

ZINC FOR CHILD HEALTH IMPLICATIONS OF RESEARCH FINDINGS

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ABSTRACT

Malnutrition and various micronutrient deficiencies are widespread in developing countries. Although the role of vitamin A and iron in child health has been acknowledged for a long time, the importance of zinc has not been recognized until recently. Indeed, zinc is a micronutrient of great public health importance. Recent research has indicated that prevention of zinc deficiency among young children in developing countries could have a significant impact on health as well as the economy.

In the near future, the World Health Organization (WHO) will recommend oral zinc for the treatment of acute and persistent diarrhea in young children. The WHO has also proposed to include zinc in its essential medicine list. Several key issues regarding zinc research and the impact of zinc on child health will be discussed in this paper.

Key Words: Zinc, young children, diarrhea, child health, developing countries and Nepal.

INTRODUCTION

Zinc is an essential micronutrient and zinc deficiency is common in many developing countries leaving those affected more vulnerable to illness and death from infectious diseases.^{1,2} In many developing countries the intake of zinc dense foods such as meat and seafood is low and the intake of foods with zinc inhibitors such as phytate in cereals and legumes, is high.³⁻⁵ Frequent infections further impair the zinc status and worsen its consequences. This vicious cycle of sub-optimal nutrition and repeated infection results in a high burden of zinc deficiency in the developing countries, such as Nepal. The severe form of zinc deficiency leading to acrodermatitis enteropathica is not common, but marginal and moderate zinc deficiency is a widespread problem and is thought to affect more than 90% of the population in South Asia.^{6,7} In Nepal, two thirds of young children are malnourished.⁸ There is compelling evidence from animal and human studies that zinc

is essential for the normal cellular function involved in growth and development, in the immune system, in cell division and in differentiation of skin and epithelial cells.^{9,10} This paper will present recent evidence from studies of children in developing countries.

ESTIMATION OF ZINC STATUS IN NEPAL

Although the plasma zinc is sensitive to many conditions, such as stress, recent intake, dehydration and infection,¹¹ it is still the most widely used method to determine zinc status in humans. The prevalence of zinc deficiency in Nepalese women and children based on plasma zinc levels was found to be 84% and 69%, respectively, with a mean zinc concentration of 8.4 $\mu\text{mol/L}$.^{12,13} It should be noted that the children of whom zinc was measured were ill with diarrhea, which may have influenced the plasma zinc concentration.

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TOXICITY OF ZINC

Zinc is a non-toxic mineral and excess dietary intake is not absorbed and stored in body. However, some studies have reported increased vomiting due to zinc supplementation.^{12,14} This increased vomiting was not serious and did not affect the long-term health of the children.

ZINC FOR GROWTH AND DEVELOPMENT

Zinc is thought to enhance growth and development through several potential mechanisms, which are presented in Fig. 1.¹⁵⁻¹⁷ In a meta-analysis undertaken by Brown *et al.*, it was found that zinc supplementation resulted in a substantial increase in height and weight, the mean change in SD units height for age and weight for age was 0.35 (95% CI 0.19, 0.51) and 0.31 (0.18, 0.44), respectively.¹⁸ The effect of zinc supplementation was larger among children who were malnourished (stunted).

PREVENTION OF DIARRHEA AND PNEUMONIA WITH ZINC

Clinical trials in children of developing countries have shown that routine zinc supplementation reduces the incidence and prevalence of diarrhea.^{19,20} A pooled analysis of zinc supplementation trials from developing countries assessed the efficacy of daily zinc administration on diarrheal morbidity. This analysis showed an 18% (95% CI 7%, 28%) lower incidence rate and a 25% (95% CI 12%, 37%) lower prevalence

of diarrhea.²¹ This pooled analysis also included data for pneumonia from four trials²²⁻²⁵ and showed that routine zinc supplementation reduced the odds of pneumonia by 41% (95% CI 17, 69%). In a subsequent study involving 2500 Indian children, Bhandari *et al.* confirmed this protective effect of daily zinc administration on pneumonia.¹⁹ In this study there was no effect of zinc supplementation on mild pneumonia, but the effect was seen among those with severe pneumonia that usually included fever. The main preventive zinc supplementation trials and their effects on infectious diseases and mortality prevalence are presented in Table I.

