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Original Article

Reduced serum zinc levels while improving growth of underweight school children in trial of zinc-fortified milk in Indonesia

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Abstract

Background Most children in low-income countries have inadequate dietary zinc. The study was aimed to demonstrate the effect of iron-zinc fortified milk in improving zinc status among underweight school children in Indonesia.

Objective To evaluate the effects of milk fortification with zinc on serum zinc levels in underweight Indonesian school children.

Methods A double-blind, randomized, controlled, community-based study was conducted on 426 underweight children aged 7 to 9 years in several low economic income level elementary schools in Jakarta and Solo . Subjects were randomly allocated to receive either zinc-fortified milk (n= 217) or standard milk (n=209) for 6 months. The fortified milk provided an 2.38 mg zinc per day and the standard milk provided 0.88 mg zinc per day.

Results Among underweight children, the prevalence of stunting with a height-for-age z-score < -2.0 SD was 39.7%. Almost all subjects (98%) had zinc intake of less than 60% of the Indonesian recommended daily allowance (RDA) for that particular age group. After receiving the milk intervention, mean serum zinc concentration declined significantly in both groups (from 13.50 $\pm$ 3.05 μmol/L at baseline to 10.59 $\pm$ 1.93 μmol/L, $P< 0.05$), but growth parameters (weight and height) improved.

Conclusion Reduced mean serum zinc levels were observed in children who received standard milk, as well as those who received zinc-fortified milk. These reduction in serum zinc levels may be a part of homeostatic control mechanim for improving the negative zinc balance in zinc pools, as a negative effect on linear growth was not observed. Larger clinical trials of adequate sample size need to be conducted in order to provide better understanding on zinc regulation among underweight school children. **[Paediatr Indones. 2012;52:118-24]**.

Keywords: *zinc fortification, zinc serum, growth, underweight, school children*

Zinc's critical structural and functional roles in multiple enzyme systems are involved in gene expression, cellular growth, cellular differentiation, protein synthesis, as well as immunologic and reproductive functions.[1,2] Adequate zinc nutrition is essential for human health.[1,2] As a consequence, zinc deficiency has detrimental effects on children's physical growth, susceptibility to infections, as well as other functional abnormalities. Because of the serious consequences of zinc deficiency, it is essential to quantify the deficiency risk in populations that are most likely to be affected by this problem.[1,3,4] Nevertheless, in developing countries, there is a lack of information from national health and nutrition surveys on the population's zinc status and the prevalence of zinc deficiency. Therefore, the United Nations Children's Fund (UNICEF), the World Health Organization (WHO), and the International Zinc Nutrition Consultative Group (IZiNCG) recently published a consensus recommending the concentration of zinc

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in blood plasma or serum, dietary intake of zinc, and functional methods for assessing a population's risk of zinc deficiency. The risk of zinc deficiency is considered to be elevated and of public health concern when the prevalence of low serum zinc concentrations is greater than 20% or the prevalence of inadequate intake is greater than 25%.[1,5,6]

The International Zinc Nutrition Consultative Group (IZiNCG) has recommended strategies to control zinc deficiency and encouraged more aggressive action by improving zinc status through fortification in those who are at high risk of inadequate intake or have increased zinc requirements, such as in children undergoing periods of rapid growth.[1,7] A large percentage of children in low-income countries consume low or marginally adequate dietary zinc, which is of particular concern in times of increased need, such as during rapid growth. In this condition, compensatory homeostatic responses may come into play when there is insufficient dietary zinc in order to cover the body's requirements. But if the dietary zinc supply is very low or if a marginal intake is consumed for a long period of time, homeostatic adjustments may not be sufficient to replace zinc losses, thus leading to a negative zinc balance.[8-13] There has been little consistent data reported on zinc deficiency among primary school-aged children in Indonesia.

Zinc fortification has become an increasingly attractive strategy in lower-income countries to improve the population's micronutrient status.[1,8,14] It is a good option to increase micronutrient intake due to its economical approach and availability. It can also be regularly consumed as a complementary food for children.[6,15] Available studies have shown that zinc fortification can increase dietary zinc intake and total daily zinc absorption. Most absorption studies have also indicated that adding zinc to food does not adversely affect the absorption of other minerals, such as iron.[7,15] However, zinc fortification can be formulated with or without other micronutrients in populations at risk for micronutrient deficiencies. Evaluating zinc fortification trials is challenging because of the lack of adequate biomarkers as indicators of zinc status.[5,16,17] However, the change in serum zinc concentration following zinc fortification should be able to serve as a useful indicator of the impact of fortification interventions.[5,18] To evaluate the impact of zinc fortification on several parameters including serum zinc concentrations, we conducted a community-based, double-blind, randomized, controlled trial to compare the effect of zinc-fortified milk to standard milk in underweight school children.

