Biol Trace Elem Res (2009) 128:118–127
DOI 10.1007/s12011-008-8261-1

Effects of Zinc Supplementation on Physical Growth in 2–5-Year-Old Children

Hassan Mozaffari-Khosravi · Mehrdad Shakiba · Mohamad-Hassan Eftekhari · Farhad Fatehi

Received: 1 October 2008 / Accepted: 8 October 2008 /
Published online: 28 October 2008

Abstract Physical growth disorders in under 5-year-old children are a common health problem in many countries including Iran. The aim of this study was to determine effects of supplemental zinc on physical growth in preschool children with retarded linear growth. This study was a community-based randomized controlled trial on 2–5-year-old children with height-for-age below 25th percentile of National Center for Health Statistics growth chart. Ninety children were randomly assigned in zinc group (ZG) or placebo group (PG). After 6 months of zinc or placebo supplementation, we followed up the children for another 6 months. Anthropometric indicators were measured before the intervention and then monthly for 11 months. Forty children in ZG and 45 in PG concluded the study. Zinc supplementation increased weight gain in boys ($P=0.04$) and girls ($P=0.05$) compared to placebo but had no significant effect on mid-upper arm circumference increment in either sexes. The most significant ($P=0.001$) effect of Zinc supplementation was seen in boys' height increment at the end of follow-up period. Stunted growth rate in ZG changed significantly ($P=0.01$) from 26.7% to 2.5% throughout the study. This study showed that daily supplementation of 5 mg elemental zinc for 6 months improves physical growth in terms of height increment and weight gain in children with undesirable linear growth, especially in boys.

Keywords Zinc · Dietary supplements · Growth · Child · Preschool

H. Mozaffari-Khosravi (✉)
Department of Nutrition, Faculty of Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
e-mail: mozaffari.kh@gmail.com

M. Shakiba
Department of Pediatrics, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

M.-H. Eftekhari
Department of Nutrition, Faculty of Health, Shiraz University of Medical Sciences, Shiraz, Iran

F. Fatehi
Yazd Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Introduction

Human zinc deficiency was reported among adolescents in Iran and Egypt at first by Prasad et al. in 1961 [1]. Zinc deficiency is a neglected public health problem in many developing countries, including Iran [2, 3]. Several studies indicate that zinc deficiency results in poor growth in infants [4, 5] and children [6–8], and also depressed appetite [7, 9]. Zinc deficiency may also lead to impaired motor development in infants [10, 11] and, thus, can interfere with cognitive performance. Furthermore, zinc is essential for the integrity of the immune system, and its deficiency can result in reduced immunocompetence and decreased resistance to infection [12–14].

The global stunting and underweight prevalences were reported from 27% to 34% and 22% to 27%, respectively. High prevalences were reported in Eastern and Southeastern Asia, while South-central Asia continued to suffer from large scales of malnutrition. Meanwhile, in Africa, numbers of stunted and underweight children increased from 40 to 45 million, and 25 to 31 million, respectively [15]. Approximately 70% of the world's malnourished children live in Asia, resulting in the region having the highest concentration of childhood malnutrition. About half of the preschool children are malnourished ranging from 16.0% in the People's Republic of China to 64.0% in Bangladesh. Prevalence of stunting and underweight are high especially in South Asia where one in every two preschool children is stunted [16, 17]. Some studies showed that the prevalence of stunting, wasting, and underweight in different areas of Iran vary from 8% to 57% [18–20].

It is now well established that malnourished children, including those with diarrheal diseases, are in negative zinc balance and would, therefore, benefit from zinc supplementation [21–25]. However, zinc supplementation studies on growth-retarded but relatively healthy children in developing countries have not been conclusive. Researchers in Gambia [26] and Guatemala [27] found positive changes in body composition favoring the zinc-supplemented children, but there was no overall effect of zinc supplementation on the growth of the children. The present study was, therefore, undertaken to further investigate the role of zinc in the nutrition of growth-retarded but relatively healthy children. Our hypothesis was supplementing zinc to preschool children with retarded linear growth would have positive effects.

Materials and Methods

Study design and location The study was designed as a community-based randomized, double-blind, placebo-controlled supplementation trial. The subjects were preschool children who were below the 25th percentile of height for age according to National Center for Health Statistics (NCHS) data. The study protocol was approved by the research council and ethics committee at Shahid Sadoughi University of Medical Sciences in Yazd. The study was carried out in the primary health center of Azad-shahr, a low-income suburb of Yazd city in central Iran between March 2005 and February 2007.

