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The effect of zinc supplementation on growth and development in preterm neonates

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Objective

This study aimed to show the effect of zinc supplementation on growth and development in preterm neonates in the first 6 months of life.

Background

Preterm infants have impaired zinc status because of low body stores as 60% of fetal zinc is acquired during the third trimester of pregnancy in addition to their limited capacity to absorb and retain micronutrients, coupled with increased endogenous losses associated with organ immaturity.

Patients and methods

The present study was carried out in the Department of Obstetrics in Nasr City Health Insurance Hospital on 80 healthy preterm infants between 32 and 36 weeks of age divided into two groups: a zinc-supplemented group fed with breast milk, and supplemented with multivitamins and zinc (2 mg/kg/day) since the first day of life, and a non-zinc-supplemented group fed breast milk with multivitamins only (without zinc supplementation). Both groups were followed for 6 months for growth with assessment of development by the Age and Stage Questionnaire at 4 and 6 months of corrected age and serum levels of zinc, alkaline phosphatase, and hemoglobin at corrected age of 3 and 6 months.

Results

The zinc-supplemented group showed a significant increase ($P < 0.001$) in both weight and length (figures and centiles) at chronological ages of 3 and 6 months and acquired higher head circumference centiles compared with the non-zinc-supplemented group.
There was a highly significant increase in the serum zinc levels of the zinc-supplemented group compared with the non-zinc-supplemented group, in addition to a significant positive correlation between zinc level and both weight and length at 3 and 6 months of age.
Also, the developmental score of the zinc-supplemented group was significantly higher ($P < 0.001$) than that of the non-zinc-supplemented group in all tested domains.

Conclusion

Zinc supplementation in the first 6 months of life was found to be an effective enhancer for both the growth and the development of preterm infants.

Keywords:
development, growth, preterm, zinc

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Introduction

Preterm infants are at an increased risk of death, acute and long-term morbidities often associated with nutritional compromise and impaired growth. With about 13 million preterm babies born each year worldwide, the burden is disproportionately concentrated in Africa and Asia, where about 85% of all preterm births occur (31 and 54%, respectively) [1].

Preterm infants are especially susceptible to zinc deficiency because of low body stores, limited capacity to absorb and retain micronutrients, coupled with increased endogenous losses associated with organ immaturity, high nutrient demand to support catch-up growth, and inadequate intakes because of exclusive breastfeeding [2].

Zinc is the most universal of all trace elements involved in human metabolism. It is required for the normal structure and function of zinc-containing enzymes involved in the production of growth hormones and in transcribing and translating DNA and therefore cell division [3].

Zinc plays an essential rule in neurodevelopment as zinc-dependent enzymes are involved in brain growth, zinc-finger proteins participate in brain structure and neurotransmission, zinc-dependent neurotransmitters are involved in brain memory function, and finally zinc is involved in the precursor production of neurotransmitters [4].

Patients and methods

The present study was carried out on 80 healthy preterm infants in Nasr City Health Insurance Hospital in the Obstetrics and Neonatal Departments between July

2012 and July 2013. Neonates included were followed for corrected age of 6 months and were divided into two groups: a zinc-supplemented group, which included 40 healthy exclusively breast-fed preterm neonates, gestational age (GA) 34.10 ± 1.24 weeks, weight 2188.9 ± 203 g, 25 (62.5%) males, 15 (37.5%) females, supplemented with multivitamins and zinc (2 mg/kg/day) from day 1 to corrected age of 6 months, and a non-zinc-supplemented group, which included 40 healthy exclusively breast-fed preterm neonates, GA 34.10 ± 1.24 weeks, weight 2186.3 ± 202.3 g, 25 (62.5%) males, 15 (37.5%) females, supplemented with multivitamins only (without zinc) for the same period.

Both groups fulfilled the same inclusion and exclusion criteria.

The inclusion criteria were as follows: GA between 32 and 36 weeks, birth weight (BW) between 1800 and 2500 g, appropriate for GA (BW between the 10th and the 90th percentile for GA), and in a stable clinical condition without any evidence of disease likely to influence growth and neurodevelopment.

