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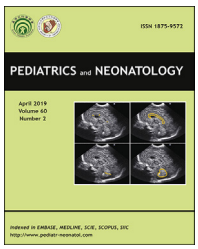

Original Article

Effects of oral zinc supplementation on zinc status and catch-up growth during the first 2 years of life in children with non-organic failure to thrive born preterm and at term

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Key Words
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Abstract *Background:* We aimed to analyze the effect of oral zinc supplementation on serum insulin-like growth factor-1 (IGF-1) levels and catch-up growth in infants with non-organic failure to thrive (NOFTT) who were born preterm as compared to those born at term.
Methods: Totally, 105 NOFTT infants aged 2 years or less were enrolled and divided into two groups according to gestational age at birth. Oral zinc sulfate was administered for 6 months to 49/66 children born at term, and 21/39 children born preterm. Serum zinc, IGF-1, weight, and height were measured at baseline and at 6 months.
Results: There were no differences in baseline serum zinc levels between the two groups. In preterm NOFTT infants, zinc supplementation significantly increased serum zinc levels compared to those in the non-supplementation group (Δ zinc $_{0-6\ month}$ 10.3 ± 26.4 μg/dL *vs.* -8.8 ± 23.7 μg/dL, $p = 0.018$), but it did not significantly change serum IGF-1 levels or weight- and height for age Z-scores. In NOFTT infants born at term who received zinc supplementation, serum zinc levels, IGF-1, weight for age Z-score, and height for age Z-score increased at 6 months ($p = 0.001$, $p = 0.014$, $p = 0.049$, and $p = 0.029$, respectively), but this increase was not significantly greater than in the non-supplementation group. Only the increase in serum zinc levels was significant after 6 months (Δ zinc $_{0-6\ month}$ 16.8 ± 32.0 μg/dL *vs.* -10.0 ± 22.6 μg/dL, $p = 0.002$).
Conclusion: Zinc supplementation in NOFTT infants improves serum zinc status, regardless of gestational age at birth. Zinc supplementation in NOFTT infants born at term may improve serum IGF-1 levels and growth, but it does not in NOFTT infants born preterm. Overall nutritional support rather than supplementation of a single nutrient may be more effective for catch-up growth in NOFTT infants born preterm.

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1. Introduction

Failure to thrive (FTT) is defined as an inadequate growth rate in early childhood as compared with the norm for children of the same age and sex (weight and/or height below the 5th percentile).[1] Prolonged, severe malnutrition or under nutrition of children with FTT negatively affects future growth and cognitive development. It is mainly related to non-organic causes, and underlying organic diseases are found in only about 10% of children with FTT.[2]

During the third trimester of pregnancy, accretion of protein, glycogen, fat-soluble vitamins, minerals, and trace elements occurs.[3,4] Preterm infants experience significant energy and nutrient deficit due to inadequate nutritional intake along with comorbid disease, incomplete digestion and absorption in the immature gastrointestinal tract, and limited reserves of trace elements. Consequently, FTT in early childhood and nutritional deficits are very common in preterm infants.[5]

Zinc, an essential nutrient, is an important cofactor of many enzymes regulating cell growth and hormone levels. Its deficiency is associated with growth retardation, reduced appetite, delayed wound healing, and immune dysfunction.[6] Several studies in children with FTT reported positive effects of zinc supplementation on weight gain and/or linear growth.[7,8] Similarly, improved weight gain and linear growth was noted after zinc supplementation in short children with mild to moderate zinc deficiency.[9] Decreased growth of children with NOFTT might therefore be partly attributable to zinc deficiency. It is hypothesized that zinc deficiency may start in infancy, and inadequate provision of zinc is one of the factors contributing to NOFTT.[10] The growth-enhancing action of zinc supplementation is likely mediated by insulin-like growth factor (IGF)-1. In a previous study, induced zinc deficiency in rats resulted in reduced circulating IGF-1 levels and decreased IGF-1 gene expression in the liver.[11]

However, to date, few have studied the influence of oral zinc supplementation in children with FTT; and no study has reported the effect of zinc supplementation on growth and serum IGF-1 levels in growth-retarded children born preterm. Therefore, we aimed to analyze the effect of oral zinc supplementation on serum IGF-1 and catch-up growth in children with NOFTT born preterm compared to that in those born at term.