Subjects and procedures Ninety children, 50 boys and 40 girls, within the range of 25–69 months old (38.8±11.3 months; mean ± SD) qualified to participate in the trial. The children were randomly assigned to either Zinc Group (ZG) or Placebo Group (PG). ZG received 5 mg of zinc sulfate in form of syrup everyday, and PG received the same syrup in color, odor, and taste without zinc. The supplementation continued for 6 months in both groups. Both syrups contained 5% sugar, 6% B-complex syrup, and deionized distilled water as solvent. Vahidi pharmacy assigned codes to the different syrups and sent them to corresponding researcher, where they were kept secured until the end of the study.

The mothers of children were given one 150-ml bottle of syrup and instructed to feed their child one spoonful of syrup every morning after breakfast. Also, they were asked to save the bottle after consuming the syrup and to request a replacement if the bottle was broken or lost. After 30 days, the mother along with her child came to the primary health center and was then given another 150-ml bottle. Each mother was asked whether she had encountered any problem when feeding the syrup and was asked about compliance of syrup by her child. The children consumed the syrups for 6 months and were followed up for the next 6 months with measuring the growth parameters. Not consuming 10% or more of dosage would cause the child to be excluded from the study.

Anthropometry measurements Weight, height, and mid-upper arm circumference (MUAC) of the children were taken at the beginning of the trial (baseline) and each month for 12 months after the start of the trial by a health worker in the Azad-shahr primary health center. Weight was measured using a Rasa balance beam scale (Rasa Co., Tehran, Iran) which was regularly calibrated and controlled against standard weights. Children were allowed to wear a minimum of light clothes. The standing height of the children was measured with a locally produced height board that was fixed vertically on a wall. MUAC was taken with a flexible non-stretch measuring tape. Measures included weight to the nearest 0.1 kg, height to the nearest 1.0 cm, and MUAC to the nearest 0.5 cm. Anthropometric measurements were usually performed by the same health worker following standard techniques. The *Z* scores for height-for-age (HAZ), weight-for-age (WAZ), and weight-for-height (WHZ) were calculated in comparison to the NCHS standard population. Stunting, underweight, and wasting were defined as HAZ≤−2, WAZ≤−2, and WHZ≤−2, respectively [28].

Statistical Analysis

Weight gain was calculated by subtracting initial weight from final weight. Height gain was calculated by subtracting initial height from final height. Values are reported as *mean* ± *SD*. Differences between ZG and PG group were assessed by student's *t* test. Categorical data were analyzed by Fisher's exact test. The *P* value ≤0.05 was considered as significant. All *P* values were two-tailed. SPSS version 11(SPSS Inc., Chicago, IL, USA) was used for data analysis.

Ethical Considerations

An Informed consent was obtained from the mother of each child at the beginning of the trial. They could quit the study freely, whenever they liked. The research ethics committee of the Shahid Sadoughi University of Medical Sciences approved the study protocol.

Results

There were 90 children in both groups at the beginning of the study from who 85 people concluded the study. Five children from ZG group stepped out on grounds of going on trips, illness or other reasons (Fig. 1). The remaining 85 participants included 55.3% female and 44.7% male. Despite majority of female gender among the participants, the sex distributions