The exclusion criteria were as follows: term neonates (>37 weeks of gestation), intrauterine growth restriction, congenital malformations, chromosomal abnormalities, suspected inborn errors of metabolism, multiple gestations, congenital heart disease, and perinatal asphyxia (APGAR < 3, longer than 5 min).

All candidates were subjected to a thorough medical examination, immediately after birth, and anthropometric measurements (weight, length, and occipitofrontal circumference) were recorded. Blood samples for capillary blood gas, basal serum hemoglobin (Hb), alkaline phosphatase (ALP), and zinc levels were withdrawn on the first day.

At 3 and 6 months of chronological age, anthropometric measurements (weight, length, and head circumference) for all infants were recorded again. Together with previous measurements, all were plotted on TNO (Netherlands Organization for Applied Scientific Research) preterm growth charts [5] to follow their growth on centiles.

At 3 and 6 months of corrected age, blood samples for zinc, Hb, and ALP were taken and all results were recorded for comparison.

At 4 and 6 months of corrected age, the Age and Stage Questionnaire (ASQ) was applied for all candidates' parents in Arabic to assess their developmental milestones for the following items: gross motor development, fine motor development, communication skills, problem solving, and personal social development. This involved detailed questions to the parents for previous aspects of development at 4 and 6 months of age of their infants after correction as postnatal age should be corrected for prematurity before application [i.e. corrected age = postnatal age in weeks-(40 weeks-GA)] [4].

Then, the results were recorded for assessment of the score of every aspect [6].

Approval

Oral informed consents were obtained from the parents of the preterm infants studied.

The ethics committee of the Faculty of Medicine, Menoufia University, approved the study.

Data management and statistical analysis

This phase included the following: coding of collected data and data entry into the computer and statistical analysis of the collected data. The collected data were entered into the computer using the statistical package for social sciences (SPSS; SPSS Inc., Chicago, Illinois, USA) program for statistical analysis. Two types of statistical analyses were carried out: descriptive statistics [e.g. number, %, mean (X), and SD] and analytical statistics (e.g. Student's t-test, Mann–Whitney test, χ^2-test, paired t-test, and Pearson's correlation coefficient). A P-value of less than 0.05 was considered statistically significant.

Results

The 80 healthy exclusively breast-fed preterm infants were divided equally into two groups: zinc supplemented and non-zinc-supplemented.

In the present study, on comparison between both groups for anthropometry, it was observed that the zinc-supplemented group had significantly higher ($P < 0.001$) weight and length at 3 and 6 months of chronological age and acquired higher head circumference centiles compared with the non-zinc-supplemented group, indicating a significant effect of zinc supplementation on the growth of preterm infants.

Also, the zinc-supplemented group had higher weight and length centiles at chronological ages of 3 and 6 months compared with the non-zinc-supplemented group.

Our study also found a highly significant increase in the serum zinc levels of the zinc-supplemented group compared with the non-zinc-supplemented group, in addition to a significant positive correlation between zinc level, and both weight and length at 3 and 6 months of age.

In the present study, on comparing both groups in terms of ALP, Hb, and serum zinc levels, it was found that the supplemented group acquired significantly higher levels compared with the other group at corrected ages of 3 and 6 months, respectively.

In terms of developmental milestones, on comparison between both groups using the ASQ, it was found that the developmental score of the zinc-supplemented group was significantly higher ($P < 0.001$) than that of the non-zinc-supplemented group in all tested domains (Tables 1–5).

Discussion

Zinc is a key component of the cell architecture and function in the organism. It is required for the production of over 200 enzymes, including phosphatases, metalloproteinases, oxidoreductases, and transferases, which are involved in protein synthesis, nucleic acid metabolism, and immune functions. In addition, it is a structural component of various proteins, hormones, and nucleotides [7].

The aim of our study was to assess the response of preterm infants after supplementation with zinc for 6 months of corrected age in terms of their growth parameters, developmental milestones, and serum levels of zinc, Hb, and ALP.

