Zinc Deficiency among Indian Children

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ABSTRACT: An important essential trace element found in every tissue of the human body is zinc. The pervasive role of zinc in the metabolic function of the body results from its function as a cofactor of a multitude of enzymes. As zinc metalloenzymes are found in every known class of enzymes, the element plays an important function in every conceivable biochemical pathway. It is now clearly established that zinc confers no additional benefits to an individual with adequate zinc status while it can potentially lead to harmful effects by disturbing the milieu of other trace metals in the body. Information on the zinc status of Indian children is meager perhaps due to lack of reliable parameters. The present paper briefly discusses the extent, causes and effects of zinc deficiency among Indian children, along with its biomarkers and supplementation.

INTRODUCTION

Zinc is a trace metal which is essential for human health. The pervasive role of zinc in the metabolic function of the body results from its function as a cofactor of a multitude of enzymes. The essentiality of zinc for humans and its deficiency was recognized way back in 1963 (*cf.* Prasad, 2012). During the past 50 years, it has become apparent that zinc deficiency is a highly prevalent phenomenon among humans. It is estimated that nutritional deficiency of zinc potentially affects nearly 2 billion individuals in the developing countries.

As this element is found in every tissue in the body, and because zinc metallo-enzymes are present in every known class of enzymes, the metal has a function in every conceivable type of biochemical pathway (Evans, '86). Over 300 enzymes require zinc for their activation, and nearly 2000 transcription factors require zinc for gene expression. (*cf.* Prasad, 2012) Beside catalytic activity, it has useful and significant contributions in immune function, protein synthesis, wound healing, DNA synthesis, cell division, neurogenesis, neural migration and synaptogenesis. Zinc also supports normal growth and development during pregnancy, childhood and adolescence and is required for the proper sense of taste and smell. Zinc is essential for cell mediated immunity and is also an effective anti-oxidant and anti-inflammatory agent (*cf.* Prasad, 2012).

Zinc cannot be stored in the human body as a result of which a daily intake of zinc is necessary for each individual. Its deficiency is largely related to inadequate intake or absorption of zinc from the diet (Gibson,'94). Zinc deficiencies range from severe genetic disorder like acrodermatitis enteropathica to milder manifestation such as growth disorders, diarrhea and respiratory problems. It also impairs mental and fetal development. Consumption of cereal proteins high in phytate decreases the availability of zinc for absorption. Conditioned deficiency of zinc is also very common. Growth retardation, hypogonadism in males, rough skin, impaired

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immunity, neuro-sensory disorder and cognitive impairment are some of the clinical manifestations of zinc deficiency. Micronutrients deficiencies along with that of zinc increase the susceptibility to infectious diseases as well as impact its course and outcome (Bhaskaram, 2002). It has been clearly established that zinc confers no additional benefits to an individual with adequate zinc status while it can potentially lead to harmful effects by disturbing the milieu of other trace metals in the body (Bhaskaram and Hemalatha, '95). In therapeutic dosages, zinc has been used for the treatment of acute diarrhoea in infants and children, common cold, Wilson's disease, sickle cell disease and for prevention of blindness in patients with age related macular degeneration.

Zinc deficiency is common in children from developing countries due to lack of intake of animal foods, high dietary phytate content, inadequate food intake and increased fecal losses during diarrhoea (Bhatnagar and Natchu, 2004). Information on the zinc status of Indian children is meager. One of the principal causes could be a lack of a reliable parameter. This situation compels most of research to rely on randomized, placebo-controlled intervention trials to ascertain the prevalence and clinical consequences of zinc deficiency. Apart from the understanding etiology of various infectious diseases, interventional studies also have preventive benefits. However, there are good numbers studies (Thakur *et al.*, 2004, Singhal *et al.*, 2008, Tupe and Chiplonkar, 2010, Kawade, 2012) which utilized blood serum for investigating zinc deficiency along with some food analysis.

The Recommended Dietary Allowances (RDA) of zinc in different physiological age group as reported by Food and Nutrition Board (2000) and the report of a joint venture of World Health Organization (WHO) and Food and Agriculture Organization (FAO) of the United Nations (2004) are summarized in Table 1.

The Indian Council of Medical Research (2009) constituted an Expert Group to revise and upgrade the earlier RDA of nutrients for the Indian population and the details are given in Table 2.