2. Methods

2.1. Subjects

We enrolled 105 children with NOFTT aged ≤24 months (range: 1.2–24 months). Participants were identified from among those who visited the nutrition clinic for children at the Seoul National University Bundang Hospital between January 2012 and July 2015 for poor weight gain. Children with underlying organic causes of FTT or children on multivitamin and mineral supplementation within the previous 3 months were excluded. Children with acute weight loss or poor appetite secondary to acute illness were also excluded.

FTT was defined as a decrease in body weight and/or height beneath the fifth percentile, or a decrease across two percentile curves on standardized Korean national growth charts for at least 3 months.[12] NOFTT was defined in cases of FTT without an organic condition associated with growth retardation.

The subjects were divided into two groups according to gestational age at birth: children born preterm (n = 39), and children born at term (n = 66). Preterm birth was defined as the delivery of an infant before 37 weeks of gestation. The study subjects were further divided into two subgroups according to the presence of oral zinc supplementation.

2.2. Anthropometric and laboratory measurements

Demographic, parental socioeconomic, and clinical data were retrospectively reviewed in all recruited subjects. Paternal and maternal education were retrospectively reviewed, based on the self-reported completed educational level. Paternal occupation was classified in 3 categories: professional/service, agricultural/manual, and not working. Serum zinc, IGF-1 level, weight, and height were assessed in all subjects, regardless of zinc supplementation, at baseline and 6 months.

Anthropometric measurements were performed in all subjects at baseline and 6 months. Height was measured to the nearest 1.0 mm in a supine or standing position according to age; body weight was measured using a calibrated digital scale to the nearest 0.1 kg. The Z-score of weight for age and the Z-score of height for age were calculated from Korea National Center for Health Statistics reference data.

Laboratory tests were performed on all subjects at baseline and at 6 months, including serum zinc and serum IGF-1 levels. To measure serum zinc concentrations, trace element tubes were used, and levels were determined by inductively coupled plasma mass spectrometry (ICP-MS; Agilent Technologies, Santa Clara, California, USA). The normal reference range of serum zinc was 70–150 μg/dL, and serum zinc level <70 μg/dL was defined as zinc deficiency. Serum IGF-1 levels were quantified using an immunoradiometric assay with commercially available kits (Immunotech, Marseille, France).

2.3. Zinc supplementation

The zinc-supplementation group (n = 70) received 5 mg of elemental zinc per day, whereas the non-

supplementation group (n = 35) received none. Oral zinc sulfate 22 mg (5 mg elemental zinc) was administered for 6 months to 49 of 66 children born at term and 21 of 39 born preterm.

2.4. Statistics

The results were analyzed using the PASW Statistics for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation for quantitative continuous variables. Student's *t*-test of two independent samples was used to compare two continuous variables because the data in each group showed normal distribution. *Chi*-square tests were performed to compare categorical variables. Paired *t*-test was used to assess and compare the effect of oral zinc supplementation on serum zinc, IGF-1 level, and growth (height and weight) between baseline and at 6 months. Student's *t*-test was applied to evaluate the differences in the change in serum zinc and IGF-1 levels and growth between the zinc-supplementation group and the non-supplementation group. *P*-values <0.05 were considered significant.

2.5. Ethics

The study was conducted with the approval of the Institutional Review Board of Seoul National University Bundang Hospital (B-1606-349-104). Informed consent was waived by the Institutional Review Board.

3. Results

3.1. Patient characteristics

Totally, 105 young children aged ≤24 months and diagnosed with NOFTT (55 boys and 50 girls, mean age 12.0 ± 6.9 months) were included during the study period. Table 1 shows baseline demographic and anthropometric data of the study participants. There were no differences between NOFTT children born preterm and those born at term in regard to age, gender, baseline serum zinc levels, and baseline height Z-scores (Table 1). Gestational age, birth weight, and weight, height, weight Z-scores at baseline were significantly lower in preterm NOFTT infants than in term NOFTT infants (Table 1). The average baseline serum IGF-1 level was significantly higher in preterm NOFTT infants than in term NOFTT infants (83.9 ± 56.5 ng/mL vs. 45.6 ± 24.4 ng/mL, $p = 0.002$) (Table 1). Parental socioeconomic status based on paternal education, occupation, and maternal education was not significantly different between zinc-supplemented and non-supplemented groups of NOFTT children born preterm and term (Tables 2 and 3). Baseline serum zinc levels were significantly different between zinc-supplemented and non-supplemented groups of NOFTT children born preterm and term ($p = 0.001$, and $p < 0.001$, respectively) (Tables 2 and 3).

