

Effects of zinc supplementation on catch-up growth in children with failure to thrive

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BACKGROUND/OBJECTIVES: Although globally the numbers of children diagnosed with failure to thrive (FTT) have decreased, FTT is still a serious pediatric problem. We aimed to investigate the effects of zinc supplementation for 6 months on growth parameters of infants and children with FTT.

SUBJECTS/METHODS: In this retrospective study, of the 114 participants aged between 4 months and 6 years, 89 were included in the zinc supplementation group and were provided with nutrition counseling plus an oral zinc supplement for 6 months. The caregivers of the 25 participants in the control group received nutrition counseling alone. Medical data of these children, including sex, age, height, weight, serum zinc level, and serum insulin-like growth factor 1 (IGF1) level were analyzed.

RESULTS: Zinc supplementation for 6 months increased weight-for-age Z-score and serum zinc levels (5.5%) in the zinc supplementation group of underweight category children. As for stunting category, height-for-age Z-score of the participants in the zinc supplementation group increased when compared with the baseline, and serum zinc levels increased in the normal or mild stunting group. Serum IGF1 levels did not change significantly in any group. Thus, zinc supplementation was more effective in children in the underweight category than those in the stunted category; this effect differed according to the degree of the FTT.

CONCLUSION: These findings suggest that zinc supplementation may have beneficial effects for growth of infants and children with FTT, and zinc supplementation would be required according to degree of FTT.

Nutrition Research and Practice 2017;11(6):487-491; <https://doi.org/10.4162/nrp.2017.11.6.487>; pISSN 1976-1457 eISSN 2005-6168

Keywords: Failure to thrive, zinc, growth, child

INTRODUCTION

Failure to thrive (FTT) is a state of undernutrition due to inadequate caloric intake or caloric absorption resulting from behavioral or psychosocial issues. FTT is a general term referring to children whose rate of weight and height gain is much lower than those of others at similar age [1]. FTT has been classified as organic (underlying medical condition) or non-organic (unknown medical condition). Non-organic FTT is the most common type of FTT, and it includes children who are not receiving enough food due to environmental neglect (e.g., lack of food) or psychosocial problems [2]. However, most children have mixed etiologies [3]. FTT is a common problem that usually occurs during the first or second years of life and may occur in any child [4]. Approximately 94% of children experience FTT between 6 months and 30 months of age [5]. FTT is often defined as height and weight values falling below the 3rd or

5th percentiles, weight being < 80% of the ideal weight for age, or downward change in growth across 2 major growth percentiles in the standard growth chart [6]. The World Health Organization (WHO) uses a Z-score cutoff point of < -2 SD to define moderate malnutrition and < -3 SD to define severe malnutrition [7]. FTT can often be resolved through simple interventions. Thus, primary care providers can manage children with FTT except for those with other illnesses or constant weight loss [8]. Cole *et al.* [9] reported that the most important factor for FTT management in outpatient evaluation is obtaining precise information on a child's food habits and energy intake. In the US, FTT is observed in 1-5% of pediatric inpatients, about 10% of primary care patients, 15-30% of patients in urban emergency rooms, and 15-25% of inpatients under two years of age. The prevalence of FTT can vary depending on the definition of the term and the participant to be observed [6, 10,11]. FTT is seen frequently in economically disadvantaged

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government(MSIP) (No.2013R1A1A3010917).

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Received: June 16, 2017, Revised: July 13, 2017, Accepted: September 28, 2017

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rural and urban areas [12].

Zinc is a trace element that plays important roles in cell growth and differentiation, protein and lipid metabolism, and the immune system [13,14]. It is essential for numerous metabolic activities, including catalysis and synthesis, degradation of nutrients, and regulatory functions [14]. Zinc deficiency in infants and children has been known to cause FTT and loss of appetite [15,16]. It is reported that zinc deficiency is mainly caused by zinc-deficient diets and food intake with high phytic acid, which interferes with zinc absorption [17]. The staple food in Korea is cereal grains rich in phytic acid; consequently, zinc deficiency appears frequently [18]. Zinc deficiency symptoms include FTT, lack of appetite, male hypogonadism in adolescents, mental lethargy, rough skin, delayed wound healing, immune dysfunctions, and abnormal neurosensory changes [14]. Especially, maternal zinc deficiency during pregnancy may lead to delayed cell growth, which may result in adverse pregnancy outcomes for the mother and fetus [19]. The mean intake of zinc was 75.7% of reference nutrient intake among children aged 3-5 years, and serum zinc levels positively correlated with their height and weight [20]. Therefore, deficient zinc intake may cause FTT. Previous studies on zinc nutritional status have included cases of adults and children with normal growth; no studies in this regard have been conducted in children with FTT in Korea. Therefore, this study aimed to evaluate the effects of zinc supplementation for 6 months on growth indicators, such as weight and height, in infants and children with FTT.

