

## **Zinc: The Next Global Agenda?**

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### **INTRODUCTION**

The importance of zinc in human nutrition was first recognized during the 1960s, when it was found to be the underlying cause of growth stunting, and of delayed sexual development, in Egyptian adolescents (Prasad, 1990). The interests of nutrition scientists in zinc were renewed during the 1980s and 1990s when it was observed that zinc supplements improved the growth of growth-stunted, predominantly Mexican-American preschool children (Walravens *et al.*, 1989) and failure-to-thrive infants (Hambidge *et al.*, 1985) in Denver, Colorado, and malnourished children in Ecuador (Dirren *et al.*, 1994). During the past decade, there has been a substantial increase in the number of intervention studies conducted to determine whether zinc supplements improve growth and reduce the morbidity of infants and children, or improve pregnancy outcome. These studies are summarized in this article, with the overall purpose of evaluating whether there is a need to pay more attention to zinc deficiency in the global agenda of improving micronutrient status.

### **THE BIOLOGY OF ZINC**

Zinc is the most abundant trace element in the cytoplasm of humans, but 90% of the mineral is located in the muscle, bone and liver. Zinc makes strong, exchangeable complexes with organic molecules, including proteins, nucleic acids and membranes. It is associated with more than 200 metalloproteins, and is required for the activity of many enzymes, for nucleic acid and protein synthesis, and for the synthesis of hormones including insulin, adrenal corticosteroids and testosterone. It is therefore not surprising that a deficiency of this nutrient impairs many functions. Examples include delayed growth and sexual maturation, poor skin and wound healing, reduced taste acuity and appetite, increased incidence and duration of diarrheal disease, slower dark adaptation, and poorer cognitive performance. Zinc deficiency has its strongest impact on rapidly turning over cells such as those in the intestinal mucosa and the immune system. Zinc requirements are highest during periods of greatest growth such as pregnancy, infancy and early childhood.

### **ZINC REQUIREMENTS AND PREVALENCE OF DEFICIENCY**

The most recent recommendations for dietary zinc intakes are provided in Table 1 (Institute of Medicine, 2001). While zinc intakes of many people in the world are lower than these recommended levels, the global prevalence of zinc deficiency is still uncertain. In the 1950s zinc deficiency was recognized to be common in the Middle East, where poor absorption of zinc was

due to the high phytate content of unleavened bread, consumption of soil (geophagia), and hookworm (Prasad, 1990). These environmental factors, as well as low intakes of animal products which are good sources of absorbable zinc, are thought to be the main predictors of zinc status worldwide, but this has been difficult to confirm because estimates of the bioavailability of zinc from foods vary widely depending the assessment method used, and there are no good indicators of zinc deficiency in humans. Where low ( $<70$  ug/dL,  $<10.7$  umol/L) concentrations of plasma zinc are common, a zinc deficiency problem is probable, but many individuals probably exist in a state of marginal deficiency with plasma zinc concentrations above this level. Another uncertainty is the extent to which higher efficiency of zinc absorption and lower endogenous secretion can compensate for low intakes of absorbable zinc (King *et al.*, 2000). Diarrhea, especially if persistent, is also likely to be a key determinant of zinc status because high fecal zinc losses occur in this condition (Rosado *et al.*, 1997). While it is often stated that the best indicator of zinc deficiency is improved function (such as faster growth or less morbidity) in response to supplementation, this criterion assumes that the improved function is due to alleviation of deficiency, rather than to a pharmacological effect.

**Table 1.** Dietary Reference Intake Values for Zinc by Life Stage Group.<sup>5, a</sup>

Life Stage	EAR (mg/d)		RDA (mg/d)		Criterion
	Males	Females	Males	Females	
0 to 6 mo	-	-	2	2	Average zinc in breast milk <sup>b</sup>
7 mo to 3 y	2.2	2.2	3	3	Factorial analysis
4 to 8 y	4.0	4.0	5	5	Factorial analysis
9 to 13 y	7.0	7.0	8	8	Factorial analysis
14 to 18 y	8.5	7.5	11	9	Factorial analysis
19 to >51 y	9.4	6.8	11	8	Factorial analysis
Pregnant # 18 y		10.5		13	EAR for age + fetal zinc
Pregnant 19 to 50 y		9.5		11	EAR for age + fetal zinc
Lactation # 18 y		11.6		14	EAR for age + milk zinc
Lactation 19 to 50 y		10.4		12	EAR for age + milk zinc

<sup>a</sup> EAR = Estimated Average Requirement, RDA = Recommended Dietary Allowance.