TREATMENT OF DIARRHEA WITH ZINC

Sachdev and coworkers were the first to assess the therapeutic effects of zinc during diarrhea.²⁶ In a study on acute diarrhea they found that children who were given 40 mg of daily elemental zinc had shorter diarrheal duration and lower stool frequency than the controls. Following this publication, several trials on zinc supplementation during acute and persistent diarrhea have been conducted and the results from many of these trials have been summarized in two pooled analyses.²⁷ The analysis that included children with acute diarrhea showed that there was a 15% reduction of the duration in children receiving zinc (Table II) (Hazard ratio: 0.85, 95% CI 0.76, 0.95). In the trials that enrolled children with persistent diarrhea, therapeutic zinc reduced the time till recovery of diarrhea by 24% (Hazard ratio: 0.76, 95% CI 0.63, 0.91) and the risk of treatment failure or death by 42% (95% CI 10, 63%) (Table III).²⁷

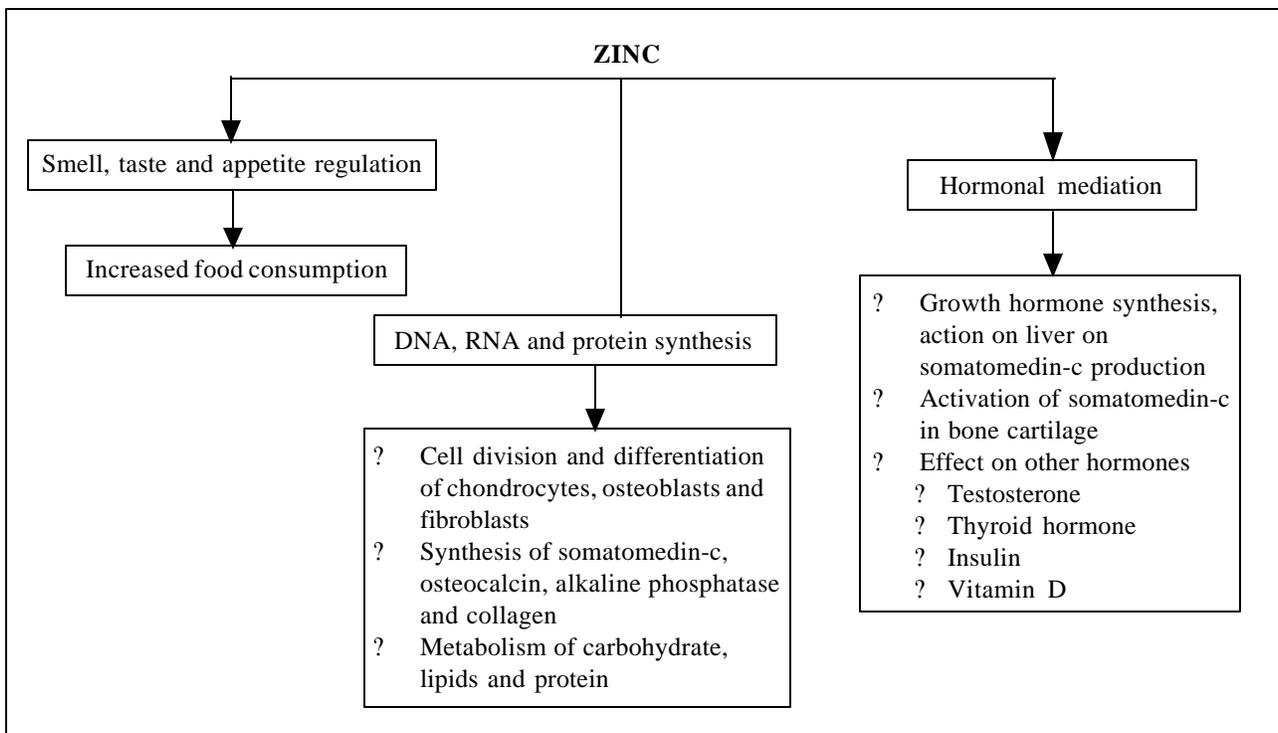


Fig. 1 : The mechanisms of zinc for growth and development (Reproduced from reference 15)

Table I : Effects of zinc in prevention of diarrhea, pneumonia, malaria and mortality in children