Our study found a significant effect of zinc ($P < 0.001$) on increasing body weight and length at 3 and 6 months of follow-up, but did not find a similar significant effect on head circumference.

This was in agreement with Friel *et al.* [8], who concluded that increased zinc intake in early infancy may be beneficial to preterm infants, and Aminul *et al.* [9], who reported that zinc supplementation in preterm infants led to greater weight gain and fewer problems such as infections, convulsions, and jaundice; there was no adverse effect in the zinc-supplemented group.

Also, Islam *et al.* [10] reported improved weight gain and linear growth and reduced incidence of diarrhea after zinc supplementation to 100 preterm infants and recommended its inclusion in child health survival programs in developing countries with a high incidence of preterm infants.

Others found no significant effect of zinc on linear growth such as Anjana *et al.* [11] and Mazariegos *et al.* [12].

In this study, there was a significant increase in the serum levels of ALP and Hb in response to increased serum zinc, indicating the essential role of zinc in bone growth and a protective role against anemia in infancy. This was in agreement with Díaz-Gómez *et al.* [13] and Hyun-Ju *et al.* [14].

In this study, we found that the developmental score of the zinc-supplemented group was significantly higher in all tested domains ($P < 0.001$) than the non-zinc-supplemented group using the ASQ at 4 and 6 months of corrected age [5].

This was in agreement with Friel *et al.* [8], who reported improved motor development in preterm infants randomized to term formula with zinc supplements up to 6 months post-term.

However, Pamela *et al.* [15] reported that zinc supplementation in preterm low BW infants did not lead to achievement of motor or language milestones.

This result may be explained by assuming that the studied infants may have had more severe micronutrient deficiencies and protein-energy malnutrition than most other populations studied. Thus, other deficiencies may

Table 1 Comparison between the studied groups in their anthropometry (weight, length, and head circumference)

Variables	Mean ± SD		Test of significance	*P* value
	Zinc supplemented	Non-zinc-supplemented		
Weight (day 1) (g)	2188.9 ± 203.0	2186.3 ± 202.3	0.06	0.95
Weight (3 months) (g)	4849.9 ± 369.3	4542.4 ± 369.4	3.72	<0.001
Weight (6 months) (g)	7015.8 ± 432.6	6665.3 ± 438.2	3.60	0.001
Length (day 1) (cm)	44.5 ± 2.8	45.1 ± 1.4	1.21	0.23
Length (3 months) (cm)	55.9 ± 1.5	53.4 ± 2.5	5.53	<0.001
Length (6 months) (cm)	64.8 ± 1.3	61.6 ± 1.4	10.64	<0.001
Head circumference (day 1) (cm)	31.7 ± 0.8	31.6 ± 0.9	0.24	0.81
Head circumference (3 months) (cm)	39.1 ± 0.8	38.9 ± 0.7	0.72	0.47
Head circumference (6 months) (cm)	42.7 ± 0.9	42.6 ± 0.9	0.39	0.69

Table 2 Comparison between the studied groups in their serum zinc, hemoglobin, and alkaline phosphatase levels

Variables	Mean ± SD		Test of significance	*P* value
	Zinc supplemented	Non-zinc-supplemented		
Zinc (day 1) (μg/dl)	48.3 ± 7.5	49.4 ± 7.4	0.91	0.37
Zinc (3 months) (μg/dl)	91.5 ± 9.9	68.9 ± 8.9	10.63	<0.001
Zinc (6 months) (μg/dl)	117.0 ± 8.9	83.9 ± 10.2	15.47	<0.001
Hb (day 1) (mg/dl)	17.4 ± 1.5	17.0 ± 1.3	1.21	0.23
Hb (3 months) (mg/dl)	11.7 ± 0.8	10.7 ± 0.8	5.61	<0.001
Hb (6 months) (mg/dl)	14.2 ± 0.9	12.9 ± 1.0	5.97	<0.001
ALP (day 1) (U/l)	68.4 ± 19.1	62.8 ± 12.1	1.59	0.12
ALP (3 months) (U/l)	148.4 ± 30.0	103.1 ± 16.3	8.39*	<0.001
ALP (6 months) (U/l)	273.1 ± 33.9	167.1 ± 31.9	14.38	<0.001

ALP, alkaline phosphatase; Hb, hemoglobin.