<sup>b</sup> Values for 0 to 6 months are recommendations for adequate intakes.

<sup>5</sup> Institute of Medicine, 2001

## GROWTH RESPONSE TO ZINC SUPPLEMENTATION

The classic studies of Prasad (1990) in the Middle East were among the first to demonstrate that without doubt zinc supplementation can improve the growth of stunted children in regions of severe zinc deficiency. In the United States, short, 2 to 6 year old Mexican-American boys (but not girls) in Colorado responded to zinc supplements (5 mg/d for 12 months) with improved growth in height and an associated increase in food intake (by 600 kcal/d) (Walravens *et al.*, 1989). Likewise, a dramatic improvement in height gain was reported when undernourished Ecuadorian children aged 13 to 50 months were supplemented with 10 mg zinc per day for 15 months (Dirren *et al.*, 1994). This effect was statistically significant within 6 months of starting the supplementation but only in the male children (although it approached significance for the females). Over the 15 months of the study the males gained 1 cm more, and the females 0.6 cm

more, than the placebo group. These studies stimulated further research on the growth-promoting benefits of zinc supplements but subsequent research produced apparently inconsistent results. For example, Rosado *et al.* (1997) found no effect on length or weight of providing zinc supplements to 18-36 month old short or stunted children in a rural Mexican population with a low intake of absorbable zinc. Twenty mg/d was given under supervision for 6 days a week for 12 months (Rosado *et al.*, 1997). In contrast, stunted (length-for-age  $<-2$  Z) Guatemalan infants responded with faster linear growth when they were given a 10 mg/d zinc supplement for about 7 months (Rivera *et al.*, 1998).

To clarify the effect of zinc supplements on growth, we conducted a meta-analysis of zinc intervention studies that had been designed for this purpose (Brown *et al.*, 1998). By reviewing the literature, 25 randomized, controlled trials were identified as being suitable for this analysis. The meta-analysis revealed that zinc supplements produced a small (0.22 SD) but highly significant improvement in height gain in the trials overall. However, this effect was only significant in studies where the children's initial mean height-for-age Z score was  $<-2$ . For these studies the average effect size was +0.46 SD in height or length gain. The size of the effect was unrelated to the dose of zinc used (which was usually 10-20 mg/d) or the duration of the supplementation trial or age of the child. The effect of zinc on weight gain was smaller (average +0.26 SD) and inversely related to initial plasma zinc concentration. There was no effect of the supplement on weight-for-length. The mechanisms by which zinc increases the growth of such children is uncertain, but it may improve appetite or disease resistance, or affect tissue synthesis through hormonal or other factors. This meta-analysis reveals that children are more likely to respond to zinc supplementation if they are initially stunted ( $<-2$  Z in height or length), and/or have low plasma zinc. What is less clear, as discussed above, is what predicts these conditions in human populations.

## **MORBIDITY RESPONSE TO ZINC SUPPLEMENTATION**

Several investigators reported an improvement in the incidence and/or duration of diarrheal disease when zinc supplements were given to children in developing countries. For example, in the Mexican study by Rosado *et al.* (1997) in which the 20 mg/d supplements failed to improve growth, there was a significant reduction in the number of episodes of diarrhea over the year even though the overall incidence of diarrhea was relatively low. In Guatemala, supplementation with 10 mg/d zinc for 7 months significantly reduced the incidence of diarrhea within one month, although this effect was larger in boys and among children who initially had a low weight-for-length (Brown *et al.*, 1998). There was also a 67% reduction in the percent of children who had one or more episodes of persistent diarrhea. In a pooled analysis of seven such studies of children with acute or persistent diarrhea, zinc supplements reduced the probability of continuing acute diarrhea on a given day by 15%, of continuing persistent diarrhea by 24%, and of treatment failure or death from persistent diarrhea by 42% (Zinc Investigations' Collaborative Group, 2000). In the four studies in which it was measured, zinc also reduced the incidence of pneumonia by about 40%. In at least two studies, zinc supplements lowered morbidity associated with malaria (Black, 1998).

