and increased risks for infection diseases[4].

The effect of micronutrient supplementation on children growth was evaluated by many

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investigators, but the results were not consistent. In this study, a double blind, placebo-controlled micronutrient-intervention trial was performed among children from Luoyang City, Henan Province. Growth-retarded children were given zinc or/and calcium or/and vitamin A for 12 months to evaluate the effect of supplementation on height, weight, days and times of illness and bone age.

SUBJECTS AND METHODS

Subjects

There were 1 885 children aged 3-5 years in kindergartens of the Truck Factory of Luoyang City, Henan Province. Children whose height was below −1SD height for age of the standard were selected. They were called "growth retarded" in this study. They had to live in local communities for at least 2 years, without any chronic or acute diseases. Those who were absent consistently for more than 30 days were excluded. A total of 156 children were finally recruited. Another 34 children of normal height were selected as normal control. The sample size required for detecting a difference of 1.2cm height gain with 90% and a type I error of 5% by assuming a SD of 1.32cm, was estimated for 25 children in each group. The study was approved by the Ethical Review Committee of the Chinese Academy of Preventive Medicine.

Study Design

The study was a double blind one. One hundred and fifty six growth-retarded children were divided into five groups and randomly assigned to different supplementations shown in Table 1.Micronutrients were added to milk powder or in the form of tablets and provided alternately. The placebos were indistinguishable from supplies in both appearance and taste, either by milk powder or by tablets. Supplementation period was from November of 1998 to October of 1999, for five days a week. Other vitamins or minerals were not allowed during this period. Anthropometric mesurement was made every three months, dietary intake was assessed every six months, and bone age was tested at baseline and at the end of supplementation.

TABLE 1

Groups and Micronutrients Supplementation

Group	Sample Size	Condition	Micronutrients Supplementation		
			Zn (mg)	Ca (mg)	VA (μg)
N-control	34	Normal	0	0	0
S-control	28	Growth slow	0	0	0
+Zn	34	Growth slow	3.5	0	0
+ZnCa	37	Growth slow	3.5	250	0
+ZnCaVA	28	Growth slow	3.5	250	200
+CaVA	29	Growth slow	0	250	200

Anthropometry and Dietary Intake

The measurements of height and weight were done by identical machines and persons every time. Times and days of illness were obtained by parents inquiry, X films were made on wrist in Radiation Department of Luoyang Hospital (XG-200, Shanghai) and estimated by doctor from Capital Children Institute of China, using CHN score method, compared with a criterion reference.

Dietary intake was assessed by a 72 h dietary record in October, 1998, April, 1999 and October, 1999 and quantified in grams. The intake of energy, protein, vitamin A, calcium, zinc, iron etc was calculated based on the Food Composition Table of China[5].

Statistical Methods

Data were inputted by using Foxpro 5.0 software. ANOVA test or Kruskal-Wallisteat or x^2 test was used to determine statistical differences among the groups.

RESULTS

Subjects Characteristics

The average age, birth weight and sex in each group were similar, and the average height in N-control group was higher than that in the other groups, but there was no significant difference in the other five groups. The average weight in N-control group was also significantly higher than that in +ZnCaVA group and +CaVA group, as shown in Table 2.

TABLE 2

Baseline Characteristics of Children in Six Groups.

Group (*n*)	N-control (33)	S-control (27)	+Zn (34)	+ZnCa (37)	+ZnCaVA (26)	+CaVA (29)
Age($\bar{x}\pm s$, Year)	3.88±0.61	4.11±0.62	4.08±0.66	4.04±0.59	3.90±0.92	3.95±0.50
Sex Boy %	27.3	55.6	44.1	54.1	46.2	55.2
Girl %	72.7	44.4	55.9	45.9	53.8	44.8
Birth Weight ($\bar{x}\pm s$ g)	3283.5 ±492.1	3052.5 ±461.6	3130.6 ±466.8	3139.2 ±377.4	3007.6 ±416.5	3127.7 ±381.8
Baseline Height ($\bar{x}\pm s$, cm)	99.52±4.30	96.73±4.36[a]	95.99±4.96[a]	96.56±4.73[a]	95.15±7.29[a]	95.70±3.56[a]
Baseline Weight ($\bar{x}\pm s$, kg)	14.87±1.11	14.58±1.49	14.09±1.36	14.47±1.36	13.78±1.70[a]	13.79±1.14[a]

[a] Compared with N-control group, $P<0.05$.

There was no difference in the characteristics of parent's occupation, career, age, educational level and family income per month etc in children among the six groups. It meant that the children in each group had the same background (Table 3).