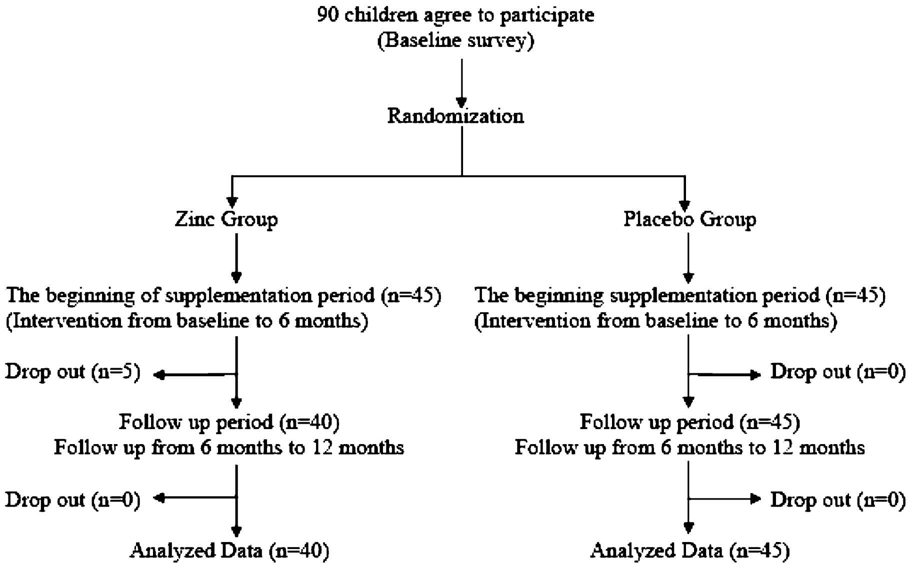

Fig. 1 Sampling scheme for the study

in the two groups did not show statistically significant difference. The mean of age in ZG and PG were 39.1±10.8 and 39.4±11.2 months, respectively (P=0.8). Table 1 shows initial data in both groups. There were no statistically differences between anthropometric measurements of these two groups at baseline.

Mean of children's weight gain is shown in Table 2. The figures are presented in the first 6-month (supplementation) period and the second 6-month (follow-up) period, as well as the whole year (overall) period of time. The mean of weight gain during the whole year of study in PG and ZG among girls were 2.0±0.9 and 2.6±1.1 kg (P=0.05), respectively, and these figures for boys were 2.1±0.8 and 2.7±0.8 kg (P=0.04), respectively. It is clearly

Table 1 Baseline Characteristics of Zinc and Placebo Groups

Variables	Zinc group (n=40) Mean ± SD	Placebo group (n=45) Mean ± SD	Student's t test P value
Girls			
Age (month)	38±8.8	41±12	0.3
Birth height (cm)	48.6±3.2	49.4±3.2	0.4
Birth weight (g)	2976.6±455	2911.7±425	0.6
Z-score HAZ	−1.45±0.44	−1.84±1.22	0.1
Z-score WAZ	−1.33±0.45	−1.21±0.66	0.4
Z-score WHZ	−0.71±0.57	−0.45±0.74	0.1
Boys			
Age (month)	40.7±13	37.8±9.9	0.6
Birth height (cm)	48.9±2.9	49.4±3.7	0.4
Birth weight (g)	3100.6±630	3022.7±433	0.6
Z-score HAZ	−1.83±1.32	−1.32±1.06	0.1
Z-score WAZ	−1.59±0.92	−1.16±0.67	0.1
Z-score WHZ	−0.80±0.67	−0.39±1.0	0.1

Table 2 Weight Gain (kg) in Zinc and Placebo Groups

Periods of study	Zinc group		Placebo group		Student's *t* test *P* value
	Number	Mean ± SD	Number	Mean ± SD	
First 6 months					
Girls	24	0.92±0.41	23	0.92±0.55	0.9
Boys	16	1.06±0.76	22	0.90±0.83	0.5
Second 6 months					
Girls	24	1.68±1.04	23	1.08±0.77	0.03
Boys	16	1.65±0.75	22	1.20±0.66	0.05
Throughout the study					
Girls	24	2.6±1.10	23	2.0±0.90	0.05
Boys	16	2.7±0.80	22	2.1±0.80	0.04

shown that the weight gain happened significantly in the second 6-month period of study among both sexes.

Mean of MUAC increment by the end of study in PG and ZG among girls were 1.23±0.46 and 1.70±0.1 cm (P=0.8), respectively, and these figures for boys were 1.43±0.51 and 1.19±0.39 (P=0.1), respectively (Table 3). It was clearly shown the MUAC increment was not significantly different between the two groups throughout the study in either sexes.

Mean of height increment during 1 year of study in PG and ZG among girls were 8.28±2.23 and 9.64±1.7 cm (P=0.02) and among boys were 8.34±3.14 and 11.7±1.96 (P=0.001), respectively (Table 4). When comparing the zinc group with placebo group, the only significant increase in the height of children was seen in the second 6-month period among boys.

Considering status of wasted and stunted children throughout of the study, the prominent benefit of zinc supplementation appeared in declining rate of stunted child from 15% to 2.5% in ZG, compared to minimal decrease in PG from 26.7% to 20% (Table 5). The results did not show the same positive effect on the rate of wasted child during and at the end of study.