3.2. Changes in zinc and growth status in NOFTT children born preterm according to zinc supplementation

Oral zinc sulfate was administered to 21 of the 39 NOFTT children born preterm. The changes in serum zinc levels, IGF-1 levels, weight Z-scores, and height Z-scores during the 6-month follow-up period, with or without oral zinc supplementation, in infants born preterm are shown and compared in Table 4.

In the zinc-supplementation group, there were no significant changes in serum zinc levels, IGF-1 levels, weight for age Z-scores, and height for age Z-scores after 6 months (Table 4). In the non-supplementation group of NOFTT children born preterm, there were no significant changes in serum zinc level or serum IGF-1 level, but there were significant changes in weight for age Z-scores and height for age Z-scores after 6 months ($p = 0.022$ and $p = 0.047$, respectively) (Table 4).

In NOFTT infants born preterm, the increase in serum zinc levels was higher in the zinc-supplementation group after 6 months of oral zinc supplementation than in the non-supplementation group (Δ zinc $_{0-6\ month}$

Table 1 Baseline demographic and anthropometric data of NOFTT infants according to gestational age at birth.

Variables	Preterm NOFTT (n = 39)	Term NOFTT (n = 66)	*p* value
Age (months, corrected age) at first visit	10.8 ± 7.2 (1.2–24)	12.0 ± 6.0 (1.2–24)	0.071
Sex (male) (n, %)	23 (58)	32 (48)	0.201
Gestational age (wks) at birth	32.4 ± 4.1	39.1 ± 0.9	**<0.001**
Birth weight (kg)	1.4 ± 0.6	2.8 ± 0.4	**<0.001**
Serum zinc level at baseline (μg/dL)	89.5 ± 5.2	81.4 ± 18.7	0.064
Zinc deficiency (n, %)	9 (23)	20 (30)	0.285
Serum IGF-1 level at baseline (ng/mL)	83.9 ± 56.5	45.6 ± 24.4	**0.002**
Weight at baseline (kg)	7.0 ± 2.0	7.8 ± 1.7	**0.032**
Height at baseline (cm)	68.2 ± 10.4	71.9 ± 8.3	**0.045**
Weight for age z-scores at baseline	−2.58 ± 1.35	−1.84 ± 0.80	**0.010**
Height for age z-scores at baseline	−1.89 ± 1.42	−1.35 ± 1.05	0.119

Data are presented as mean ± standard deviation or numbers (%).
NOFTT, non-organic failure to thrive; IGF, insulin-like growth factor.
Bold values emphasize the statistically significant *p* value < 0.05.

Table 2 Baseline demographic and anthropometric data of NOFTT infants born preterm, according to oral zinc supplementation.

Variables	Zinc supplemented group (n = 21)	Non-supplemented group (n = 18)	*p* value
Age (months, corrected age) at first visit	11.8 ± 7.2 (1.2–24)	9.6 ± 8.4 (1–24)	0.156
Sex (male) (n, %)	15 (71.4)	8 (44.4)	0.088
Gestational age (wks) at birth	31.5 ± 4.7	33.3 ± 3.2	0.331
Birth weight (kg)	1.3 ± 0.6	1.6 ± 0.6	0.102
Maternal education (n, %)*			0.560
Completed university or higher	12 (80)	12 (85.7)	
Completed high school	3 (20)	2 (14.3)	
Incomplete secondary	0	0	
Paternal education (n, %)*			0.175
Completed university or higher	12 (80)	13 (92)	
Completed high school	3 (20)	1 (8)	
Incomplete secondary	0	0	
Parental occupation (n, %)*			
Professional, service occupation	15 (100)	14 (100)	
Agricultural, manual labor	0	0	
Not working	0	0	
Serum zinc level at baseline (μg/dL)	78.0 ± 17.8	102.8 ± 26.4	**0.001**
Zinc deficiency (n, %)	9 (42.9)	0 (0)	**0.002**
Serum IGF-1 level at baseline (ng/mL)	104.5 ± 67.4	57.1 ± 41.5	0.069
Weight at baseline (kg)	7.5 ± 2.1	6.4 ± 1.9	0.078
Height at baseline (cm)	70.5 ± 9.7	65.4 ± 10.8	0.063
Weight for age z-scores at baseline	−2.14 ± 1.13	−2.33 ± 1.35	0.535
Height for age z-scores at baseline	−1.38 ± 1.26	−1.80 ± 1.57	0.526