Dietary Intake

The intakes of energy, protein in three different periods of time were not significantly different in the six groups and approximately met the Chinese recommended dietary allowance (RDA) of 1988 (Table 4). The intake of iron, vitamin B1, B2, C, E etc also approached or exceeded Chinese RDA, but zinc, calcium and vitamin A were much lower, only about 20%-30%, 60%-70% and 30%-50% of RDA respectively; protein sources were rational with animal food supplying 40%-50% of the dietary protein. Energy from carbohydrate, fat and protein was 55%-61%, 23%-31% and 12%-15% respectively, approximately meeting the Chinese standard (Table 5).

TABLE 3

Comparison of the Background of Children

Group (n)	N-control (33)	S-control (27)	+Zn (34)	+ZnCa (37)	+ZnCaVA (26)	+CaVA (29)
Educational Level of Mother						
Lower Than High Middle School %	30.3	40.7	29.4	45.9	38.5	37.9
Higher Than High Middle School %	69.7	59.3	70.6	54.1	61.5	62.1
Educational Level of Father						
Lower Than High Middle School %	39.4	40.7	35.3	35.1	38.5	41.4
Higher Than High Middle School %	60.6	59.3	64.7	64.9	61.5	58.6
Occupation of Mother						
Workers %	54.5	66.7	67.7	43.2	57.7	48.3
Others %	45.5	33.3	32.3	56.8	42.3	51.7
Occupation of Father						
Workers %	48.5	59.3	58.8	59.5	69.2	72.4
Others %	51.5	40.7	41.2	40.5	30.8	27.6
Income of Family Per Month						
<900 %	48.5	55.6	76.5	67.6	65.4	62.1
≥900 %	51.5	44.4	23.5	32.4	34.6	37.9
Average Age of Mother ($\bar{x}\pm s$, Year)	29.59±1.76	29.46±1.89	30.19±2.59	30.14±2.36	30.42±3.34	29.41±2.12
Average Age of Father ($\bar{x}\pm s$, Year,)	30.93±1.81	31.21±1.72	32.10±2.40	32.17±2.96	32.13±3.75	31.30±2.20

TABLE 4

Daily Intake of Nutrients in Three Different Periods of Time Compared with Chinese RDA of 1988

Time	Energy RDA(%)	Protein RDA(%)	Calcium RDA(%)	Iron RDA(%)	Zinc RDA(%)	Vitamin A RDA(%)	Vitamin B1 RDA(%)	Vitamin B2 RDA(%)	Vitamin E RDA(%)
Oct. 1998	88.02± 25.42	86.18± 26.58	29.11± 14.52	94.34± 26.82	61.51± 18.02	51.33± 79.88	53.64± 16.61	62.60± 27.90	363.02± 187.04
Apr. 1999	88.02± 18.98	102.32± 27.34	22.49± 5.94	116.74± 27.29	64.47± 16.41	43.54± 11.47	70.02± 13.31	75.50± 19.94	194.77± 65.71
Oct. 1999	90.69± 15.28	85.83± 15.50	24.42± 4.65	109.99± 18.41	67.49± 13.45	29.68± 7.17	60.40± 11.37	67.42± 11.34	171.57± 41.60

TABLE 5

Sources of Protein and Energy in Three Periods of Times

	Protein Sources (%)		Energy Sources (%)		
	Animal Source	Other Source	Protein	Fat	Carbohydrates
Oct. 1998	43.06±7.34	56.94±7.34	13.28±1.36	31.38±5.42	55.38±5.73
Apr. 1999	41.49±4.46	58.50±4.46	15.58±1.36	23.36±1.52	61.03±2.55
Oct. 1999	40.14±6.30	59.85±6.30	12.65±0.52	27.65±1.51	59.70±1.49

Growth

Height. Difference was detected after 6 months' supplementation between +Zn group and S-control group; after 12 months, the height gains in +Zn group and +ZnCa group were higher than those in S-control group ($P<0.05$) and N-control group ($P>0.05$) and were also higher in other supplemental groups than those in S-control group ($P>0.05$) (Table 6).

TABLE 6

The Average Height Gains of Children in Different Periods ($\bar{x}\pm s$, cm)

Group	3 Months	6 Months	9 Months	12 Months
N-control	1.80±0.76	3.81±1.12	5.53±0.83	7.48±1.04
S-conreol	1.90±0.60	3.51±0.71	5.10±0.78	6.74±1.10
+Zn	2.33±0.65	4.41±0.81[a]	5.81±0.99	7.84±1.12[a]
+ZnCa	2.04±1.09	3.80±1.58	5.75±1.52	7.70±1.63[a]
+ZnCaVA	1.91±0.95	3.55±1.22	5.25±1.31	7.42±1.04
+CaVA	1.82±0.79	3.72±0.83	5.55±1.41	7.47±1.51

[a] Compared with S-control group, $P<0.05$.