## **ZINC SUPPLEMENTATION AND PREGNANCY OUTCOME**

A 1998 meta-analysis of nutritional interventions intended to prevent intrauterine growth retardation found that in the four studies which provided zinc supplements (total n=720 supplemented women) the odds ratio for a term, low birth weight infant was 77% of that in non-supplemented women (total n=698), but that the effect of the zinc was not statistically significant (DeOnis *et al.*, 1998). Another review of ten zinc supplementation trials conducted up to 1996 showed mixed results; in 4 out of 10 trials birthweight was higher in the supplemented group (Ramakrisnan, 1999). In three of these trials (in 2 of which birthweight was increased) the preterm delivery rate was lowered by zinc. Most of the trials were judged to be methodologically impaired and all except two were in industrialized countries. More recently, investigators found no significant effect of 15 mg zinc per day, provided with 60 mg iron and 250 ug folic acid in a randomized placebo controlled trial, on newborn weight, length or gestational age in 1295 Peruvian women with low zinc intakes (Caulfield *et al.*, 1999). However, the zinc supplements did significantly improve the development of fetal heart patterns and increased femur length (Merialdi *et al.*, 2001a; 2001b). Whether these responses result in positive postnatal effects remains to be determined. Osendarp *et al.* (2000a) more recently completed a randomized, placebo-controlled trial on 559 very poor women in Bangladesh. Thirty mg zinc was given starting at 12-16 weeks of gestation. No effect on pregnancy outcomes was observed. However, the prenatal zinc substantially reduced the postnatal incidence of acute diarrhea, dysentery and impetigo in the low birthweight (but not in normal birthweight) infants (Osendarp *et al.*, 2000b). Taken together, the weight of the evidence concerning zinc supplementation in pregnancy in developing countries shows it to be of relatively little benefit to in-utero growth but it may have more subtle effects on infant development and postnatal disease resistance.

## **INTERACTIONS BETWEEN ZINC AND VITAMIN A**

Zinc is essential for the synthesis of retinol binding protein and for the oxidative conversion of retinol to retinal. However, a review of randomized controlled zinc supplementation trials in human populations concluded that these have produced inconsistent effects on vitamin A status (Christian & West, 1998).

## **STRATEGIES TO IMPROVE ZINC STATUS**

Supplementation with zinc alone is an intervention that has been used predominantly in research studies. It is difficult to conceive of situations where zinc alone (i.e. without the inclusion of other micronutrients) would be a sensible public health strategy. One such situation might be for the treatment of persistent diarrhea, however, where fecal zinc losses are high. Even then, it is known that losses of copper and other micronutrients are also large. A more reasonable strategy in developing countries might be to ensure that zinc is included in multi-micronutrient supplements. Fortification of cereals with zinc is currently receiving some attention. For example, in Mexico it is included as one of the fortificants of commercial maize flour. The appropriate amount of fortification zinc will depend on the usual amount of the cereal consumed, and the need to keep total zinc intake safely below the recommended upper limit. The WHO has

set has set this limit at 60 mg/d, and the Institute of Medicine, at 7 to 34 mg/d for children and adolescents (depending on their age), and 40 mg/d for adults. The effectiveness of this strategy for improving health and function of populations needs to be assessed, but this may be difficult given that the cereal is likely to be fortified simultaneously with other nutrients such as iron and the B vitamins. In general there seems little reason not to include zinc with iron as a fortificant for cereals, although the efficacy and effectiveness of this strategy need to be evaluated.

Another strategy to improve zinc status is to encourage the consumption of foods rich in zinc. These include animal products (especially meat and shell fish), which of course also supply important amounts of iron, retinol, vitamin B-12 and other vitamins and minerals. This strategy deserves more attention, including efforts to increase local and household small animal and poultry production. Whole grains and legumes, some seeds (sesame, pumpkin, poppy) and leafy vegetables (spinach, endive) also contain substantial amounts of zinc. However, the bioavailability of zinc from plant sources can be much lower than that in foods derived from animals. Phytate in plants is particularly inhibitory to zinc absorption. Where foods are reasonably high in zinc but especially high in phytate (such as legumes), local or regional efforts to reduce phytate content by soaking, germinating or fermenting cereals may be helpful (Gibson *et al.*, 1998). However, the improvement in zinc status or health that can be accrued from such food preparation practices, and their sustainability, remain to be demonstrated. Plant breeding to lower phytate content and/or increase zinc content (Ruel & Bouis, 1998) is being evaluated for its ability to increase zinc absorption and improve zinc status.

## **FUTURE RESEARCH**

Further efforts are needed to develop better indicators of zinc status; to better predict the relative susceptibility of different populations to zinc deficiency and their response to zinc supplementation; to assess the bioavailability of zinc from specific foods and the extent to which it can be increased by practical processing methods; and assess interactions among zinc and other micronutrients in supplements or fortificants.

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