

Long term zinc supplementation in improving growth of adolescents: zinc alone or with iron?

Manjula Hettiarachchi¹, Chandrani Liyanage^{1,2}, PHN Suranga¹, LAS Dharmapriya¹

¹Nuclear Medicine Unit, ²Department of Community Medicine, Faculty of Medicine, University of Ruhuna, Galle.

Abstract

Multi-micronutrient supplementation has beneficial effects on the improvement of nutritional status, work productivity, health and diseases. A long term supplementation is needed to better understand the biological basis for potential interactions observed in functional outcomes such as growth and development. A stratified sample of adolescent school children (n=821; M= 327, F= 494) of 12-18 years of age were randomized into one of four groups on a double blind approach at class room level. Children in each group received two capsules daily containing either iron (50 mg/d) or zinc (14 mg/d) or iron and zinc combined or placebo capsule for a period of 36 weeks. Their anthropometric measurements were made and a medical examination carried out prior to study and after the intervention. Mean change of weight and height in the placebo group was 0.53 kg and 0.73 cm. Iron alone group had 0.89 kg gain in weight and 1.0 cm in height. Zinc alone group had higher gain in weight (2.27 kg) and height (2.37 cm) whereas 1.52 kg and 1.63 cm gains were observed with the combined supplement group. The body mass index (BMI) of all the supplemented groups significantly increased from their respective baseline status (0.32 in supplemented, 0.04 in placebo; $p < 0.001$). The increase in z scores in zinc supplemented groups was marginally significant when compared with the placebo group ($p < 0.05$). After correcting for confounding effects of age and the respective baseline values of weight, height and BMI, the zinc alone supplemented group had the best anthropometric improvement. It appears therefore, that long term zinc supplementation had positive impact on the growth of children.

Key words: iron, zinc, micronutrient supplementation, adolescent growth, Sri Lanka,

Introduction

Undernutrition is manifested in most developing countries by early growth with stunting and a high prevalence of micronutrient deficiencies. In Sri Lanka, recent surveys¹ have revealed a high prevalence of under weight (47.2%) and stunting (28.5%) and, an overweight of 2.2% among adolescents of 10 to 15 years of age. In 2003, we reported that 31.1% of adolescent school children of 12 to 16 years of age in Galle district were underweight and 21.5% were stunted². Severe malnutrition was observed in 14.9% in this study. Stunting has been shown to be associated with habitual consumption of a diet low in animal products and accompanying micronutrients, and high in plant constituents such as phytate that inhibit the absorption of minerals³. In a cohort of Sri Lankan adolescents we have shown that the dietary intake of both macro and micronutrients are less than 50% of recommendation⁴. Surprisingly, we observed that 62% had habitually not eaten breakfast before going to school although it has been previously reported as 10.4% subjects missed breakfast during schooling¹.

Although single-micronutrient supplementation trials have been useful to confirm the effects of specific micronutrients on growth outcomes, programmes that provide supplements of only one nutrient may not be the most cost-effective way of preventing growth faltering and associated adverse health outcomes because of the co-existence of multiple-micronutrient deficiencies in many populations⁵. Multiple-micronutrient supplements are expected to be more efficacious in preventing growth faltering in at-risk populations, as all possible growth-limiting micronutrient deficiencies may be corrected simultaneously.

Because zinc supplementation has improved the growth and/or body composition of stunted children in countries such as the United States, Canada, Ecuador, China, and Guatemala^{6,7}, the present study was designed to measure the effect of zinc supplementation on the growth and body composition of Sri Lankan school children. Unlike most of the previous zinc-supplementation studies reported in the literature, iron supplements were also provided because of the high prevalence of iron deficiency in this community⁸. There is some, albeit limited, evidence that iron deficiency causes poor appetite and growth stunting⁹, so we were concerned that simultaneous iron deficiency might have limited any zinc induced growth response.