Methods

This trial was conducted in over 400 school children from 10 elementary schools in urban-poor areas of Jakarta and Solo, Indonesia, from August 2007 to February 2008. We included underweight children (weight-for-age $<10^{th}$ percentile, CDC) who were aged 7-9 years (2^{nd} and 3^{rd} grade of elementary school). At the time of recruitment, none had chronic illness such as renal, congenital, or thyroid disease, diarrhea, or thalassemia. Written informed consent was obtained from all subjects and parents after a thorough explanation of data collection procedures. The study protocol was approved by the Ethics Committee, Faculty of Medicine at the University of Indonesia. A detailed baseline assessment, including physical examination by a physician and socio-demographic information collection was done by trained interviewers. We excluded those with severe anemia (Hb < 8 g/dl), documented lactose intolerance, documented cow's milk allergy, and concomitant medication during 4 weeks prior to enrollment. This study was designed as a randomized, two-parallel group, double-blind, controlled community trial. Eligible subjects were randomly divided into two groups, those receiving zinc-fortified milk (n= 217) and those receiving standard milk (n=209) for 6 months. Randomization tables were used to allocate subjects at each study site. Two milk sachets (27 g per sachet), containing either 2.38 mg zinc (zinc-fortified milk-A) or 0.88 mg zinc (standard milk-B) were given to each child per day.

Assessments were performed by trained observers at baseline, 3 months, and 6 months. Blood specimens were obtained by venipuncture, collected in vacutainer tubes and processed within 2 hours. All blood collection was done at the beginning of the school session under non-fasting conditions. Serum zinc concentration was estimated by atomic absorption spectrometry. Low serum zinc level was considered to be < 10.7 μmol/L, while normal serum zinc levels was considered to be 12-18 μmol/L.[3,5]

Three-day food record surveys were conducted to investigate dietary nutrition intake. Subjects recorded all food and drink consumed for three consecutive days. The 24-hour recall method was used in all subjects, and reported nutrition intake with this technique was compared to three-day food record surveys for all subjects. For analyses of nutrition intake, NutriSurvey for Windows (Copyright © 2003 Dr. J. Erhadt, Hohenheim University) was used to calculate intake energy and nutrient content per day. The mean result of the nutrition intake was further analyzed by Independent-Samples T test. We found no difference between the zinc-fortified milk group and standard milk group ($P>0.05$).

We provided two single-serving, (27 g per sachet) per day of powdered, full cream, zinc-fortified or standard milk (Nestle, Indonesia) to the subjects. Sachets were indistinguishable in package and color and were coded either as milk-A or milk-B, with compositions shown in **Table 1**. The codes remained unknown to both investigators and participants until the study was completed, all data had been entered, and initial analyses had been performed. At the time of enrollment, teachers were shown how to reconstitute the powdered milk. Teachers prepared one milk serving for consumption at the school, and provided one sachet per subject to be consumed at home in the afternoon. Teachers collected and recorded the returned sachets every week.

Conversion to anthropometrical *z*-scores was done by EPI INFO 2005 software (version 3.4; Centers for Disease Control and Prevention, Atlanta) and the 2000 Centers for Disease Control and Prevention reference growth data. We used SPSS version 15, SPSS Inc, Chicago for other analyses. Mean differences between subjects before and after milk intervention was analyzed by one-sample T-test. Chi-square tests were used to analyze the significance between variables. Mutivariate logistic regression was used to analyze variables influenced by zinc level between the two groups of subjects.

Table 1. Zinc-fortified and standard milk composition

Nutrient per serving	Unit	Zinc-fortified milk (27 g)	Standard milk (27 g)
Energy	Kcal	100.0	100.0
Fat	g	3.7	3.7
Protein	g	4.0	4.0
Carbohydrate	g	12.7	12.7
Glucose	g	6.4	6.4
Sodium	mg	59.0	59.0
Vitamin A	IU	396.0	396.0
Vitamin D 3	IU	51.0	51.0
Vitamin E	IU	5.0	5.0
Vitamin K	mcg	9.1	9.1
Zinc	mg	1.19	0.44

Results

A total of 426 subjects (96%) completed the 6-month milk intervention. Sixteen subjects dropped out due to moving to different schools (5 subjects), absence from school without notice for more than one week (3 subjects), parental refusal (4 subjects), and refusal of blood examination (4 subjects). Drop-out rates were similar in both groups, as were the reasons for discontinuation. There was no significant difference in milk intake compliance between the two groups during 6 months of milk intervention, with 78.1% compliance in the zinc-fortified milk group and 76.3% compliance in the standard milk group ($P= 0.23$).