Table 3 Mid Upper- arm Circumference Increase (cm) in Zinc and Placebo Groups

Periods of study	Zinc group		Placebo group		Student's *t* test *P* value
	Number	Mean ± SD	Number	Mean ± SD	
First 6 months					
Girls	24	0.52±0.47	23	0.36±0.43	0.2
Boys	16	0.34±0.35	22	0.52±0.47	0.09
Second 6 months					
Girls	24	0.67±0.31	23	0.86±0.42	0.2
Boys	16	0.85±0.28	22	0.91±0.58	0.6
Throughout the study					
Girls	24	1.70±0.51	23	1.23±0.46	0.8
Boys	16	1.19±0.39	22	1.43±0.51	0.1

Table 4 Height Increment (cm) in Zinc and Placebo Groups

Periods of study	Zinc group		Placebo group		Student's *t* test *P* value
	Number	Mean ± SD	Number	Mean ± SD	
First 6 months					
Girls	24	5.02±1.54	23	4.50±1.43	0.2
Boys	16	5.21±1.40	22	4.52±2.93	0.3
Second 6 months					
Girls	24	4.62±1.21	23	3.78±2.04	0.09
Boys	16	6.56±1.68	22	3.81±1.27	0.001
Throughout the study					
Girls	24	9.64±1.70	23	8.28±2.23	0.02
Boys	16	11.70±1.96	22	8.34±3.14	0.001

Discussion

The results of this study showed significant weight gain in ZG compared to PG among both girls (2.6 vs. 2.0 kg) and boys (2.7 vs. 2.1 kg) as shown in Table 2. It is interesting that significant changes occurred in the second 6-month period of the study. We could not explain this pattern of weight gain. Some studies have reported positive effect of zinc supplementation on weight gain [6, 29–32] but some others have not [33–37]. Although some studies have shown different responses from girls and boys to weight gain due to zinc supplementation, but this issue should be supported by further studies [38].

Height increment was more prominent in boys than girls so that the mean of total height increment in PG and ZG for girls were 8.28 and 9.64 cm ($P=0.02$), respectively. However, these figures for boys were 8.34 and 11.7 cm ($P=0.001$). This amount of height increment is biologically significant. Higher rate of stunted growth among boys (25%) comparing to girls (8.3%) at the beginning of the study could explain this result. Various studies have shown better responses of stunted children to zinc supplementation [6, 29, 39, 40]. Similar

Table 5 Frequency Distribution of the Participants by Wasted and Stunted Status

Phase of study	Wasted		Stunted	
	Number	Percentage	Number	Percentage
Baseline				
Zinc group	6	15	6	15
Placebo group	4	8.9	12	26.7
PV[a]	0.2		0.2	
6th month				
Zinc group	3	7.5	1	2.5
Placebo group	2	4.4	9	2.5
PV	0.4		0.01	
12th month				
Zinc group	3	7.5	1	2.5
Placebo group	1	2.2	9	2.5
PV	0.2		0.01	

[a] Fisher's exact test

to weight gain, significant increment of height took place in second half of the study during the follow-up, when zinc supplementation was stopped. This finding indicated that zinc needs time to promote growth with different mechanisms. This finding needs to be confirmed by larger scale studies.

Attained height is the result of the interaction between genetic endowment and both macro- and micronutrient availability during the growth period. Longitudinal growth occurs through a process of cell proliferation, the addition of new cells to the growth plate of the bone and hypertrophy, resulting in the expansion of the growth plate [29]. Although the control of the bone growth in its different phases is not entirely understood, the key roles of growth hormone (GH) and insulin-like growth factor I (IGF-I) have been identified. Evidence from animal models indicates that energy and protein restriction reduces IGF-I plasma concentration, which returns to normal upon replacement [40].

Several mechanisms of growth retardation and hypogonadism due to zinc deficiency have been suggested. Zinc affects GH metabolism. Conversely, GH affects zinc metabolism. Zinc deficiency may result in reduced GH production and/or IGF-I. Zinc deficiency may also affect bone metabolism and gonadal function. The interrelationships among zinc, growth, gonadal function and GH–IGF-I axis appears to be complex [41].