Weight. The data in table 7 showed a significantly higher average weight gain in +ZnCaVA group and +CaVA group than that in S-control group ($P<0.05$) after 9 months, also a higher trend than that in N-control group ($P>0.05$). The difference remained after 12 months' supplementation.

TABLE 7

The Average Weight Gain of Children in Different Supplemental Periods ($\bar{x}\pm s$, kg)

Group	3 Months	6 Months	9 Months	12 Months
N-control	1.12±0.56	1.10±0.66	1.71±0.87	2.48±1.01
S-conreol	0.98±0.62	0.93±0.59	1.24±0.70	2.19±1.08
+Zn	0.66±0.35	1.06±0.58	1.14±0.66	2.17±0.62
+ZnCa	0.78±0.47	1.10±0.87	1.19±0.84	2.05±1.29
+ZnCaVA	0.88±0.58	1.28±0.63	2.01±1.83[a]	2.57±1.22[a]
+CaVA	1.08±0.54	1.62±0.64[a]	2.14±0.78[a]	2.77±1.02[a]

[a] Compared with S-control group, $P<0.05$.

TABLE 8

The Bone Maturity of Children in Different Groups

Group	Bone Age Delayed (Year)	Bone Age (Year)		Bone Age Gain (Per Year)
		Before	After	
N-control	-0.1±0.8	3.82±1.07	4.85±1.10	1.03±0.55
S-control	-0.8±1.1	3.49±1.02	4.37±1.00	0.88±0.54
+Zn	-0.6±0.9	3.37±1.08	4.38±1.05	1.01±0.53
+ZnCa	-0.5±1.0	3.87±1.11	4.70±1.05	0.93±0.37
+ZnCaVA	-0.6±0.7	3.61±1.08	4.54±1.28	0.93±0.57
+CaVA	-0.7±0.9	3.46±1.06	4.32±1.22	0.86±0.65

Note. Bone age delayed = bone age – life age.

Bone Age. Bone age is more accurate than life age reflecting the actually maturation of a child, so it is called mature indicator. In this study, the bone age of children before and after supplementation was not significantly different in the six groups, as shown in Table 8.

Episodes and Days of Illness. The total episodes and days of illness in this study were marked by respiratory, skin, diarrheal and other diseases. Respiratory diseases occurred more frequently in N-control group than in +ZnCaVA group and +CaVA group ($P<0.05$); Children in +Zn group and +ZnCa group had less skin disease with a shorter length than in S-control group ($P<0.05$). The total episodes and days of illness in four supplemental groups were fewer than in the two control groups ($P<0.05$), as shown in Table 9.

TABLE 9

Episodes and Days of Illness in Six Groups During the Supplemental Period ($\bar{x}\pm s$)

Group	*n*	Times of Illness				Days of Illness			
		Respiratory Disease	Skin Disease	Diarrhea	Total Times	Respiratory Disease	Skin Disease	Diarrhea	Total Days
N-control	29	2.47±1.90	0.07±0.25	0.24±0.57	3.58±3.25	13.51±13.84	0.14±0.58	3.65±9.45	22.8±25.7
S-control	22	1.72±1.66	0.18±0.39	0.36±0.65	3.31±2.57	12.86±14.40	0.59±1.33	2.72±5.57	23.7±19.0
+Zn	33	1.54±1.92	0.06±0.24^{b}	0.03±0.17	2.00±2.09^{a,b}	11.30±15.56	0.09±0.38^{b}	0.21±1.21	13.1±15.8^{a,b}
+ZnCa	33	1.84±2.10	0.06±0.24^{b}	0.06±0.24	2.28±2.20^{a,b}	10.72±14.10	0.09±0.38^{b}	1.57±7.88	15.8±25.6^{a,b}
+ZnCaVA	24	1.29±1.33^{a}	0.08±0.40	0.08±0.28	1.58±1.4^{a,b}	11.00±11.90	0.05±0.24^{b}	1.41±6.14	12.9±13.9^{a,b}
+CaVA	26	1.34±1.62^{a}	0.08±0.27	0.15±0.46	2.11±2.02^{a,b}	8.92±13.94	0.19±0.69	1.23±4.15	11.9±14.8^{a,b}

^{a} Compared with N-control group, $P<0.05$; ^{b} Compared with S-control group, $P<0.05$.

DISCUSSION

The total energy and protein intake of children in this study met the Chinese RDA for 4 years old children, but the intake of calcium, zinc and vitamin A remained very low, similar to the data from the Nationwide Nutrition Survey of China in 1992 and other investigations[1].It showed that deficiency of zinc, calcium and vitamin A might constitute a serious factor limiting the growth of children.