The prevalence of children with height-for-age *z*-score less than −2.0 SD (stunted) was 39.67%, with almost subjects (98.1%) (n= 418) having zinc intake of less than 60% of the RDA. A consensus conference convened by WHO, UNICEF, and IZiNCG concluded that stunting prevalences of greater than 20% and

Table 2. Subjects' characteristics at baseline

	Intervention (n=217)	Control (n=209)
Anthropometry		
Mean weight, kg +SD	19 ± 1.75	18.95 ± 1.72
Mean height, cm +SD	117.05 ± 4.65	116.9 ± 4.62
Nutritional status, n (%)		
Wasted	18 (39)	51 (24.4)
Stunted	88 (40.6)	81 (38.8)
Laboratory results		
Mean hemoglobin, g/dL +SD	13.01 ± 0.91	12.92 ± 0.89
Mean zinc, µmol/L +SD	13.50 ± 3.05	13.46 ± 3.08
Morbidity, n (%)		
Elevated CRP level (>5 mg/L)	2 (0.9)	2 (1.0)
Dietary intake < 60% RDA, n (%)		
Calories	140 (64.5)	139 (66.5)
Zinc	212 (97.7)	206 (98.6)
Iron	131 (60.4)	166 (79.4)
Calcium	179 (82.5)	188 (90.0)
Vitamin C	155 (71.4)	166 (79.4)

inadequate zinc intake prevalences of greater than 25% can be used to identify subpopulations with an elevated risk of zinc deficiency. Therefore, children in our trial were categorized as having high risk of zinc deficiency and needing a zinc-fortified milk intervention to increase their dietary zinc intake.

Before the intervention, subjects had mean serum zinc concentrations of 13.50 $\pm$ 3.05 μmol/L and 13.46 $\pm$ 3.08 μmol/L in the intervention and control groups, respectively. Mean serum zinc concentration was also not significantly different (P > 0.05) at baseline between the two groups (**Table 2**). After receiving the 6 month milk intervention, mean serum zinc concentrations declined significantly in both groups (13.50 $\pm$ 3.05 μmol/L at baseline to 10.59 $\pm$ 1.93 μmol/L in the zinc-fortified milk group and 13.46 $\pm$ 3.08 μmol/L at baseline to 10.34 $\pm$ 1.90 μmol/L in the standard milk group. The difference between the mean was also significant (P=0.00) in both groups (**Table 3**).

Interestingly, serum zinc reduction was not accompanied by growth retardation after 6 months of milk intervention. As shown in **Table 3**, height, MUAC, and sitting height showed significant improvement and was correlated to the milk intervention. Zinc-fortified milk group showed better growth improvement than standard milk group eventhough there was no significant difference between the groups (P > 0.05).

When we analyzed data using multivariate regression to find out the most possible factors influencing the zinc level, intervention of fortified milk produced the changes in serum zinc concentration during the first three months period of intervention; those declined 1.25 μmol/L (P = 0.05) of zinc concentration. Interestingly, those serum zinc concentration during the last three months period of intervention increased 1.50 μmol/L, significant interaction with intervention of fortified milk (P = 0.01) (**Table 4**). Statistically, other variables

Table 3. Zinc serum, anthropometry and nutritional status at baseline and after 6 months of milk intervention

Variables	Baseline		After 6 months intervention	
	Zinc-fortified milk A	Standard milk B	Zinc-fortified milk A	Standard milk B
Mean serum zinc, µmol/L* (SD)	13.50 (± 3.05)	13.46 (± 3.08)	10.59 (± 1.93)	10.34 (± 1.90)
Mean anthropometry (SD)				
Weight, kg	19 (± 1.75)	18.95 (± 1.72)	20.37 (± 1.98)	20.25 (± 2.00)
Height, cm*	117.05 (± 4.65)	116.9 (± 4.62)	120.09 (± 4.71)	119.89 (± 4.74)
MUAC, cm*	16.63 (± 0.90)	16.83 (± 0.86)	17.08 (± 0.83)	17.18 (± 0.96)
Sitting height, cm*	61.85 (± 3.05)	61.78 (± 3.02)	64.38 (± 2.49)	64.16 (± 2.47)
Nutritional status, n (%)				
Underweight	122 (56.2)	125 (59.8)	107 (49.3)	120 (57.4)
Stunted	88 (40.6)	81 (38.8)	77 (35.5)	74 (35.4)
Wasted	39 (18)	51 (24.4)	26 (12)	30 (14.4)