SUBJECTS AND METHODS

Participants

The participants' medical records included reports on sex, age, height, weight, serum zinc, and serum insulin-like growth factor I (IGF1) levels. The study collected data from January 2012 through August 2015. Seoul National University Bundang Hospital's Institutional Review Board (IRB) and Changwon National University's IRB approved this retrospective medical record review (IRB No. B-1603/338-110 and IRB No. 104027-201601-HR-001, respectively).

Experimental design

This was a retrospective study using patients' medical records. Participants aged 4 months to 6 years whose weight-for-age Z-score (WAZ) or height-for-age Z-score (HAZ) was under -1 were included. They were divided into groups according to their

Table 1. Division of groups based on being underweight and stunted

Category	Group	Mean
Underweight	-2 < WAZ < 0	Normal or marginally underweight (Well-nourished or mildly malnourished)
	-3 < WAZ < -2	Moderately underweight (Moderately malnourished)
	WAZ < -3	Severely underweight (Severely malnourished)
Stunted	-2 < HAZ < 0	Normal or marginally stunted (Well-nourished or mildly malnourished)
	HAZ < -2	Moderately stunted (Moderately malnourished)

WAZ, weight-for-age Z-score; HAZ, height-for-age Z-score

WAZ and HAZ, regardless of age. Of the total 114 participants, 89 participants who received nutrition counseling and zinc supplementation (zinc sulfate 22 mg/day equivalent to elemental zinc 5 mg in infancy, zinc sulfate 44 mg/day equivalent to elemental zinc 10 mg in children) were included in the zinc supplementation group (Zn group) [22,23]. Twenty-five participants whose caregivers received nutrition counseling alone were included in the control group. The trained dietician provided 50 min of nutrition counseling, including components of a balanced diet, roles of nutrients, and importance of food choice. The data were analyzed based on general characteristics, age, sex, weight, and height. To evaluate the severity of FTT, we classified the participants into the underweight and stunting categories. The underweight and stunting categories were further classified into three and two groups according to their WAZ and HAZ, respectively (Table 1). WAZ and HAZ were calculated based on the WHO reference, using the least mean squares method.

Statistical analysis

Statistical analyses were performed using SPSS software version 21.0 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Measured variables were presented as mean \pm SD. The difference between the control and Zn groups was analyzed using t-test. The values for baseline and 6 months after the zinc supplementation were compared using paired t-test. *P*-value < 0.05 was considered statistically significant.

RESULTS

General characteristics

The changes in the general characteristics of the control and Zn groups are summarized in Table 2. Children in both the control and Zn groups showed significant increases in their weight and height as compared to the baseline.

Changes in growth index

Changes in growth index between 0 month and after 6 months in the control and the Zn groups are shown in Table 3. The WAZ and HAZ of children in the Zn group increased as compared with the baseline, whereas no significant changes were noted in the control group. Serum zinc levels increased in the Zn group, while serum zinc levels in the control group

Table 2. General characteristics of the participants in the control and the zinc supplementation groups at baseline and at 6-month visits

Variables		Zinc (n = 89)	Control (n = 25)
Age (yrs)	Baseline	2.4 \pm 1.8	1.9 \pm 1.7
	6 months	2.9 \pm 1.8	2.4 \pm 1.0
	Difference	0.5 \pm 0.1*	0.5 \pm 0.1*
Weight (kg)	Baseline	10.3 \pm 3.5	9.4 \pm 3.5
	6 months	11.6 \pm 3.2	10.8 \pm 3.3
	Difference	1.4 \pm 0.9*	1.5 \pm 0.7*
Height (cm)	Baseline	82.4 \pm 14.9	77.8 \pm 14.6
	6 months	88.1 \pm 12.9	83.8 \pm 12.4
	Difference	5.7 \pm 3.6*	6.0 \pm 3.1*

Values are presented as mean \pm SD.