If iron and zinc are to be provided together, it is important to determine whether they interact biologically, and if so, how. Because they have chemically similar absorption and transport mechanisms, iron and zinc have been thought to compete for absorptive pathways¹⁰. New evidence based on cell culture studies has shown that iron may inhibit zinc absorption in some cells at very high ratios of iron to zinc, but not vice versa¹¹. However, evidence at low ratios of iron to zinc also is needed to assess any biochemical and functional effects of dual supplementation. A long term supplementation is needed to better understand the biological basis for potential interactions observed in functional outcomes such as growth and development. The experimental design of this study will provide some valuable information on the effect of iron, zinc or combined supplements on adolescent growth.

Subjects and methods

Schoolchildren of 12 to 16 years of age attending schools in Galle District constituted the study population. Three schools (1 girls' school and 2 mixed schools) were randomly selected. It was observed that these schools had both urban and rural children almost in equal proportions. Principals of the selected schools were first contacted and class teachers were briefed about the study, after obtaining written permission from the Secretary, Ministry of Education, Sri Lanka. The study received approval from the Ethics committee of the Faculty of Medicine, University of Ruhuna, Sri Lanka.

Screening

In selecting the sample, 845 children who presented with written consent from their parents were subjected to a comprehensive physical examination, including measurements of height and body weight using standardized scales. A sample of venous blood (3 ml) was drawn for the initial assessment of haemoglobin by cyanmethaemoglobin method.

Enrolment

Children with a haemoglobin level ≥ 80 g/L were eligible for the study. Others were referred for treatment and further investigations (n=5). Further, children suffering from acute or chronic diseases or inflammatory conditions and on any drug other than paracetamol or antihistamines for minor ailments (n=4) and, currently consuming nutrient supplements (n=15) were also excluded from the study. The selected subjects (n=821) were treated for parasites by giving mebendazole 500mg as a single oral dose approximately two weeks prior to the start of the study. A letter was given to their family physicians requesting notification if they wished to prescribe additional micronutrient supplements during the study period.

Drug supplementation

Subjects were randomized into one of four groups and randomization was stratified by classroom assignment. Each child was supplemented with two capsules per day containing either iron (50mg/d) in the form of ferrous fumarate or zinc (14mg/d) in the form of zinc sulfate or iron+zinc (50+14mg/d) or placebo made of anhydrous lactose. The subjects received capsules daily on school days for a period of 36 weeks from their classroom teacher. They consumed capsules each morning at the time daily attendance

was taken. Teachers were instructed to ensure that their students consumed the capsules daily. As this was a double blind technique, neither the subjects nor their teachers knew the contents of the capsules. Capsules were provided to the classroom teachers by the investigators every two weeks; the teachers were asked to sign a checklist when the doses were given to the subjects. These checklists were randomly checked for accuracy and compliance. For use during weekends and school holidays, a separate pack of capsules was given to each subject with a letter to parents. Either the mother or the father was asked to sign the checklist once the child took the capsules. Supplementation was started on 20th January 2003 and continued until 7th November 2003. The final assessment was carried out one week after the end of the intervention (36 weeks of supplementation), during which anthropometric measurements were taken and a medical examination done.

Statistical analysis

The sample size was calculated on the basis of the estimated prevalence of anaemia (defined as Hb<120.0 g/L) in this age group in Sri Lanka¹². To demonstrate a 15% reduction in anaemia prevalence with an alpha error of 5% and beta error of 10% each group needed 180. This was inflated to 200 per group with an assumption of a 25% dropout rate during follow-up period. A one-sample Kolmogorov-Smirnov test was used to investigate whether the anthropometry (weight, height and BMI) were normally distributed. The 1978 CDC/WHO growth reference curves were used from Epi-info version 3.0 (2003) to generate values for z-scores of weight-for-age (underweight), and height-for-age (stunting).

Differences between groups in anthropometric indices at baseline and post-intervention were investigated using multivariate analysis of variance (MANOVA) repeated-measures design with supplement type as a between-subject factor (four groups) and treatment effect (baseline compared with after intervention) as a within-subject factor. Baseline values for weight-for-age z score (in 2 classifications: <-2.0 and \geq -2.0) and height-for-age z score (in 2 classifications: <-2.0 and \geq -2.0) were also included in the analysis as between-subject factors to correct for their possible confounding influence on the change in weight and height. All analyses were done using SPSS version 10.0 for WINDOWS (SPSS Inc, Chicago).