The height gain of children in +Zn group (7.84cm per year) and +ZnCa group (7.70cm per year) was significantly higher than that in S-control group ($P<0.05$) and in N-control group ($P>0.05$), indicating that zinc supplementation plays an important role in stimulating the height growth of retarded children, possibly by stimulating the synthesis of protein and nucleic acid. Our results agreed with those of some investigators but not completely, probably because of different doses of supplementation used or different basic zinc status of subjects[6, 7].

Children in +CaVA group maintained the highest weight gain during the supplementation period, which was significantly higher than that in S-control group ($P<0.05$); After 9 months, the weight gain in +ZnCaVA group caught up and also had significant difference in comparison with that in S-control group at the end of trial ($P<0.05$), suggesting that vitamin A supply could improve the weight growth of children. This result was consistent with other studies[8, 9].

Bone age is highly associated with the terminal height of a person. Martorell reported that bone development of children with growth retardation was delayed[10]. In our study, growth-retarded children had delayed bone age compared with life age (-0.5~-0.8), whereas life age was -0.1 in N-control group. The factors that promote the height growth can always accelerate the bone maturity. After one year's supplementation, the height gain in +Zn group and +ZnCa group was significantly higher than that in other groups, but there was no difference in bone age gain among six groups, indicating that micronutrient supplementation could stimulate height growth, rather than accelerating bone maturity, so it would not affect the terminal height of children.

Many investigators reported that zinc and vitamin A supplementation could reduce the incidence of respiratory diseases in children[11, 12], while some demonstrated dose-reaction relationship between vitamin A level and incidence of respiratory diseases[13]. In our study, zinc could help reduce the frequency and length of skin diseases; vitamin A could prevent children from respiratory diseases. The total frequency and days of illness in four supplemental groups were less than those in the two control groups, showing that micronutrient supplementation could do good to the health of children. Few studies found relation of calcium supplementation with diseases, neither we found any significant effect of calcium on disease.

In summary, micronutrient supplementation can stimulate the height and weight growth in children aged 3-5 years who grow slower, and also reduce the incidence of diseases, but fails to accelerate the maturity of bone, indicating that micronutrient supplementation can do good to the growth of children whose intake of micronutrients are insufficient.

REFERENCES

1. Ge, Ke-You (1999). *The Dietary and Nutrition Status of Chinese Population—Children and Adolescence.* People's Medical Publishing House, BeiJing.
2. Zhu, Lian-Zhen (1994). *Trace Element in Human and Animal Nutrition.* Qingdao Publishing House.
3. Wen, Zhi-Mei and Chen, Jun-Shi (1998). *Present Knowledge on Nutrition.* People's Medical Publishing House, Beijing.
4. Buyukgebiz, A. and Bober, E. (1997). Vitamin A and beta carotene levels in constitutional delay of growth and puberty. *J. Pediatr. Endocrinol. Metab.* **10** (1), 51-54.
5. Institute of Nutrition and Food Hygiene. (1990) *Chinese Food Composition Tables*, People's Medical Publishing House, Beijing.
6. Bates, C.J. and Evans, P.H. (1993). A trial of zinc supplementation in young rural Gambian children. *Br. J. Nutr.* **69**, 243-255.
7. Meeks, G.J., Witter, M.M., and Ramdath, D.D. (1998). Zinc supplementation: effects on the growth and morbidity of undernourished Jamaican children. *Eur. J. Clin. Nutr.* **52**, 34-39.
8. Chen, Lie, and Chang, Ying (1994). Effect of vitamin A supplementation on the growth of children. *J. Hygiene Res.* **23**(1), 37-39. (in Chinese)
9. Lai, Xiao-Quan and Zhu, Qing-Hua (1994). Effect of vitamin A and β-carotene supplementation on the morbidity and growth of children. *J. Tongji Med. Uni.* **23**(6), 497-500. (in Chinese)
10. Martorell, R. (1990). Malnutrition, body size, and skeletal maturation: inter-relationship and implication for catch up growth. *Hum. Biol.* **51**, 371-389.
11. Rajiv Bahl (1998). Plasma zinc as a predictor of diarrhea and respiratory morbidity in children in an urban slum setting. *Am. J. Clin. Nutr.* (Suppl) **68**, 414s-417s.
12. Lira, P.I. and Ashworth, A. (1998). Effect of zinc supplementation on the morbidity, immune function, and growth of low-birth weight, full-term infants in northeast Brazil. *Am. J. Clin. Nutr.* **68** (Suppl), 418s-424s.
13. Kirkwood, B.R. and Ross, D.A. (1996). Effect of vitamin A supplementation on the growth of young children in northern Ghana. *Am. J. Clin. Nutr.* **63**, 773-781.

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