* Significant differences within group were statistically analyzed by paired t-test

Table 3. Changes in growth indices of the control and zinc supplementation groups at baseline and 6-month visits

Variables		Zinc (n = 89)	Control (n = 25)
WAZ (Z-score)	Baseline	-2.0 ± 1.0	-1.7 ± 1.0
	6 months	-1.6 ± 1.0	-1.4 ± 1.0
	Difference	-0.4 ± 1.0*	-0.3 ± 0.6
HAZ (Z-score)	Baseline	-1.5 ± 1.2	-1.5 ± 1.0
	6 months	-1.2 ± 1.1	-1.2 ± 1.0
	Difference	-0.3 ± 0.8*	-0.3 ± 0.7
Zinc (µg/dL)	Baseline	80.6 ± 25.5	95.8 ± 23.9 [†]
	6 months	89.2 ± 24.3 [†]	80.7 ± 12.5
	Difference	8.6 ± 35.6*	-15.0 ± 26.3*
IGF1 (ng/mL)	Baseline	75.9 ± 58.0	68.3 ± 57.0
	6 months	83.4 ± 56.2	71.7 ± 42.4
	Difference	7.5 ± 52.7	3.4 ± 24.5

Values are presented as mean ± SD.

WAZ, weight-for-age Z-score; HAZ, height-for-age Z-score; IGF1, insulin-like growth factor 1

* Significant differences within group were statistically analyzed by paired t-test

[†] Significant differences between groups were statistically analyzed by t-test

decreased when compared with the baseline. In addition, serum zinc levels in the Zn group increased significantly after 6 months as compared to the control group. There was no significant difference in serum IGF1 levels between baseline and after 6 months in the control and Zn groups.

Growth index measurements in underweight

Changes in growth index between the baseline and after 6 months in the control and Zn groups according to WAZ are presented in Table 4. We divided the underweight category into three groups according to the WAZ. The variables were compared in each group, and the data of the control group and the Zn group after 6 months were compared to the baseline data. In case of normal or mildly underweight ($-2 < \text{WAZ} < 0$), WAZ did not show significant difference after zinc supplementation for 6 months compared to the baseline. WAZ of moderately and severely underweight children ($-3 < \text{WAZ} < -2$ and $\text{WAZ} < -3$, respectively) increased in the Zn group compared to the baseline. Serum zinc levels of normal or mildly underweight children increased after 6 months in the Zn group, whereas significant decreases were noted in the control group between the baseline and after 6 months. This indicates that inadequate zinc supplementation in children who are in the early stage of growth retardation poses a risk of sharp decline in the serum zinc concentration, which leads to poor growth over long periods. After 6 months, serum zinc levels of the Zn group significantly increased compared to baseline in children who were severely underweight. There were no differences in serum IGF1 levels between baseline and 6 months in the control and Zn groups according to WAZ.

Table 4. Changes in growth indices of the control group and the zinc supplementation group according to weight for age at baseline and 6-month visits

Variables		-2 < WAZ < 0		-3 < WAZ < -2		WAZ < -3	
		Zinc	Control	Zinc	Control	Zinc	Control
WAZ	Baseline	-1.3 ± 0.6	-1.3 ± 0.6	-2.3 ± 0.2	-2.4 ± 0.3	-3.9 ± 0.8	-4.0 ± 1.5
	6 months	-1.2 ± 0.9	-1.1 ± 0.7	-2.0 ± 0.6	-2.0 ± 0.4	-2.2 ± 1.4	-3.4 ± 1.3
	Difference	0.1 ± 1.0	0.2 ± 0.7	0.4 ± 0.5*	0.4 ± 0.5	1.7 ± 1.5*	0.7 ± 0.1
Zinc (µg/dL)	Baseline	80.7 ± 29.2	93.2 ± 20.1 [†]	81.9 ± 21.8	109.2 ± 34.6	75.7 ± 19.6	85.5 ± 27.6
	6 months	93.4 ± 27.5 [†]	79.9 ± 11.5	85.4 ± 1.3	78.2 ± 16.1	82.8 ± 13.6	94.0 ± 7.1
	Difference	12.7 ± 39.7*	-13.2 ± 20.5*	3.5 ± 32.8	-31.0 ± 40.7	7.1 ± 22.0*	8.5 ± 20.5
IGF1 (ng/mL)	Baseline	76.1 ± 55.1	62.5 ± 44.3	75.0 ± 64.1	106.0 ± 91.6	78.4 ± 55.1	27.0 ± 8.1
	6 months	87.9 ± 59.2	67.7 ± 33.5	79.2 ± 53.2	104.9 ± 58.2	77.0 ± 55.8	24.7 ± 14.2
	Difference	11.8 ± 58.6	5.2 ± 22.5	4.2 ± 43.9	-1.1 ± 37.2	-1.4 ± 53.9	-2.3 ± 6.1