TABLE 1

RDA values for zinc (adopted values)

Group		NIH (mg/d)	FAO/ WHO (mg/d)
Young children (1-3 years)		10	5.5 (3.3-11)
Pre-adolescents (11-14 years)	Male	15	9.3-12.1
	Female	12	8.4-10.3
Adults (25-50 years)	Male	15	9.4
	Female	12	6.5
Pregnancy			7.3-13.3
Lactation			12.7-9.6

BIOMARKERS OF ZINC

One of the foremost issues that come up here is that of a reliable biomarker for zinc. A biomarker is an objective biological measure that can be utilized to assess health or make a diagnosis of disease. According to the National Institute of Health (Biomarkers Definitions Working Group, 2001), a 'biomarker' is "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". The lack of indicators of zinc status for identifying individuals with zinc deficiency is now the main problem associated with our current understanding of the public health implications of inadequate intake of this element. Till date, plasma zinc concentration as a biomarker is of enormous importance for estimating zinc deficiency in both clinical set up and population based studies. Estimating the prevalence of zinc deficiency among different populations of developing countries is difficult because reporting on plasma or serum zinc concentrations is scare. As a matter of fact, proper zinc assessment surveys have not been done in the developing countries mainly from the points of view of methodological problems and costs. Furthermore, there is no common consensus of any universal standard for estimation of zinc levels from nails and urine. Studies have use 70 µg/g hair zinc level is used as standard for children below four years of age (Hambidge *et al.*, '72, Vaghri *et al.*, 2008, Xue-Cun, '85, O'Leary *et al.*, '80, etc). Widely used cut-off values for zinc level in serum recommended by International Zinc Nutrition Consultative Group (2007) shown in Table 3.

TABLE 2

RDA levels of zinc for the Indian population

Group		RDA for zinc (mg/d)
Adult Man		12
Adult Woman (NPNL)		10
	Pregnant	12
	Lactating 0-6 m	12
	Lactating 6-12 m	12
Children	1-3 y	5
	4-6 y	7
	7-9 y	8
Boys	10-12 y	9
Girls		
Boys	13-15 y	11
Girls		
Boys	16-17 y	12
Girls		

TABLE 3

Cutoff values for serum zinc concentration

Time of the day and fasting status	Cut off values (µg/dl)		
	< 10 years	≥ 10 years	
	Male and females	Non-pregnant females	Males
Morning, fasting	Not-available	70	74
Morning, non-fasting	65	66	70
Afternoon, non-fasting	57	59	61

The absence of a reliable biomarker for zinc increases dependence of research on supplementation studies including growth delay, diarrhoea, pneumonia, other infections, disturbed neuropsychological performance and abnormalities of fetal development. There are studies from India that have utilized biomarkers such as thymulin (Bhaskaram and Hemalatha, '95) and superoxide dismutase (Thakur *et al*., 2004). Another important development is the Adolescent Micronutrient Quality Index (AMQI). Kawade (2012) demonstrated the use of AMQI to assess quality of diets, while Chiplonkar and Tupe (2010) observed that higher AMQI scores were associated with higher concentrations of plasma vitamin C (r = 0.26), beta carotene (r = 0.34), and zinc (r = 0.12) levels. The AMQI appears to be a useful measure of the dietary adequacy and micronutrient quality of the diets of adolescent girls consuming lacto-vegetarian diets.

Dietary zinc supplementation among human leads to an increase in the levels of monocyte metallothionein mRNA on the Competitive Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and this response could serve as a more useful biomarker than the conventional plasma zinc (Sullivan and Cousins, '97). Very recent studies have examined the expression patterns of zinc transporter genes in human primary tissues as zinc transporters remain integral to the maintenance of intracellular zinc concentrations. Andree *et al*. (2004) investigated the use of lymphocyte gene expression such as zinc transporters in human lymphoblastoid cells ZNT1 and ZIP1 as biomarkers for zinc status in humans. After measuring the expression levels of ZIP1 and ZNT1 in the peripheral leukocytes, they explored the potential of ZIP1 as a biomarker of zinc status in humans. The positive association between the mRNA of ZNT1 and ZIP1, which have reciprocal roles in zinc transport across the plasma membrane, can provide insight into the coordinated control of zinc homeostasis in humans (Foster *et al*., 2011). The relative insensitivity or imprecision of plasma, various blood cell types and hair, measurements has resulted in general disappointment in their use to assess marginal zinc status. Therefore, the search continues to find a useful and reliable marker of marginal zinc deficiency (Wood, 2000). However, a systematic review by Lowe *et al*. (2009) of 32 potential biomarkers confirmed that among healthy individuals, plasma, urinary, and hair zinc are reliable biomarkers of zinc status. Further high quality studies using these biomarkers are required, particularly in infants, adolescents, and tribal population of India for whom there are limited data. Studies are also required to fully assess a range of additional potential zinc biomarkers.