Table 3 Comparison between the studied groups in their developmental milestones at corrected ages of 4 and 6 months according to Age and Stage Questionnaire

Variables	Zinc-supplemented	Non-zinc-supplemented	Test of significance	*P* value
Communication (4 months)	53.25 ± 6.16	44.50 ± 5.97	6.45	<0.001
Gross motor (4 months)	54.13 ± 5.05	44.88 ± 5.72	7.67	<0.001
Fine motor (4 months)	52.38 ± 6.98	41.00 ± 6.43	7.58	<0.001
Problem solving (4 months)	51.63 ± 5.71	42.38 ± 6.40	6.82	<0.001
Personal social (4 months)	52.38 ± 4.67	42.00 ± 5.97	8.66	<0.001
Communication (6 months)	53.00 ± 5.16	41.75 ± 5.83	9.13	<0.001
Gross motor (6 months)	48.63 ± 6.89	38.38 ± 7.46	6.13	<0.001
Fine motor (6 months)	48.00 ± 6.68	38.38 ± 7.46	6.08	<0.001
Problem solving (6 months)	50.25 ± 6.69	40.00 ± 6.60	6.89	<0.001
Personal social (6 months)	51.88 ± 6.06	41.13 ± 8.43	6.55	<0.001

Table 4 Comparison between the studied groups in their anthropometry (centiles)

Variables	Zinc-supplemented (*N* = 40)	Non-zinc-supplemented (*N* = 40)	Test of significance (*t*)	*P* value
Weight (day 1) (g)	46.3 ± 18.1	46.8 ± 18.9	0.15[a]	0.88
Weight (3 months) (g)	47.4 ± 19.9	35.1 ± 17.8	3.26	0.001*
Weight (6 months) (g)	47.6 ± 18.8	35.0 ± 15.6	3.79	<0.001*
Length (day 1) (cm)	48.4 ± 20.6	48.6 ± 20.3	0.11[a]	0.91
Length (3 months) (cm)	43.9 ± 22.4	34.3 ± 9.6	2.49	0.02*
Length (6 months) (cm)	49.5 ± 18.1	34.6 ± 12.3	4.86	<0.001*
Head circumference (day 1) (cm)	50.8 ± 17.7	49.3 ± 18.1	0.51[a]	0.61
Head circumference (3 months) (cm)	48.1 ± 19.1	42.3 ± 19.2	2.35[a]	0.02*
Head circumference (6 months) (cm)	50.3 ± 19.7	45.1 ± 18.3	2.34[a]	0.02*

[a]Mann–Whitney *U*-test; $P > 0.05$, not significant; $P < 0.05$, significant; $P < 0.001$, highly significant.

Table 5 Correlation between zinc level at day 1, 3, and 6 months with anthropometric measures

Parameters	*R*	*P*-value
Weight		
Day 1	−0.16	0.17
3 months	0.26	0.02*
6 months	0.29	0.009*
Length		
Day 1	−0.22	0.06
3 months	0.35	0.001*
6 months	0.64	<0.001*
Head circumference		
Day 1	−0.16	0.15
3 months	0.02	0.87
6 months	0.02	0.86

R, Pearson's correlation; $P > 0.05$, not significant; $P < 0.05$, significant; $P < 0.001$, highly significant.

have been so severe that any actual benefit of zinc supplementation did not manifest.

Conclusion

Our study concluded that zinc supplementation in preterm infants enhances their linear growth and confers some protection against the expected decrease in Hb.

Also, zinc is essential for maturation of the central nervous system, which was indicated by a significant increase in the achievement of developmental milestones in preterm infants during the first 6 months of life.

Acknowledgements
Conflicts of interest
There are no conflicts of interests.

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