Author, year (Reference no)	Country	Diarrhea incidence (% lower)	Pneumonia incidence (% lower)	Malaria incidence (% lower)	Mortality incidence (% lower)
Bates, 1993[47]	The Gambia			32	
Ninh, 1996[24]	Vietnam	44 ¹	44 ¹		
Rosado, 1997[48]	Mexico	37			
Sazawal, 1998[25] [46]	India	8	43 ¹		68 ¹
Ruel, 1997 [49]	Guatemala	18 ¹			
Shankar, 2000[35]	Papua New Guinea	12		38 ¹	
Meek-Gardner, 1998[22]	Jamaica	8	88		
Penny, 1999[23]	Peru	12 ¹	15		
Umeta, 2000 [50]	Ethiopia	55 ¹			
Muller, 2001 [51]	Burkina Faso	16 ¹	57	2	58
Bhandari, 2002[19]	India		26 ¹		

¹ Statistically significant, i.e. $p < 0.05$
(Reproduced from reference 6)

Table II : Studies evaluating therapeutic effects of zinc supplementation in the treatment of acute diarrhea

Author, year (Reference no)	Country	No. of subjects zinc/placebo	Dose of zinc (elemental)	Difference in mean duration in days (95% CI)
Sachdev, 1988 [26]	India	25/25	40 mg	-0.4 (-1.4,0.6)
Faruque, 1999 [52]	Bangladesh	341/340	14.2 or 40 mg	-1.0 (-1.8,-0.2)
Dutta, 2000 [53]	India	44/36	40 mg	-1.4 (-1.6,-1.1)
Sazawal, 2001	India	547/547	5 or 10 mg	0.1 (-0.2, 0.3)
Cuevas, 2001	Brazil	37/37	22.5 or 45 mg	-1.3 (-1.9,-0.6)
Relative Hazards (95% CI)				
Hidayat, 1998 [54]	Indonesia	739/659	4.5 mg/kg	0.92 (0.83, 1.02)
Sazawal, 1997 [20]	India	456/481	20 mg	0.79 (0.69, 0.90)
Roy, 1997 [55]	Bangladesh	57/54	20 mg	0.85 (0.57, 1.28)
Bhatnagar, 2004 [29]	India	132/134	15 or 30 mg	0.77 (0.59, 0.99)
Bahl, 2002 [14]	India	404/401	15 or 30 mg	0.89 (0.80, 0.99)
Strand, 2002 [12]	Nepal	442/449	15 or 30 mg	0.79 (0.68, 0.93)
Baqui, 2002 [32]	Bangladesh	620/632	20 mg	0.77 (0.69, 0.86)

(Reproduced from reference 30)

Table III : Studies evaluating therapeutic effects of zinc on episodes of prolonged diarrhea (>7 days)

Author, year (Reference no)	Country	No. of subjects zinc/placebo	Dose of zinc (elemental)	Odds ratio (95% CI)
Hidayat, 1998[54]	Indonesia	739/659	4.5 mg/kg	0.72 (0.48, 1.07)
Sazawal, 1997 [20]	India	456/481	20 mg	0.85 (0.60, 1.19)
Roy, 1997[55]	Bangladesh	57/54	20 mg	0.77 (0.33, 1.79)
Bahl, 2002[14]	India	404/401	15 or 30 mg	0.61 (0.33, 1.12)
Strand, 2002[12]	Nepal	442/449	15 or 30 mg	0.57 (0.38, 0.86)

(Reproduced from reference 30)

After these pooled analyses were published, more studies on the therapeutic use of zinc in diarrhea have been completed.^{12,14,28,29} The findings from these studies were presented in a WHO meeting in New Delhi in 2001 and the report from this meeting³⁰ states: "Based on the results of this review, it is concluded that there is now enough evidence demonstrating the efficacy of zinc supplementation on the clinical course of diarrhea, with regard to the severity and

duration of the episode".