Results

On the random grouping there were 202 children in iron supplemented group, 213 in zinc supplemented group, 216 in iron and zinc combined group and 190 in the control group who were treated with placebo capsules. Mean age of iron group (170 months \pm 19) and placebo group (166 months \pm 16) were significantly different ($p>0.05$) from zinc group (163 months \pm 20) and combine supplemented (159 months \pm 15) group. However, the initial weight and height (Table 1) and the prevalence of underweight (defined by \leq 2SD of WAZ) and stunting (defined by \leq 2SD of HAZ) were not different between these four groups. Overall 21.8% ($n= 179$) were dropped by the end of the intervention.

The baseline and post intervention weight, height and other derived parameters (body mass index (BMI), WAZ and HAZ) are illustrated in Table 1 according to their group allocation. Following 36 weeks of supplementation all four groups had a significant improvement ($p>0.05$) in mean weight and height from their respective baseline values. All anthropometric parameters evaluated were significantly improved ($p<0.05$) in zinc supplemented groups (zinc only and combine supplemented) when compared with iron only and placebo groups (Table 1).

Table 1: Effect on anthropometry with micronutrient supplementation¹

Group	n	Iron	n	Zinc	n	Combined	n	Placebo
Weight (Kg)								
Baseline	202	37.35 (7.45)	213	37.11 (8.42)	216	38.42 (8.91)	190	37.23 (8.77)
Final	161	38.31 (7.45) ^a	166	39.36 (8.23) ^b	172	40.58 (8.92) ^b	143	37.44 (7.54) ^a
Height (cm)								
Baseline	202	150.2 (8.49)	213	149.9 (9.61)	216	149.8 (8.12)	190	150.8 (9.14)
Final	161	151.1 (8.20) ^a	166	152.0 (9.18) ^b	172	152.0 (7.96) ^b	143	150.6 (8.72) ^a
BMI								
Baseline	202	16.39 (2.26) ^a	213	16.35 (2.44) ^a	216	16.95 (2.72) ^b	190	16.19 (2.53) ^a
Final	161	16.64 (2.25) ^a	166	16.87 (2.39) ^b	172	17.31 (2.98) ^b	143	16.38 (2.26) ^a
WAZ								
Baseline	202	-1.69 (0.76) ^a	213	-1.51 (1.23) ^a	216	-1.24 (0.93) ^b	190	-1.59 (0.96) ^a
Final	161	-1.70 (0.78) ^b	166	-1.52 (0.90) ^b	172	-1.24 (0.98) ^b	143	-1.94 (0.78) ^a
HAZ								
Baseline	202	-1.37 (0.94) ^a	213	-1.23 (1.07) ^a	216	-1.08 (0.95) ^b	190	-1.20 (1.05) ^a
Final	161	-1.33 (0.97) ^b	166	-1.27 (1.10) ^b	172	-1.08 (1.00) ^b	143	-1.66 (0.97) ^a

¹Results expressed as mean (SD) values with same superscripts are not significantly different

Mean change in placebo group was 0.53 kg and 0.73 cm during the period of intervention. Iron alone group had 0.89 kg gain in weight and 1.0cm in height respectively. Zinc alone group had 2.27 kg gain in weight and 2.37 cm gain in height whereas combined supplementation had achieved 1.52 kg and 1.63 cm gain in weight and height respectively (Figure 1 and Figure 2). These effects also reflected in improvements in weight-for-age and height-for-age z scores in zinc supplemented groups and it was marginally significant when compared with the placebo group ($p < 0.05$). After correcting for confounding effects of age and the respective baseline values of weight, height and BMI, the zinc supplemented group had the best anthropometric improvement.