Data are presented as mean ± standard deviation or numbers (%).
NOFTT, non-organic failure to thrive; IGF, insulin-like growth factor.
*Data were only available for 15 of 21 zinc-supplemented and 14 of 18 non-supplemented cases.
Bold values emphasize the statistically significant *p* value < 0.05.

10.3 ± 26.4 μg/dL *vs.* −8.8 ± 23.7 μg/dL, $p = 0.018$) (Table 4). However, the gains in weight Z-scores and height Z-scores, as well as changes in serum IGF-1 levels, were not significantly different between the zinc-supplementation group and the non-supplementation group in NOFTT children born preterm (Table 4).

3.3. Changes in zinc and growth status in NOFTT children born at term according to zinc supplementation

Oral zinc sulfate was supplied to 49 of the 66 NOFTT children born at term. The changes in serum zinc levels, IGF-1 levels, weight Z-scores, and height Z-scores during the 6-month follow-up period, with or without oral zinc supplementation, in infants born at term are listed and compared in Table 5.

In the zinc-supplementation group, serum zinc levels, IGF-1 levels, weight for age Z-score, and height for age Z-score significantly increased after 6 months of oral zinc supplementation ($p = 0.001$, $p = 0.014$, $p = 0.049$, and $p = 0.029$, respectively) (Table 5). Changes in serum zinc levels of the zinc-supplementation group during the 6-month period were significantly different from those of the non-supplementation group (Δ zinc $_{0-6\ \text{month}}$ 16.8 ± 32.0 μg/dL *vs.* −10.0 ± 22.6 μg/dL, $p = 0.002$) (Table 5). However, no significant differences were observed between the two groups regarding the changes in serum IGF-1 level, weight for age Z-scores, and height for age Z-scores (Table 5).

4. Discussion

Adequate nutrition during first 2 years of life in FTT infants is essential to promote catch-up growth and neurodevelopment. If catch-up growth does not take place early in life, the likelihood that it will occur later in life is low.[13,14] In infants, this critical period includes the first year of life with respect to development of head circumference, and the first 3 years of life with respect to final height.[15,16] During this period, the rapidly developing brain is particularly vulnerable to nutrient deficiency.[17] Therefore, nutritional management of FTT includes the provision of adequate energy, and protein, as well as specific micronutrient supplementation including iron, zinc, and other vitamins or trace elements depending on the deficiency status. Especially in preterm infants, FTT in early childhood and nutritional deficits are very common. Preterm infants with weight or length below the 10th percentile of the reference curve at post-conceptional age 35–36 weeks are at high-risk for long-term growth impairment, neurodevelopmental abnormality, and behavior problems.[18,19] Therefore, early "aggressive" nutrition providing a diet high in energy, and protein, as well as

Table 3 Baseline demographic and anthropometric data of NOFTT infants born at term, according to oral zinc supplementation.