The association between nutritional status and the IGF-I system also has been observed in human: IGF-I is reduced during acute protein deficiency and protein energy malnutrition [40]. Some micronutrients also affect the IGF-I system. For example, it is well documented that zinc deficiency in rats causes not only growth retardation but also a decrease in both IGF-I plasma concentration and GH receptors, which return to normal after zinc repletion [42]. Additionally, through its influence on the GH–IGF-I system effects, zinc deficiency has been observed to affect bone metabolism [41]. The role of zinc in growth also may be explained, in part, through its participation in DNA synthesis [43]. Vitamin D and calcium deficiencies also affect bone development as manifested through the condition known as rickets [44]. Deficiencies of some micronutrients, such as iron, magnesium, and zinc result in anorexia [43, 45]. Therefore, these nutrient deficiencies also may contribute to growth retardation indirectly by reducing the intake of other growth limiting factors such as energy and protein; also, several micronutrients including zinc, iron, and vitamin A are associated with immune function and risk of mortality which in turn affect growth.

In addition, factors like dietary intake, composition of meal, and dietary practice have been well demonstrated to be determinant in bioavailability of trace elements including zinc. Several studies conducted in the past four decades in Iran supported this idea [46–49]. Meanwhile, a recent national survey in Iran showed that bread and cereals food group account for 49.2% of energy intake. This food group not only is a poor source of zinc but also contains several elements, including phytic acid, that lower zinc bioavailability. This survey also reported that dietary intake of hi-moderate zinc bioavailable foods like animal food sources were low in dietary intake [50].

Limitations of study include no record of dietary intake and lack of IGF-I and other growth-related hormones measurement. Meanwhile, the strengths of this study include high compliance rate in the two groups and proper randomization so that at the beginning of study, the recorded confounding variables were not significantly different between the two groups (Table 1). Although many studies investigated effects of zinc supplementation on physical growth, including two meta-analysis [6, 29] and most of them supported positive effects of zinc supplementation, their results are not comparable due to different dosage, product form, route of administration, and duration of supplementation of zinc.

In conclusion, this study, similar to some other studies, showed that daily elemental zinc supplementation for 5 mg can improve physical growth in preschool children, especially height increment in boys with undesirable linear growth. As physical growth depends on other micro- and macronutrient than zinc, multi-supplementation should be investigated. Also, regarding different responses to zinc supplementation in girls and boys, further studies should be carried out to explain this difference. Modification of dietary behavior is a fundamental solution for improving suboptimal zinc intake.

Acknowledgement We thank department of medical research at Shahid Sadoughi University of Medical Sciences for funding this project. We also appreciate the efforts of personnel of Azad-shahr Primary Health Center who helped us in data collection.

Conflicts of interests, source of funding, and authorship The authors declare that they have no conflicts of interest. This study was fully funded by the Department of Research Administration, Shahid Sadoughi University of Medical Sciences in Yazd, Iran.

Dr. H. Mozaffari-Khosravi who is a senior lecturer in Human Nutrition Department at SSUMS designed and supervised this study. Mehrdad Shakiba and Mohamad-Hassan Eftekhari participated in case selection and writing the draft of manuscript. Farhad Fatehi facilitated with data analysis and writing the manuscript. H. Mozaffari-Khosravi, M. Shakiba, and F. Fatehi are employed by SSUMS, but M. Eftekhari has no conflict of interest. All authors critically reviewed the manuscript and approved the final version submitted for publication.