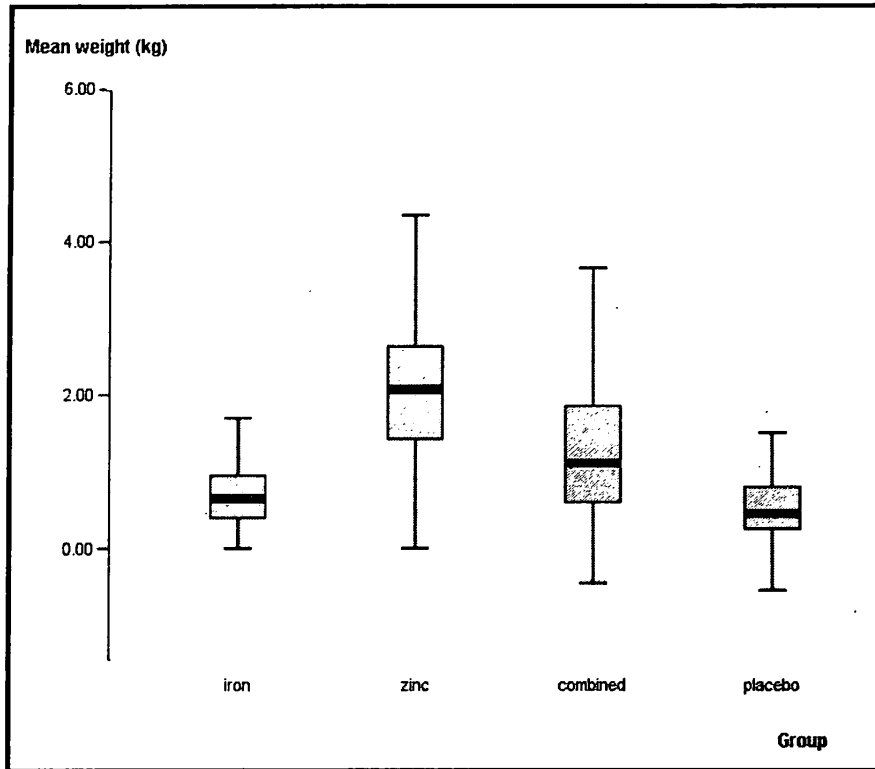


Figure 1: Effect of supplementation on weight

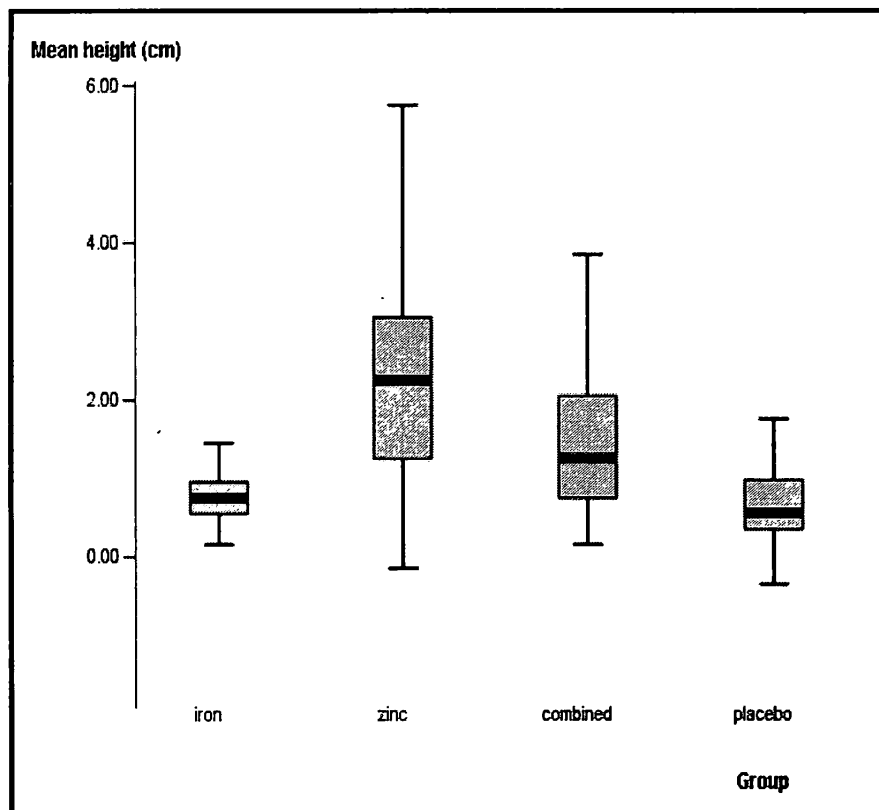


Figure 2: Effect of supplementation on height

Discussion

This study was designed to test whether daily zinc supplementation with or without iron, enhance growth in children. The strengths of this study included its randomized, double blind design and the supervised administration of the supplements.

The composition of the daily supplement used in the present study was decided based on the daily recommended allowances (RDA) by the World Health Organization¹³ for zinc and global guidelines for iron supplementation provided by the International Anemia Consultative Group¹⁴. These recommendations resulted in a ratio of iron (mg) to zinc (mg) of 3.6:1. A previous metabolic balance study carried out among infants¹⁵ the iron to zinc ratios of 5.4:1 and 1.3:1 demonstrated no significant effect of iron on zinc absorption (zinc absorption 15.6% and 20.35 respectively). In another study¹⁶, increasing molar ratio of iron to zinc from 1: 1 to 2.5: 1 did not affect absorption of zinc but iron to zinc ratio of 25:1 decreased zinc absorption, when ingested with water.

The essential role of several micronutrients in growth has been demonstrated clearly by clinical-based human trials of supplementation with micronutrients¹⁰. The micronutrients with the strongest relationship to growth are iron and zinc and to a lesser extent vitamin A, which are commonly deficient in low-income populations where dietary quality often is poor¹⁷. The positive impact of community-based supplementation trials indeed confirms that iron and zinc are common growth-limiting nutrients. However, iron appears to be limiting to growth only when deficiencies of these nutrients are severe, whereas growth may be limited even by mild to moderate deficiency of zinc¹⁸. This is consistent with the known metabolic and physiologic activity of these nutrients: zinc has direct effects on the primary hormonal system that controls growth in the postnatal phase when the majority of stunting occurs. On the other hand, iron does not appear to influence this system directly, but more likely exert its effects on growth when their functional stores have been depleted and/or when deficiency results in increased morbidity, which in turn contributes to growth faltering¹⁷.