Variables	Zinc supplemented group (n = 49)	Non-supplemented group (n = 17)	*p* value
Age (months, corrected age) at first visit	13.9 ± 6.3 (1–24)	10.9 ± 6.1 (1–21.6)	0.104
Sex (male) (n, %)	25 (51)	7 (41.2)	0.484
Gestational age (wks) at birth	39.2 ± 0.9	39.1 ± 1.0	0.942
Birth weight (kg)	2.9 ± 0.4	2.8 ± 0.3	0.901
Maternal education (n, %)*			0.774
Completed university or higher	33 (80)	11 (78.5)	
Completed high school	8 (20)	3 (21.5)	
Incomplete secondary	0	0	
Paternal education (n, %)*			0.885
Completed university or higher	34 (83)	12 (85.7)	
Completed high school	7 (17)	2 (14.3)	
Incomplete secondary	0	0	
Parental occupation (n, %)*			
Professional, service occupation	41 (100)	14 (100)	
Agricultural, manual labor	0	0	
Not working	0	0	
Serum zinc level at baseline (μg/dL)	77.4 ± 18.4	92.7 ± 25.2	**<0.001**
Zinc deficiency (n, %)	19 (38.8)	1 (5.9)	**0.011**
Serum IGF-1 level at baseline (ng/mL)	47.1 ± 24.7	37.7 ± 20.2	0.433
Weight at baseline (kg)	8.0 ± 1.7	7.3 ± 1.7	0.170
Height at baseline (cm)	72.8 ± 8.1	69.4 ± 8.7	0.085
Weight for age z-scores at baseline	−1.86 ± 0.85	−1.87 ± 0.55	0.676
Height for age z-scores at baseline	−1.35 ± 0.99	−1.58 ± 1.04	0.233

Data are presented as mean ± standard deviation or numbers (%).
NOFTT, non-organic failure to thrive; IGF, insulin-like growth factor.
*Data were only available for 41 of 49 zinc-supplemented and 14 of 17 non-supplemented cases.
Bold values emphasize the statistically significant *p* value < 0.05.

Table 4 Changes in serum zinc levels, IGF-1 levels, weight Z-scores, and height Z-scores during the 6-month follow-up period in NOFTT infants born preterm.

Variables	Zinc supplemented preterm group (n = 21)			Non-supplemented preterm group (n = 18)			*p* value†
	Baseline	6 months	*p* value*	Baseline	6 months	*p* value*	
Serum zinc (μg/dL)	78.0 ± 17.8	88.4 ± 27.6	0.068	102.8 ± 26.4	94.0 ± 20.6	0.134	
Δ zinc $_{0-6\ month}$	10.3 ± 26.4			−8.8 ± 23.7			**0.018**
Serum IGF-1 level (ng/mL)	104.5 ± 67.4	97.9 ± 70.5	0.643	57.1 ± 41.5	75.9 ± 61.0	0.121	
Δ IGF-1 $_{0-6\ month}$	−6.5 ± 47.5			18.8 ± 34.8			0.176
Weight (kg)	7.5 ± 2.1	9.1 ± 1.3	**<0.001**	6.4 ± 1.9	8.0 ± 1.6	**<0.001**	
Δ weight $_{0-6\ month}$	1.6 ± 1.3			1.7 ± 0.6			0.068
Height (cm)	70.5 ± 9.7	78.2 ± 7.2	**<0.001**	65.4 ± 10.8	72.9 ± 7.7	**<0.001**	
Δ height $_{0-6\ month}$	7.6 ± 3.7			8.5 ± 3.8			0.475
Weight for age Z-scores	−2.14 ± 1.13	−1.75 ± 1.16	0.229	−2.33 ± 1.35	−1.94 ± 1.22	**0.022**	
Δ weight Z-score $_{0-6\ month}$	0.39 ± 1.45			0.39 ± 0.63			0.997
Height for age Z-scores	−1.38 ± 1.26	−1.07 ± 1.00	0.071	−1.80 ± 1.57	−1.34 ± 1.29	**0.047**	
Δ height Z-score $_{0-6\ month}$	0.30 ± 0.74			0.530.95			0.411

Data are presented as mean ± standard deviations.
* *p* value; Each of the 6 months values as compared to the baseline measurement, *p*-value calculated by paired *t*-test.
† *p* value; Each of the Δ values of zinc supplemented group as compared to those of non-supplemented group, *p*-value calculated by *t*-test.
Δ; change in serum zinc levels, IGF-1 levels, weight, height, weight for age Z-scores, and height for age Z-scores during the 6-month follow-up period.
NOFTT, non-organic failure to thrive; IGF-1, insulin-like growth factor-1.
Bold values emphasize the statistically significant *p* value < 0.05.

Table 5 Changes in serum zinc levels, IGF-1 levels, weight Z-scores, and height Z-scores during the 6-month follow-up period in NOFTT infants born at term.