The results from a trial we undertook in 1,792 Nepalese children aged 6 to 35 months with acute diarrhea were included in this report.¹² In this trial the risk of persistent diarrhea was reduced from 5.2% to 2.7%, corresponding to a risk reduction of 2.5% (95% CI 0.2%, 5%) in those given zinc.³¹ A nearly fifty percent reduction in the risk of persistent diarrhea is indeed

promising and is supported by a recently published cluster-randomized trial in Bangladeshi children.³² This study also showed that there was a 50% reduction in mortality in clusters where children were given zinc along with standard treatment against diarrhea. It should be noted that there were only 40 fatalities and that children in the clusters that received zinc also had a higher intake of ORS.³⁰

ZINC AS ADJUVANT THERAPY FOR THE TREATMENT OF PNEUMONIA

Studies on routine zinc supplementation for the prevention of disease indicated substantial reductions in the prevalence of acute lower respiratory infection (ALRI). There is, however, limited information on zinc as adjuvant therapy for the treatment of ALRI. In a pneumonia study with Indian children there was an effect of zinc among boys, but not among girls.³³ Another recently published study from Bangladesh among 270 young children with severe pneumonia indicated that zinc supplementation reduced the duration (relative hazard (RH)= 0.70 (0.51, 0.98)) and hospital stay (RH 0.75 (0.57-0.99)).³⁴ Currently, we are undertaking a randomized clinical trial in Bhaktapur involving 2500 young children with WHO defined pneumonia to evaluate the effect of zinc as an adjuvant therapy. The main outcome is time till recovery and proportion with treatment failure.

ZINC SUPPLEMENTATION FOR THE TREATMENT AND PREVENTION OF MALARIA

The results from studies evaluating the relation between zinc supplementation for the prevention and treatment of malaria are still inconclusive. Studies from Gambia and Papua New Guinea³⁵ revealed reductions of about one-third in the rate of visits to health facilities due to malaria among zinc supplemented children. However, a multicenter trial in Ecuador, Uganda and Zambia that assessed zinc as adjuvant therapy during plasmodium falciparum malaria in 1087 young children concluded that, "Zinc does not appear to provide a beneficial effect in the treatment of acute, uncomplicated falciparum malaria".³⁶

ZINC AND IMMUNITY

Zinc supplementation has been shown to improve cell mediated immunity (CMI) in children.²⁰ Besides effect on CMI, the roles of zinc in modulating phagocytes and NK cell activity are also well described.³⁷⁻³⁹ The size of thymus, which is a central organ for maturation and differentiation of T-lymphocytes also decrease during zinc deficiency, a process that is reversed after zinc supplementation.^{40,41} Although both acquired and innate immunity seems to play an important role in the effect of zinc

during infections,^{42,43} the relative importance of these parts of the immune system remains to be determined. Furthermore, zinc metabolism is altered in infectious diseases. During inflammation, the plasma zinc is shifted into the liver causing depletion in other tissues.⁴⁴ Children who have poor zinc nutriture may thus be at a high risk of entering a vicious cycle of infection and zinc depletion. Breaking this vicious cycle is probably of great importance and may be the mechanism behind the beneficial effect on reduction of childhood morbidity and mortality.

ZINC FOR THE REDUCTION OF CHILDHOOD MORTALITY

As mentioned above, zinc administration in children of developing countries have shown a substantial reduction in the prevalence and severity of common infectious diseases such as pneumonia and diarrhea. Pneumonia and diarrhea are still major causes of under five-childhood mortality, so it is logical to consider that there will be a reduction in childhood mortality with a correction of zinc deficiency. Indeed, the Bellagio child survival study estimates that 5% of under five deaths can be averted by the implementation of a preventive zinc interventions program.⁴⁵ This figure is supported by the findings from a trial in 1,154 small for gestational age children where zinc supplementation resulted in a 68% reduction in the risk of dying.⁴⁶ A reduced death risk was also found among children belonging to clusters that received zinc as adjuvant therapy for acute diarrhea trial in Bangladesh.³² The WHO has followed up the promising results of these trials and is currently supporting three large clinical trials in India, Zanzibar and Nepal to evaluate the effect of zinc supplementation on childhood mortality.

Thus, there is compelling evidence that zinc is beneficial for the improvement of child health, particularly in developing countries where zinc deficiency is estimated to be a widespread public health problem. Oral zinc should be included in routine treatment for acute diarrhea and actions to improve zinc nutriture should be pursued. These actions would include dietary diversification / modification to enhance the availability, access and utilization of zinc dense foods, food fortification, supplementation, and most importantly, poverty reduction.

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