* Significantly different and correlated by zinc milk fortification
MUAC: Mid-upper arm circumference

Table 4. The change of zinc status (µmol/L)

Variable	Month 0-3			Month 0-6			Month 3-6		
	Adjusted estimation			Adjusted estimation			Adjusted estimation		
	B	P	95% CI	B	P	95 % CI	B	P	95 % CI
Intervention of milk A	- 1.24*	0.048	-2.49 to (-0.01)	-0.33	0.28	-0.92 to 0.27	1.50*	0.01	0.36 to 2.65
Iron intake	0.07	0.503	-0.14 to 0.28	0.11	0.05	-0.00 to 0.22	-0.08	0.44	-0.29 to 0.13
Zinc intake	-0.04	0.890	-0.55 to 0.48	-0.14	0.05	-0.28 to (-0.00)	0.06	0.68	-0.21 to 0.32
Calsium intake	0.00	0.227	-0.01 to 0.00	0.00	0.03	0.00 to 0.00	0.01	0.00	0.00 to 0.01
Vitamin C intake	0.00	0.911	-0.02 to 0.03	-0.01	0.32	-0.02 to 0.01	-0.02	0.06	-0.04 to 0.00
Δ step test score	.000	0.000	0.00 to 0.00	-8.82E-006	0.48	0.00 to 0.00	1.14E-005	0.70	0.00 to 0.00
	n observed : 426			n observed : 426			n observed : 426		
	Adjusted R2 : 0.05			Adjusted R2 : 0.02			Adjusted R2 : 0.06		
	P value : 0.00 *			P value : 0.04			P value : 0.00*		

i.e. zinc intake, calsium intake and step test score also influenced the zinc level; however those results did not clinically have significant difference.

Discussion

The recommended dietary requirement for children 4-8 years of age is 4-5 mg of zinc per day.[6] For both groups, almost all subjects had dietary zinc intake of less than their estimated average requirement (EAR) during the course of the study, despite the daily nutrient increase in both the intervention and control groups. After 6 months of intervention, the prevalence of children with zinc intake of less than 60% RDA declined from 97.7% to 85.7% in the control group, and from 98.6% to 70.8 % in the intervention group. Although we gave subjects zinc-fortified milk, many children still had zinc intakes of less than 60% RDA. This is probably caused by low consumption of good sources of zinc, such as meat, seeds, nuts, poultry, and eggs which are rarely consumed due to their cost. These subjects likely have a high consumption of rice, which is high in phytates. As is commonly seen in developing countries, phytates can negatively influence micronutrient absorption, because phytates form insoluble complexes with zinc in the gastrointestinal tract, thus inhibiting zinc absorption in humans.[9]

We observed a decrease in serum zinc concentration after the first three months of milk intervention, but not accompanied by growth retardation. However, after the second three months of intervention, subjects' serum zinc concentration increased (**Table 4**). These results suggest that serum zinc concentrations may further increase if milk is given for a longer period in children with chronically low zinc intake. Since the population had chronically inadequate zinc intake, it may take more time to for the homeostatic menchanism of zinc equilibrium to be established.

Currently, serum zinc concentration is the most widely used biochemical indicator of a population's zinc status and is the only biochemical indicator of zinc status for which adequate reference data is available.[5,3,18] Nevertheless, serum zinc concentration is not recommended as a reliable indicator for diagnosing mild or moderate zinc deficiency in individuals, because humans have an efficient homeostatic mechanism to maintain plasma zinc at normal levels, except when zinc depletion is prolonged and severe.[16] Our baseline data confirmed that the majority of subjects at high risk of zinc deficiency had serum zinc concentration in the normal range, although nearly all had low zinc intake. When dietary zinc supply is extremely low or after prolonged marginal intake, secondary homeostatic mechanisms stabilize serum zinc at normal or near-normal concentrations, possibly due to the change in the rate of plasma equilibrating pools, resulting in decrased zinc pools and a negative zinc balance will occur.[8,11] Considering the chronic zinc deficiency in most subjects, we assumed that the zinc pool was negative at the baseline. Thus, after the first three months of intervention, even though there was a decrease in the zinc status, there was an increase in the zinc pool. It was also possible that the zinc was utilized to support the growth as shown in the increase of growth in most subjects. As the intervention occurred, there was an increase of zinc status in the second three months. It is assumed that the zinc pool was balanced at that period of time.