Values are presented as mean ± SD.

WAZ, weight-for-age Z-score; HAZ, height-for-age Z-score; IGF1, insulin-like growth factor 1

* Significant differences within group were statistically analyzed by paired t-test

[†] Significant differences between groups were statistically analyzed by t-test

Table 5. Changes in growth indices of the control group and the zinc supplementation group according to height for age at baseline and 6-month visits

Variables		-2 < HAZ < 0		HAZ < -2	
		Zinc	Control	Zinc	Control
HAZ	Baseline	-1.1 ± 0.8	-1.1 ± 0.8	-3.1 ± 1.2	-2.9 ± 1.0
	6 months	-0.9 ± 0.7	-0.9 ± 0.9	-2.3 ± 1.3	-2.0 ± 1.3
	Difference	0.2 ± 0.7*	-0.4 ± 1.2	0.8 ± 0.9*	0.8 ± 0.8
Zinc (µg/dL)	Baseline	80.2 ± 26.4	98.0 ± 15.3 [†]	82.2 ± 22.6	86.8 ± 14.1
	6 months	89.6 ± 26.4 [†]	78.4 ± 13.8	88.0 ± 14.7	80.2 ± 12.4
	Difference	9.4 ± 38.1*	-8.3 ± 13.8*	5.8 ± 25.0	3.4 ± 14.3
IGF1 (ng/mL)	Baseline	75.2 ± 53.0	66.6 ± 49.1	78.7 ± 75.3	75.3 ± 101.6
	6 months	81.6 ± 53.5	72.4 ± 39.0	90.2 ± 66.6	69.1 ± 71.5
	Difference	6.4 ± 56.9	-3.9 ± 74.3	11.5 ± 33.7	-6.2 ± 37.0

Values are presented as mean ± SD.

WAZ, weight-for-age Z-score; HAZ, height-for-age Z-score; IGF1, insulin-like growth factor 1

* Significant differences within group were statistically analyzed by paired t-test

[†] Significant differences between groups were statistically analyzed by t-test

Growth index measurements in stunting

The changes in general characteristics of low-height groups are summarized in Table 5. In normal or mild ($-2 < \text{HAZ} < 0$) and moderate ($\text{HAZ} < -2$) stunted cases, HAZ of the Zn group increased compared to the baseline. In normal or mild stunting, serum zinc levels of the Zn group significantly increased after 6 months compared to the baseline, whereas serum zinc levels of the control group significantly decreased. These results were similar to those of the normal or mild underweight children in the underweight group. Thus, inadequate zinc supplementation in children in the early stages of growth failure may lead to decreased serum zinc concentration resulting in severe growth failure. Serum IGF1 levels at baseline and after 6 months of zinc supplementation were not significantly different between the control and Zn groups.

DISCUSSION

The prevalence of stunting and underweight in children has decreased worldwide, from 40% in 1990 to 26% in 2011 and 25% in 1990 to 16% in 2015, respectively [23]. However, FTT is still a serious problem in infants and children. Daniel *et al.* [5] investigated the causes of FTT in a children's hospital. They found that these children had nutritional deficiencies (51.5%) and short stature due to being small for gestational age, constitutional or familial short stature (28.9%), or gastrointestinal disorders (16%). Although FTT was associated with various factors, nutritional supply and absorption were prominent factors associated with FTT. Therefore, intensive nutrition therapy may help with catch-up growth. Most patients with FTT can be treated with nutritional support and dietary corrections, and more aggressive treatment is needed if they do not respond to treatment [3].

