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

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The purpose of this study was to investigate the effects of micronutrient supplementation on the growth of preschool children in China. A double-blind, placebo-controlled trial was conducted on 156 growth retarded preschool children who were randomly assigned to the following 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, calcium and vitamin A supplementation (+ZnCaVA; 3.5mgZn + 250mgCa + 200gVA/day, n=28); and calcium and vitamin A supplementation (+CaVA; 250mgCa+200gVA/day, n=29). Another 34 children of normal height were selected as a normal control (N-control). Supplementation continued for twelve months. After supplementation, the height gains in the +Zn group (7.84cm per year) and the +ZnCa group (7.70 cm per year) were significantly higher than that in the S-control group (6.74 cm per year, $P<0.05$). The weight gain in the +ZnCaVA group (2.55Kg per year) and the +CaVA group (2.57 Kg per year) was also significantly higher than that in the S-control group (2.19 Kg per year, $P<0.05$). The average number of days of illness in each group taking supplements was lower than that in the S-control group (13 days per year compared with 23 days per year). No significant differences in bone maturity were observed between the groups. In conclusion, in this study Zinc and Zinc + Calcium supplementation improved the height gain, and vitamin A improved the weight gain, in growth retarded preschool children, but these supplements did not affect the maturity of bone. Micronutrient supplementation also lowered the morbidity of these children.

Key words : zinc, calcium, vitamin A, preschool children, growth

INTRODUCTION

Growth retardation of children remains a public health problem in developing countries. A study on the overall nutrient status of the population of China in 1992 showed that the incidence of growth retardation was more than 35.7% among 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 membranes.[2)] Calcium is the main structural material of the 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 of suffering from infectious diseases.[4)]

The effects of micronutrient supplementation on the growth of children has been evaluated by many investigators, but the results have not been consistent. In this study, a double blind, placebo-controlled micronutrient-intervention trial was performed on 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 their height, weight, days and times of illness, and bone maturity.

SUBJECTS AND METHODS

1. Subjects

There were 1885 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, and are referred to as "growth retarded" in this study. The selected subjects had lived in their local communities for at least 2 years, without any chronic or acute diseases. Children who had been absent from the kindergarten for a continuous period of more than 30 days were excluded from the study. A total of 156 children were finally recruited. Another 34 children of normal height were selected as a normal control. The sample size required for detecting

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a difference of 1.2cm height gain with 90% probability and a type I error of 5% by assuming a SD of 1.32cm was estimated to be 25 children per group. This study was approved by the Ethical Review Committee of the Chinese Academy of Preventive Medicine.

2. Study Design

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

3. Anthropometry and Dietary Intake

The measurements of height and weight were completed using identical machines and persons every time. Times and days of illness were obtained from parents. X-ray films were taken of the wrist in the Radiation Department of Luoyang Hospital (XG-200, Shanghai) and analyzed by a doctor from the Capital Children Institute of China, using the CHN scoring method; the scoring criterion of bone maturity for Chinese, and comparing the results with a standard reference value.

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

4. Statistical Methods

Data were inputted using Foxpro 5.0 software. The ANOVA, Kruskal-Wallisteat, and x2 tests were used to determine statistical differences among the groups.

RESULTS

1. Characteristics of subjects

The average age and birth weight, and male/female ratio, were similar for each group. The average height of subjects in the N-control group was higher than that of the other groups, but there were no significant differences between the other five groups. The average weight

Table 1. Micronutrient supplementation by group

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

Table 2. Baseline characteristics of children in the six groups

Group (n)	N-control (33)	S-control (27)	+Zn (34)	+ZnCa (37)	+ZnCaVA (26)	+CaVA (29)
Age($\bar{x}\pm$SD, 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 ($\bar{x}\pm$SD, 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 ($\bar{x}\pm$SD, 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 ($\bar{x}\pm$SD, 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]

Values are expressed as mean ±SD
a : compared with N-control group, P<0.05

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[1)] %	54.5	66.7	67.7	43.2	57.7	48.3
Others[2)] %	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 %[3)]	48.5	55.6	76.5	67.6	65.4	62.1
≥900 %[4)]	51.5	44.4	23.5	32.4	34.6	37.9
Average age of mother ($\bar{x}\pm$SD, 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 ($\bar{x}\pm$SD, 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

1) The parents worked in the Truck factory of LuoYang city
2) The parents didn't work in this factory
3) The percent of families whose income were less than 900 yuan /month
4) The percent of families whose income were more than 900 yuan/month

Table 4. Daily Intake of Nutrients during Three Different Periods of Time Compared with the Chinese RDA of 1988 RDA(%)

Time	Energy	Protein	Calcium	Iron	Zinc	Vitamin A	Vitamin B1	Vitamin B2	Vitamin E
Oct 1998	88.02± 25.42	86.18± 26.58	29.11± 14.52	94.34± 26.82	61.51± 18.02	51.33± 19.88	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 during Three Periods of Time

	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

in the N-control group was also significantly higher than that in the +ZnCaVA group and the +CaVA group, as shown in Table 2.