We observed a significant decrease in mean serum zinc concentration in both groups after the milk intervention. In children with chronically low zinc intake, good nutrition may impact changes in zinc level. In contrast to our findings, an experimental study in school children aged 6 to 9 years in the Suba District, Kenya reported increased mean serum zinc levels after they were fed 100 grams corn-soy blend porridge. The porridge provided 5.0 mg of zinc per day for a period of three months. They observed a significant reduction ($P=0.0421$) in the number of zinc-deficiency cases, from 95.4% to 70.2%, with mean serum zinc increasing from 8.4 to 10.2 μmol/L ($P=0.002$).[19] This difference may be related to the zinc status of the study populations, the content and bioavailability of zinc in the local diets or the study methodologies, such as variations in the dose, chemical form, method of zinc administration and duration of supplementation. In the Kenyan study, at baseline nearly all (95.7%) of the school children were zinc-deficient, with low serum zinc ($<10.7\mu$mol/L). It was estimated that their population had severe zinc deficiency mostly caused by acute phase infections associated with the high prevalence of HIV, leading to homeostatic mechanism failure to maintain critical

levels of serum zinc concentration. In contrast, the baseline data of our study showed that the majority of children (83.57%) had serum zinc concentrations in the normal range (≥10.7μmol/L). Most zinc deficiency in our population was caused by long-term low zinc intake. The prevalence of HIV infection was not as high as in the Kenyan population.

However, after the fortified milk intervention, serum zinc concentration decreased significantly to mean serum zinc concentration of 10.59 ± 1.93 μmol/L, slightly lower than the normal levels of 10.7 μmol/L. Nonetheless, subjects' growth improved (weight, height, MUAC, and sitting height). Furthermore, our results suggest that a longer intervention period may yield even better effects of milk fortification. Subjects showed a decrease in serum zinc levels of 1.25 μmol/L in the intervention group during the first three months, while growth increased significantly. It is possible that the reduced serum zinc level reflected utilization of zinc by the cells for growth and improvement of the negative zinc balance in zinc pools. The level of serum zinc concentration is influenced by the amount of zinc in endogenous tissue pools; the lower the level of zinc pools, the higher the rate of plasma fractional turnover rates.[11,20] After individuals establish a state of equilibrium in zinc pool levels, serum zinc levels may also increase. After the second three months of milk supplementation, subjects had a 1.50 μmol/L increase in serum zinc levels in the intervention group, possibly indicating that a state of equilibrium in zinc pools had been established. The change in serum zinc levels in our study may reflect a secondary homeostatic mechanism to sustain critical levels of zinc in tissues until the equilibrium of the zinc pools is reached.[8,11]

In other studies, in subjects with chronic zinc-depletion, plasma zinc concentrations did not decline significantly, even though the total exchangeable zinc pools (EZPs) were decreased.[11,13] Previous studies in humans also suggest that EZPs, thought to supply the zinc required by tissues, turn over more rapidly in individuals with lower zinc intakes.[20] However, adjustment of the plasma zinc concentration may be a better marker of acute, severe depletion, whereas the total EZP may reflect zinc status of long-term low zinc intake.[11,20] Furthermore, flucuations in the serum zinc concentration in our study may not be a reliable biochemical indicator of individual zinc status with long-term, low or marginal zinc intake. Future studies using tracer techniques are needed to further measure turnover rates and zinc pool sizes, as a powerful marker of chronic zinc-depletion states.

Data from our study suggests that adjustments in zinc homeostasis in subjects with chronically low zinc intake do not occur rapidly. Changes continue to occur for months, possibly until equilibrium is established. It is highly recommended that promotion and support of a longer period of milk supplementation be implemented in children with high risk of zinc deficiency, in order to enhance their zinc status, especially during rapid growth periods. Therefore, a nutrition promotion model, such as providing a balanced diet in the form of school breakfast or lunch programs is needed for optimal growth.

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Conflict of interest statement

Leilani Lestarina was employed by Nestle Nutrition, Nestec Ltd, Indonesia during the time of the study.

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