References

1. Prasad AS (1967) Importance of zinc in human nutrition. Am J Clin Nutr 20(6):648–652
2. Mahmoodi MR, Kimiagar SM (2001) Prevalence of zinc deficiency in junior high school students of Tehran City. Biol Trace Elem Res 81(2):93–103
3. Tomkins A (2000) Malnutrition, morbidity and mortality in children and their mothers. Proc Nutr Soc 59 (1):135–146
4. Walravens PA, Hambidge KM (1976) Growth of infants fed a zinc supplemented formula. Am J Clin Nutr 29(10):1114–1121
5. Schlesinger L, Arevalo M, Arredondo S, Diaz M, Lonnerdal B, Stekel A (1992) Effect of a zinc-fortified formula on immunocompetence and growth of malnourished infants. Am J Clin Nutr 56(3):491–498
6. Brown KH, Peerson JM, Rivera J, Allen LH (2002) Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. Am J Clin Nutr 75(6):1062–1071
7. Chen XC, Yin TA, He JS, Ma QY, Han ZM, Li LX (1985) Low levels of zinc in hair and blood, pica, anorexia, and poor growth in Chinese preschool children. Am J Clin Nutr 42(4):694–700
8. Gibson RS, Vanderkooy PD, MacDonald AC, Goldman A, Ryan BA, Berry M (1989) A growth-limiting, mild zinc-deficiency syndrome in some southern Ontario boys with low height percentiles. Am J Clin Nutr 49(6):1266–1273
9. Umeta M, West CE, Haidar J, Deurenberg P, Hautvast JG (2000) Zinc supplementation and stunted infants in Ethiopia: a randomised controlled trial. Lancet 355(9220):2021–2026
10. Bentley ME, Caulfield LE, Ram M, Santizo MC, Hurtado E, Rivera JA, Ruel MT, Brown KH (1997) Zinc supplementation affects the activity patterns of rural Guatemalan infants. J Nutr 127(7):1333–1338
11. Sazawal S, Bentley M, Black RE, Dhingra P, George S, Bhan MK (1996) Effect of zinc supplementation on observed activity in low socioeconomic Indian preschool children. Pediatrics 98(6 Pt 1):1132–1137
12. Black RE (1998) Therapeutic and preventive effects of zinc on serious childhood infectious diseases in developing countries. Am J Clin Nutr 68(2 Suppl):476S–479S
13. Bhutta ZA, Bird SM, Black RE et al (2000) Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. Am J Clin Nutr 72(6):1516–1522
14. Roy SK, Tomkins AM, Haider R, Behren RH, Akramuzzaman SM, Mahalanabis D, Fuchs GJ (1999) Impact of zinc supplementation on subsequent growth and morbidity in Bangladeshi children with acute diarrhoea. Eur J Clin Nutr 53(7):529–534
15. de OM, Blossner M, Borghi E, Morris R, Frongillo EA (2004) Methodology for estimating regional and global trends of child malnutrition. Int J Epidemiol 33(6):1260–1270

16. Khor GL (2003) Update on the prevalence of malnutrition among children in Asia. Nepal Med Coll J 5 (2):113–122
17. Saxena N, Nayar D, Kapil U (1997) Prevalence of underweight, stunting and wasting. Indian Pediatr 34 (7):627–631
18. Lankarani S, Musaiger AO (1991) The state of nutrition in Fars, Iran: a review. Nutr Health 7(3):135–142
19. Sarraf Z, Goldberg D, Shahbazi M, Arbuckle K, Salehi M (2005) Nutritional status of schoolchildren in rural Iran. Br J Nutr 94(3):390–396
20. Maddah M, Mohtasham-Amiri Z, Rashidi A, Karandish M (2007) Height and weight of urban preschool children in relation to their mothers' educational levels and employment status in Rasht City, northern Iran. Matern Child Nutr 3(1):52–57
21. Golden MH, Golden BE (1981) Effect of zinc supplementation on the dietary intake, rate of weight gain, and energy cost of tissue deposition in children recovering from severe malnutrition. Am J Clin Nutr 34 (5):900–908
22. Castillo-Duran C, Heresi G, Fisberg M, Uauy R (1987) Controlled trial of zinc supplementation during recovery from malnutrition: effects on growth and immune function. Am J Clin Nutr 45(3):602–608
23. Khanum S, Alam AN, Anwar I, Akbar AM, Mujibur RM (1988) Effect of zinc supplementation on the dietary intake and weight gain of Bangladeshi children recovering from protein-energy malnutrition. Eur J Clin Nutr 42(8):709–714
24. Simmer K, Khanum S, Carlsson L, Thompson RP (1988) Nutritional rehabilitation in Bangladesh—the importance of zinc. Am J Clin Nutr 47(6):1036–1040
25. Sazawal S, Black RE, Bhan MK, Jalla S, Sinha A, Bhandari N (1997) Efficacy of zinc supplementation in reducing the incidence and prevalence of acute diarrhea—a community-based, double-blind, controlled trial. Am J Clin Nutr 66(2):413–418
26. Bates CJ, Evans PH, Dardenne M et al (1993) A trial of zinc supplementation in young rural Gambian children. Br J Nutr 69(1):243–255
27. Cavan KR, Gibson RS, Grazioso CF, Isalgue AM, Ruz M, Solomons NW (1993) Growth and body composition of periurban Guatemalan children in relation to zinc status: a longitudinal zinc intervention trial. Am J Clin Nutr 57(3):344–352
28. World Health Organization Working Group (1986) Use and interpretation of anthropometric indicators of nutritional status. Bull WHO 64:929–941
29. Rivera JA, Hotz C, Gonzalez-Cossio T, Neufeld L, Garcia-Guerra A (2003) The effect of micronutrient deficiencies on child growth: a review of results from community-based supplementation trials. J Nutr 133(11 Suppl 2):4010S–4020S
30. Kikafunda JK, Walker AF, Allan EF, Tumwine JK (1998) Effect of zinc supplementation on growth and body composition of Ugandan preschool children: a randomized, controlled, intervention trial. Am J Clin Nutr 68(6):1261–1266
31. Lind T, Lonnerdal B, Stenlund H, Gamayanti IL, Ismail D, Seswandhana R, Persson LA (2004) A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: effects on growth and development. Am J Clin Nutr 80(3):729–736
32. Ebrahimi S, Pormahmodi A, Kamkar A (2006) Study of zinc supplementation on growth of schoolchildren in Yasuj, Southwest of Iran. Pak J Nutr 5(4):341–342
33. Dijkhuizen MA, Wieringa FT, West CE, Martuti S, Muhilal (2001) Effects of iron and zinc supplementation in Indonesian infants on micronutrient status and growth. J Nutr 131(11):2860–2865
34. Rahman MM, Tofail F, Wahed MA, Fuchs GJ, Baqui AH, Alvarez JO (2002) Short-term supplementation with zinc and vitamin A has no significant effect on the growth of undernourished Bangladeshi children. Am J Clin Nutr 75(1):87–91
35. Osendarp SJ, Santosham M, Black RE, Wahed MA, van Raaij JM, Fuchs GJ (2002) Effect of zinc supplementation between 1 and 6 mo of life on growth and morbidity of Bangladeshi infants in urban slums. Am J Clin Nutr 76(6):1401–1408
36. Muller O, Garenne M, Reitmaier P, Van Zweeden AB, Kouyate B, Becher H (2003) Effect of zinc supplementation on growth in West African children: a randomized double-blind placebo-controlled trial in rural Burkina Faso. Int J Epidemiol 32(6):1098–1102
37. Penny ME, Marin RM, Duran A, Peerson JM, Lanata CF, Lönnerdal B, Black RE, Brown KH (2004) Randomized controlled trial of the effect of daily supplementation with zinc or multiple micronutrients on the morbidity, growth, and micronutrient status of young Peruvian children. Am J Clin Nutr 79:457–465
38. Garenne M, Becher H, Ye Y, Kouyate B, Muller O (2007) Sex-specific responses to zinc supplementation in Nouna, Burkina Faso. J Pediatr Gastroenterol Nutr 44(5):619–628