Variables	Zinc supplemented term group (n = 49)			Non-supplemented term group (n = 17)			p value†
	Baseline	6 months	p value*	Baseline	6 months	p value*	
Serum zinc (μg/dL)	77.4 ± 18.4	94.2 ± 28.2	**0.001**	92.7 ± 25.2	82.7 ± 10.8	0.075	
Δ zinc $_{0-6\ month}$	16.8 ± 32.0			−10.0 ± 21.6			**0.002**
Serum IGF-1 level (ng/mL)	47.1 ± 24.7	64.5 ± 42.9	**0.014**	37.7 ± 20.2	48.2 ± 17.1	0.108	
Δ IGF-1 $_{0-6\ month}$	17.4 ± 40.3			2.8 ± 32.5			0.301
Weight (kg)	8.0 ± 1.7	9.3 ± 1.5	**<0.001**	7.3 ± 1.7	8.6 ± 1.1	**<0.001**	
Δ weight $_{0-6\ month}$	1.3 ± 0.9			1.5 ± 1.2			0.435
Height (cm)	72.8 ± 8.1	79.4 ± 6.5	**<0.001**	69.4 ± 8.7	75.3 ± 5.4	**<0.001**	
Δ height $_{0-6\ month}$	6.6 ± 3.1			7.1 ± 2.7			0.564
Weight for age Z-scores	−1.86 ± 0.85	−1.59 ± 1.12	**0.049**	−1.87 ± 0.55	−1.30 ± 0.96	**0.014**	
Δ weight Z-score $_{0-6\ month}$	0.27 ± 0.92			0.57 ± 0.82			0.253
Height for age Z-scores	−1.35 ± 0.99	−1.07 ± 1.05	**0.029**	−1.58 ± 1.04	−1.29 ± 0.88	0.241	
Δ height Z-score $_{0-6\ month}$	0.28 ± 0.86			0.28 ± 0.92			0.99

Data are presented as mean ± standard deviations.
*p value; Each of the 6 months values as compared to the baseline measurement, p-value calculated by paired t-test.
†p value; Each of the Δ values of zinc supplemented group as compared to those of non-supplemented group, p-value calculated by t-test.
Δ; change in serum zinc levels, IGF-1 levels, weight, height, weight for age Z-scores, and height for age Z-scores during the 6-month follow-up period.
NOFTT, non-organic failure to thrive; IGF-1, insulin-like growth factor-1.
Bold values emphasize the statistically significant p value < 0.05.

micronutrient supplementation to promote early catch-up growth are encouraged in preterm infants, especially very low birth weight infants.[20,21]

This study evaluated the effect of oral zinc supplementation over a 6-month period on serum zinc levels, serum IGF-1 levels, and catch-up growth in NOFTT children aged ≤24 months born preterm as compared to that in those born at term. Our results revealed that oral zinc supplementation of 5 mg of elemental zinc for 6 months in young children with NOFTT born preterm might improve serum zinc status, revealing a significant difference in changes of serum zinc levels compared to those without supplementation, but it had no significant effects on serum IGF-1 levels, weight or height gains over a 6 month follow-up period. Furthermore, significant gains in weight Z-scores and height Z-scores were found even in children with NOFTT born preterm who did not receive zinc supplementation. As for zinc supplementation in children with NOFTT born at term, we found a significant improvement in serum zinc status and an increase in serum IGF-1 levels, as well as weight and height gains. With respect to growth, these weight and height gains were not significantly different from those in patients who did not receive zinc supplementation. The change in the serum zinc level was the only significant difference observed as a result of zinc supplementation in children with NOFTT born at term.

Zinc is an essential trace element that involves in metabolic pathways through its catalytic, structural, and biochemical functions. Thus, zinc is necessary for growth, immunity, tissue repair, neuropsychological functions, and hormone actions.[22] Growth retardation is one of the clinical features related to zinc deficiency. The primary regulator of growth is the growth hormone (GH)-insulin-like growth factor 1 (IGF-1) system.[23] Animal studies have demonstrated that zinc deficiency decreased expression of IGF-1 and GH receptor genes in the liver of growing rats.[11] Previous studies reported that zinc supplementation increased plasma IGF-1 levels in short children with or without zinc deficiency[24,25] and that zinc supplementation increased growth and circulating IGF-1 level in growth-retarded children.[8] However, the mechanism by which zinc supplementation affects GH secretion and IGF-1 levels is not well understood.