We investigated the effects of zinc supplementation for 6 months on catch-up growth in children with FTT. During the experimental period, participants in the Zn group were given 10 mg of zinc daily. Zinc concentration was determined based on previous studies [21,22]. After 6 months, the effects on weight, height, WAZ, HAZ, serum zinc, and IGF1 levels in participants were studied.

The WAZ and HAZ were significantly increased by zinc supplementation in the normal or mild underweight and stunting groups, respectively. In normal or mild underweight and stunting, serum zinc levels of the Zn group significantly increased after 6 months compared to baseline. In addition, serum zinc levels of the Zn group significantly increased compared to the control group. All growth parameters of the Zn group in moderate stunting showed no significant changes after 6 months compared to the baseline, except for HAZ. Thus, zinc supplementation was more effective for underweight children than stunting children, and it may play an important role in catch-up growth by significantly increasing serum zinc concentrations at the early stages of growth retardation.

It was reported that consumption of zinc (50 mg/day for 2-months) improved secretion of growth hormone in children aged 3.7-16.2 years. In addition, zinc supplementation was more effective in children with low BMI than in those with normal BMI [24]. Thus, effects of zinc supplementation differed depending

on the characteristics of children with FTT. Unlike WAZ, HAZ is known as an indicator of chronic malnutrition [25]. The catch-up growth in height is slower than catch-up growth in weight, hence, constant nutritional support is needed until HAZ reaches its normal value [26]. Our study also showed that the stunting group had less benefit from zinc supplementation than the underweight group. However, it may be necessary to conduct a long-term experiment with different concentrations of zinc supplementation depending on the degree of FTT.

Zinc is the second most abundant micronutrient in the body and plays an important role not only in physical growth, but also as a cofactor for enzymes required for DNA synthesis, brain development, cell membrane fluidity and stability, bone formation, and wound healing [27]. It is necessary to maintain a consistent intake because zinc is not stored in the body [28]. The normal range of serum zinc levels is 70-120 $\mu\text{g}/\text{dL}$ [29]. Zinc homeostasis is well maintained in the body. Even when there is a serious deficit in zinc intake, blood zinc levels do not alter significantly. Thus, it is possible that zinc deficit exists even when blood zinc levels appear to be within the normal range [30]. Our study showed that serum zinc levels increased in the Zn group, while serum zinc levels in the control group decreased compared with baseline. Therefore, it is important to diagnose growth retardation and zinc deficiency early using various indicators, and to start zinc supplementation at an appropriate time to prevent long-term zinc deficiency. In addition, to accurately investigate zinc status in the body, other samples in addition to blood should be collected and examined.

IGF1 is mostly made by the liver under the control of pituitary growth hormone (GH). IGF1 modulates GH secretion through a negative feedback mechanism. GH/IGF1 signal pathway is essential for growth in infants and children [31]. There have been many studies that associate zinc with IGF1 levels [32,21,33]. Zinc deficiency significantly reduced serum IGF1 concentrations. Furthermore, the decrease in serum IGF1 concentrations was associated with decreased IGF1 gene expression in the liver of rats with zinc deficiency [32]. Oral administration of zinc (10 mg) for 3 months increased consumption of macronutrients and plasma IGF1 levels in children aged 8-9 years [21]. Cossack [33] reported that poor zinc status has been associated with low circulating IGF1 levels despite adequate caloric intake in humans. Thus, IGF1 is zinc-dependent and could be used as an indicator for diagnosing zinc deficiency. Unlike the previous studies, our study showed that zinc supplementation did not affect serum IGF1 levels. This result may have been due to the different age range of participants or the normal range of serum zinc and IGF1 levels in participants.

This study presented that zinc supplementation for 6 months in infants and children with FTT increased growth and serum zinc levels significantly in the Zn group of mild low weight and height participants compared with the control group. In addition, the effect of zinc supplementation differed according to FTT severity, suggesting that zinc supplementation should be performed according to the stage of FTT. However, this study has some limitations. This was a retrospective study, using restricted medical records. Additionally, zinc intake and toxicity were not studied. We suggest that prospective studies should be conducted to investigate effects of zinc supplementation on

catch-up growth in infants and children with FTT and low serum zinc levels.

In conclusion, zinc supplementation may be beneficial for growth in infants and children with FTT, and supplementation based on degree of FTT is suggested.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interests.

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