39. Rivera JA, Ruel MT, Santizo MC, Lonnerdal B, Brown KH (1998) Zinc supplementation improves the growth of stunted rural Guatemalan infants. J Nutr 128(3):556–562
40. Estivariz CF, Ziegler TR (1997) Nutrition and the insulin-like growth factor system. Endocrine 7(1):65–71
41. Nishi Y (1996) Zinc and growth. J Am Coll Nutr 15(4):340–344
42. Dorup I, Clausen T (1991) Effects of magnesium and zinc deficiencies on growth and protein synthesis in skeletal muscle and the heart. Br J Nutr 66(3):493–504
43. Clausen T, Dorup I (1998) Micronutrients, minerals and growth control. Bibl Nutr Dieta 54:84–92
44. Abrams SA (2002) Nutritional rickets: an old disease returns. Nutr Rev 60(4):111–115
45. Lawless JW, Latham MC, Stephenson LS, Kinoti SN, Pertet AM (1994) Iron supplementation improves appetite and growth in anemic Kenyan primary school children. J Nutr 124(5):645–654
46. Prasad AS (2001) Recognition of zinc-deficiency syndrome. Nutrition 17(1):67–69
47. Prasad AS (2001) Discovery of human zinc deficiency: impact on human health. Nutrition 17(7–8):685–687
48. Reinhold JG (1971) High phytate content of rural Iranian bread: a possible cause of human zinc deficiency. Am J Clin Nutr 24(10):1204–1206
49. Reinhold JG, Faradji B, Abadi P, Ismail-Beigi F (1976) Decreased absorption of calcium, magnesium, zinc and phosphorus by humans due to increased fiber and phosphorus consumption as wheat bread. J Nutr 106(4):493–503
50. Ministry of Health and Medical Education, National Institute of Food and Food Industry Research (2001) National survey on household dietary pattern and nutritional status in Iran. National Institute of Food and Food Industry Research, Tehran