A recent meta-analysis of 33 studies which investigated the effect of zinc supplementation on growth of pre-pubertal children¹⁹ revealed a highly significant positive response in height and weight increments. The overall effect (expressed in standard deviation units) in height was 0.350 (CI, 0.189 - 0.511; $p < 0.0001$) and weight was 0.309 (CI, 0.178 - 0.439; $p < 0.0001$). The growth responses were greater in children with low initial weight-for-age Z-scores. Although anthropometry was improved in our study, there was no significant treatment effect on height-for-age after correcting for the confounding influences of between-group differences in initial height-for-age and age. This result is similar to those seen in other studies carried out among representative groups of pre-school children from countries such as Chile²⁰, Mexico²¹ and the Gambia²².

A similar supplementation study with iron and zinc in Vietnamese children also resulted in an improvement of height-for-age, but the average initial height-for-age z scores of these children were already low at < -2.66 ²³. It was shown in Guatemalan children who were stunted; the height was improved more than that of non-stunted peers after zinc supplementation²⁴. It appears therefore, that zinc supplementation influences the growth of children only when they have lower-than-average anthropometric measurements and are zinc deficient. This effect was observed in the present study too. In the subgroup of children who had an initial height-for-age z score < -2.0 , there was a significant treatment effect on the height-for-age of subjects in the zinc and the combined groups, whereas the values for the iron and placebo groups did not change significantly. Similar effects on weight-for-age were seen in the zinc and the combined groups.

Conclusions

It can be concluded that the linear growth of children with lower height and weight-for-age z scores can positively be improved by zinc supplementation. This study has provided evidence that combined iron and zinc supplementation is optimum and had a clinically and statistically significant effect on growth of school children.

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