In our study, zinc supplementation was associated with an increase in serum zinc levels in NOFTT infants born at term, and it had a positive effect on both serum IGF-1 levels and growth, as reported previously.[8,9,24,25] Additionally, in the present study, zinc supplementation in NOFTT infants born preterm was, to some extent, effective in maintaining serum zinc status. However, zinc supplementation itself had no significant effect on serum IGF-1 levels, linear growth, or weight gain in this group. Although a positive effect on growth and serum IGF-1 was not apparent in the preterm group, the results from our cohorts that included growth-retarded children born preterm might be meaningful in practice, as there are no previous reports on the effect of zinc supplementation on serum zinc and serum IGF-1 levels simultaneously in addition to growth effects in NOFTT children born preterm.

IGF-1 concentration is age-dependent, with a prominent early postnatal increase, followed by a decrease between 2 and 6 weeks of age,[26,27] a typical pubertal peak for girls and boys, and a pronounced decline after puberty.[28] Moreover, IGF-1 is influenced by gestational age at birth. During the first year, preterm infants had higher IGF-1 levels than term infants at 2 through 12 months.[29] Our finding of a higher

baseline IGF-1 level in preterm NOFTT children compared to term NOFTT infants was consistent with these reports. Previous studies reported that plasma IGF-1 was lower in intrauterine growth-retarded infants,[30] children with constitutionally delayed growth,[31] and growth retarded children with protein energy malnutrition.[32] In our study, IGF-1 level at baseline was not significantly different between zinc-supplemented and non-supplemented groups of NOFTT children born preterm and term (104.5 ± 67.4 ng/mL vs. 57.1 ± 41.5 ng/mL, $p = 0.069$, and 47.1 ± 2 4.7 ng/mL vs. 37.7 ± 20.2 ng/mL, $p = 0.433$). However, our cohort included small for gestational age infants, with intrauterine growth retardation or protein-energy malnutrition, and without an age-matched study group, which made it difficult to elucidate the effect of zinc supplementation on IGF-1 level in NOFTT children born preterm and term.

Regarding the duration of oral zinc supplementation for growth-retarded children, zinc supplementation over a 6-month period as adapted in our study has been previously shown to have positive effects on weight gain in children with FTT.[7,8] Weight and height gains, along with increased plasma IGF-1 levels, were noted in growth-retarded children over a 5-month period of oral zinc supplementation.[8] In contrast, zinc supplementation for 3 months had no effect on weight or height gain in infants with NOFTT, although there was an increase in serum IGF-1 levels.[33] Considering oral zinc supplementation in preterm infants, one previous study reported that zinc supplementation from 36 weeks post-conceptional age until 6 months corrected postnatal age had a positive effect on linear growth.[34] However, to date, there are limited studies addressing the duration of oral zinc supplementation for catch-up growth, especially in children with NOFTT born preterm.

In regard to the amount of oral zinc to give as a supplement to children born at term, oral zinc supplementation varying from 5.7 mg to 10 mg of elemental zinc per day was sufficient to demonstrate improvement in zinc status, IGF-level, and growth in children with NOFTT or mild to moderate zinc deficiency.[7–9] Regarding the amount of oral zinc to give as a supplement to children born preterm, two studies reported positive effects of zinc supplementation immediately after birth on serum zinc status and linear growth with a dose of oral elemental zinc varying between 3 mg and 10 mg per day.[34,35] However, these studies evaluated the effects of zinc supplementation in preterm infants regardless of FTT and the primary outcomes evaluated focused on growth. Serum zinc, IGF-1, and IGFBP3 levels were not measured in these studies.

In our study, the duration and the amount of oral zinc supplementation were similar to those described in previous studies that demonstrated an improvement in serum zinc level, IGF-1 level, and growth in children with NOFTT or mild to moderate zinc deficiency.[7–9] Therefore, factors such as the duration and the amount of zinc supplementation may not explain the lack of effect of zinc supplementation on serum IGF-1 level and catch-up growth in study subjects, especially in those born prematurely. One possible explanation for the lack of effect of zinc supplementation on catch-up growth in children with NOFTT born preterm could be the coexistence of additional micronutrient deficiencies including vitamins, and minerals or macronutrient deficiency such as protein-calorie malnutrition.