The children in each group had similar home backgrounds; there were no differences in the parents occupation, career level, age, educational level and family income per month, etc.(Table 3)

2. Dietary Intake

The subjects intakes of energy and protein in the three time periods measured during the study were not significantly different, and approximately met the Chinese recommended dietary allowance (RDA) of 1988 (Table 4). The intakes of iron, vitamin B1, B2, C, and E, etc approached or exceeded the Chinese RDA, although intakes of zinc, calcium and vitamin A were much lower, at only about 20%-30%, 60%-70% and 30%-50% of the RDA, respectively. Animal protein supplied 40%-50% of the dietary protein. Energy obtained from carbohydrate, fat and protein was 55%-61%, 23%-31% and

Table 6. The Average Height Gains of Children in Different Periods ($\bar{x}\pm SD$, 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-control	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^b	5.81±0.99	7.84±1.12^b
+ZnCa	2.04±1.09	3.80±1.58	5.75±1.52	7.70±1.63^b
+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

Value are expressed as mean ±SD
b : Compared with S-control group, P<0.05

Table 7. The average weight gain of children in different supplemental periods ($\bar{x}\pm SD$, 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^b	2.57±1.22^b
+CaVA	1.08±0.54	1.62±0.64^b	2.14±0.78^b	2.77±1.02^b

Value are expressed as mean ±SD
b : Compared with the S-control group, P<0.05

Table 8. The bone maturity of children in different groups

Group	Bone maturity delayed[1)] (years)	Bone maturity (years)		Bone maturity 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

1) Bone maturity delayed = bone maturity - chronological age

12%-15 respectively, more or less equivalent to the Chinese standard (Table 5).

3. Growth

Height : Differences were detected between the +Zn group and the S-control group after 6 months' supplementation; after 12 months, the height gains in the +Zn and +ZnCa groups were significantly higher than those in either of the S-control group (p<0.05) or the N-control group (P>0.05). Height gains after 12 months tended to be higher in all supplemental groups than those in the S-control group (P>0.05) (Table 6).

Weight : The data in Table 7 show a significantly higher average weight gain in the +ZnCaVA group and the +CaVA group than that in the S-control group (P<0.05) after 9 months, and also tended to be greater than that in the N-control group (p>0.05). These differences remained after 12 months supplementation.

Bone maturity : Bone maturity is more accurate than chronological age in reflecting the true maturation of a child, so it is called the maturity indicator. In this study, the bone maturity 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 classified according to respiratory, skin, diarrheal, and other diseases. Respiratory diseases occurred more frequently in the N-control group than in the +ZnCaVA group and the +CaVA group (P<0.05); children in the +Zn and +ZnCa groups had less skin disease with a shorter length than in the S-control group (P<0.05). The total episodes and days of illness in the four supplemental groups were fewer than in

Table 9. Episodes and days of illness in six groups during the supplemental period

Group	n	Number of 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]

Value are expressed as mean ±SD
a : Compared with the N-control group, P<0.05 b : Compared with the S-control group, P<0.05

the two control groups (p<0.05), as shown in Table 9.

DISCUSSION

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

The height gains of children in the +Zn (7.84cm per year) and +ZnCa groups (7.70cm per year) were significantly higher than those in the S-control group (P<0.05) and in the N-control group (p>0.05), indicating that zinc supplementation can play an important role in stimulating the height growth of growth-retarded children, possibly by stimulating the synthesis of protein and nucleic acid. Our results generally agreed with those of some investigators but differed in some details, probably because of different doses of supplementation used or the different basic zinc status of subjects.[6),7)]

During the supplementation period, children in the +CaVA group maintained the highest weight gain which was significantly higher than that in the S-control group (p<0.05). After 9 months, the weight gain in the +ZnCaVA group caught up with the +CaVA group was also significantly different from the S-control group at the end of trial (P<0.05), suggesting that vitamin A supplementation could improve the weight gain of children. This result is consistent with other studies.[8),9)]

Bone maturity is closely associated with the terminal height of a person. Martorell reported that bone development was delayed in children with growth retardation.[10)] In our study, growth-retarded children had lower bone maturity compared with their chronological ages (-0.5~ -0.8), whereas the delay in bone maturity was only -0.1 in the N-control group. The factors that promote growth in height can also accelerate bone maturity. After one years supplementation, the height gains in the +Zn and +ZnCa groups were significantly higher than those in other groups, but there were no significant differences in bone maturity gain among the 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 relationships between vitamin A levels and the incidences of respiratory diseases.[13)] In our study, zinc appeared to reduce the frequency and length of skin diseases, and vitamin A appeared to protect children from respiratory diseases. The total frequency and days of illness in the four supplemental groups were less than those in the two control groups, showing that micronutrient supplementation could improve the health of children. We found no significant effects of calcium supplementation on disease, and this is consistent with the fact that only very few previous studies have found any relation between calcium supplementation and diseases.

In summary, micronutrient supplementation as practiced in this study can stimulate the height and weight growth rates of growth-retarded children aged 3-5 years whose intakes of micronutrients are insufficient, and can also reduce the incidence of diseases.

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