Some Important Issues Related to Global Zinc Deficiency

Severe or clinical zinc deficiency may be defined as a condition characterized by short stature, hypogonadism, impaired immune function, skin disorders, cognitive dysfunction and anorexia (Prasad, '91). Although severe zinc deficiency is considered to be rare, mild-to-moderate zinc deficiency is prevalent throughout the world today (Sandstead, '91). It has been pointed out that a good percentage of the world's population has the potential to exhibit inadequate levels of zinc in the diet mainly due to limited access to zinc-rich foods (animal products, oysters and shellfish) and the abundance of zinc inhibitors, such as phytates, common in plant-based diets. Unfortunately, there is a lack of consensus on indicators of zinc deficiency and this has hampered efforts to document the prevalence of zinc deficiency. It is now a demonstrable fact that low zinc intake have detrimental effects of the health of children (Zinc Investigators' Collaborative Group, '99; 2000). For this reason, it is important to attempt to quantify the prevalence of zinc deficiency and its contribution to the global burden of disease. It is also very important to differentiate between zinc intake and absorption. Dietary surveys are routinely conducted in many of the developed countries, but few such surveys exist in the developing countries (WHO, '96). Even when dietary intake data are available, incomplete information on the content of zinc and its bioavailability in local foods makes the calculation of zinc bioavailability difficult.

Zinc Deficiency among Indian Children

Zinc deficiency appears to be widespread among children from the developing countries, including India. This is now being seen as an increasing area of concern in these countries. The overall picture of zinc deficiency is around 40.00% among Indian children. The prevalence is highest in Odisha (51.30%), followed by Uttar Pradesh (48.10%), Gujarat (44.20%), Madhya Pradesh (38.90%) and Karnataka (36.20%) (Kapil and Jain, 2011).

Malnourished children from India have been observed to exhibit low levels of serum zinc (Thakur *et al*., 2004). Similarly, malnourished children suffering from celiac disease also showed lower serum zinc concentrations (Singhal *et al*., 2008). Dhingra *et al*. (2009) had observed that 73.30% of the children studied were zinc-deficient (plasma zinc levels < 70 microg/dL), of which 33.8% had plasma zinc levels below 60 microg/dL. A significantly higher risk of morbidity was also prevalent among those with lower plasma zinc concentrations as compared to those with higher levels of plasma zinc. In a very recent study, Tupe and Chiplonkar (2010) investigated the diet pattern of the adolescent girls from Pune for bioavailability of zinc and they identified five diet patterns that reflected the intakes of different cereals. They further observed that the girls in the five diet patterns had inadequate intakes of energy, protein and essential trace elements including zinc when compared with the recommended dietary intakes applicable for the Indian populations. In another important study, Osei *et al*. (2010a) observed the nutritional status of primary schoolchildren in the Garhwal Himalayas and reported growth impairment and micronutrient (including zinc) deficiency among them. Kapil and Jain (2011) estimated the prevalence of serum zinc deficiency in children from 11 years to 18 years to be 49.40% (males: 50.8%; females: 48.2%) in a cross-sectional study conducted in the National Capital Territory of Delhi. Another very recent cross-sectional study (Reddy *et al*., 2011) also reported low levels of zinc among school children. Kawade (2012) also reported a high prevalence of micronutrient deficiencies including zinc, among girls aged between 10 years to 16 years.