Longitudinal growth is the combined result of genetic endowment and nutrient availability. Certainly, the relevance of nutrients is not limited to zinc; protein and other micronutrient deficiencies can cause weight stunting or growth impairment.[36] Rivera et al. showed that not only zinc but also other micronutrients affected growth, and that zinc deficiency strongly contributed to growth retardation. Additionally, vitamin A and iron deficiencies are also contributors to FTT, but only when the initial deficiency is severe.[37] In this study, overall age-appropriate nutritional counseling and intervention were provided to all patients. Fifteen of 39 (38%) NOFTT children born preterm were younger than 12 months at first visit; among these, breast feeding, formula feeding, and breast feeding plus formula feeding were performed in 41.7%, 27.7%, and 30.6% of infants, respectively, with an average amount of 150 cc/kg/day. Thirty-five of 65 (53.8%) NOFTT children born term were younger than 12 months at first visit; among these, breast feeding, formula feeding, and breast feeding plus formula feeding were performed in 45.8%, 20.9%, and 33.3% of infants, respectively, with an average amount of 160 cc/kg/day. There were no significant differences in feeding method and amount between zinc-supplemented and non-supplemented groups of NOFTT children born preterm and term. For parents of breastfed infants, more frequent breastfeeding, lactation support, and formula supplementation until catch-up growth was achieved were recommended.[12,38] Parents of formula-fed infants were instructed on how to make energy-dense formula by concentrating the ratio of formula to water during periods of catch-up growth.[39] For toddlers, a diet high in energy and protein was provided, and avoiding excessive juice or snacks was recommended because these can interfere with proper nutrition.[12] Although no positive response on growth was noted in the zinc-supplemented group compared to the non-zinc supplemented group, we found gains in the weight Z-scores and the height Z-scores, even in the non-zinc supplemented group. This suggests that overall nutritional support for other micronutrient deficiencies as well as protein-energy malnutrition might have increased the weight Z-score and the height Z-score, even in the non-zinc supplemented group of our study. The potential controversies caused by a selection bias for zinc supplementation in this retrospective study could be resolved by a future prospective study. Further studies with adequate sample size and design are needed to evaluate the role of energy, protein, and other micronutrient support in catch-up growth in NOFTT infants born preterm.

Our study has several limitations. First, there are limitations inherent to the retrospective design. In this study, oral zinc was supplemented in NOFTT children with serum zinc levels lower than 70 μg/dL or with clinical signs and symptoms of zinc deficiency despite normal serum zinc levels.[40] Therefore, baseline serum zinc level was significantly different between zinc-supplemented and non-supplemented groups of NOFTT children born preterm and term ($p = 0.001$, and $p < 0.001$, respectively). In addition, several confounding factors such as protein-energy malnutrition and other micronutrient deficiencies make it difficult to evaluate the effect of zinc supplementation in NOFTT children. Second, serum zinc status was evaluated in

this study by measuring serum zinc levels. However, it is difficult to diagnose zinc deficiency by measuring serum zinc levels, and measurements of zinc in tissues such as hair may offer a more accurate diagnosis, in combination with clinical symptoms and signs.[40]

In conclusion, oral zinc supplementation in children with NOFTT born preterm had no significant effect on serum IGF-1 level, weight gain, or height gain, despite the fact that greater changes in serum zinc levels were observed with 6 months of oral zinc supplementation as compared to those who did not receive zinc supplementation. In contrast, in children with NOFTT born at term, serum zinc levels, IGF-1 levels, weight for age Z-scores, and height for age Z-scores all significantly increased after 6 months of oral zinc supplementation. Additionally, the increase in serum zinc levels was significantly higher after 6 months of oral zinc supplementation as compared to those without supplementation. However, the changes in serum IGF-1 levels, weight for age Z-scores, and height for age Z-scores were not significantly greater than in those who did not receive zinc supplementation. Furthermore, even in non-zinc supplemented children with NOFTT, born preterm or at term, gains in weight Z-scores and height Z-scores were found but statistically they were not significant.

Therefore, although oral zinc supplementation may improve serum zinc status in children with NOFTT, overall nutritional support rather than supplementation of a single nutrient may be more effective for catch-up growth in NOFTT children regardless of gestational age at birth.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

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