Zinc Supplementation among Indian Children

Increased diarrhoea and respiratory morbidity are strongly associated with zinc deficiency (Bhandari *et al*., '96). Longer duration and severity of diarrhoeal appeared to be the greatest among infant and young children suffering from malnutrition and impaired immune status which again may be related with zinc deficiency (Sazawal *et al*., '95). The patho-physiology of protein malnutrition is also strongly related with depleted antioxidant protection, which is again due to the deficiency of zinc (Thakur *et al*., 2004). Revised estimates in the developing countries including India showed that acute diarrhoea accounted for 35%, dysentery 20% and non-dysenteric persistent diarrhoea for 45% of the total diarrhoeal deaths (Bhan *et al*., '96). In children with severe zinc deficiency, diarrhoea is common and responds quickly to zinc supplementation (Sazawal *et al*., '95, '96, '97) and to some extent in pneumonia (Bhatnagar and Natchu, 2004) for which further investigations are required. Bhandari *et al*. ('96) also reported increase morbidity among zinc deficient children suffering from respiratory infection. A dietary zinc supplementation resulted in a significant reduction in respiratory tract infection morbidity among preschool children (Sazawal *et al*., '98). The study of Osei *et al*. (2010b) also reported improvement after supplementation among the schoolchildren with lower levels of baseline serum zinc (74%) in the Himalayan areas.

Pneumonia results in two million deaths each year among children all over the world, 70% of them in Africa and South-East Asia (Singh, 2005). Although the study of Mahalanabis *et al*. (2002) on children with severe measles accompanied by pneumonia treated with antibiotics and vitamin-A did not show any additional benefit while receiving zinc supplementation, Natchu *et al*. (2008) reported that zinc supplement has been consistently shown to reduce the incidence of childhood pneumonia. However, its effect on the course of pneumonia when administered as an adjunct to antibiotic therapy remains unclear. The positive role of zinc supplement in pneumonia has also been advocated by Black (2003).

A meta-analysis of zinc supplementation trials and other essential elements by Bhandari *et al*. (2001) concluded that zinc and iron seemed to have a modest effect on linear growth in deficient populations. But it is not certain whether a combination of micronutrients, with or without additional food, would have a greater impact than that seen with zinc alone. Zinc along with iodine and folate are also required for the developing fetus (Udipi *et al*., 2000). Zinc supplementation among low birth weight babies for a year has resulted in substantial reduction in mortality (Bhatnagar and Natchu, 2004).

There is an improvement in nutritional status and memory after supplementation with multi-micronutrients fortified salt including zinc among schoolchildren (Vinodkumar *et al*., 2009). Zinc supplementation results in better motor development and more playfulness in low birth weight infants and increased vigorous and functional activity in infants and toddlers. Zinc is also believed to have impact on cognition of an individual like skills of perception, thinking, memory, learning and attention. In older school going children, the data is controversial but there is some evidence of improved neuropsychological functions with zinc supplementation (Bhatnagar and Taneja, 2001). Umamaheswari *et al*. (2011) evaluated the effects of iron and zinc deficiencies on short term memory of children in the age group of 6-11 years with supplementation therapy. They found a marked improvement in memory after supplementation. Kawade (2012) has also highlighted the impact of zinc in cognitive development.

It has been shown that the clinical presentation of zinc deficiency varies and depends on serum zinc level (Kumar *et al*., 2012). Dhingra *et al*. (2009) observed a significantly higher risk of morbidity among those subjects with lower plasma zinc as compared to those with higher levels of plasma zinc. Soil deficit in zinc also has an impact on the zinc level of food grains but serum zinc levels can be maintained by other food sources (Sunanda *et al*., '95). Rawal *et al*. (2010) reported a rise in zinc level even with Gluten Free Diet irrespective of zinc supplementation. Iron fortification of foods with NaFeEDTA also did not affect urinary zinc excretion in children (Amalrajan *et al*., 2012). A case study of the introduction of fortified wheat flour in Gujarat's Public Distribution System (PDS), Integrated Child Development Scheme (ICDS), and Mid-Day Meal (MDM) Programme to assess the coverage, costs, impact, and cost-effectiveness by Fiedler *et al*. (2012) laid emphasis on the introduction of similar reforms throughout India.

CONCLUSION

Thus it is evident from the above discussion that zinc supplementation, bio-fortification and zinc rich recipe are essential for the prevention of zinc related morbidity and mortality among children. The studies of Stein *et al*. (2007), Chiplonkar and Kawade (2012) are very pertinent here. Zinc along with iron, vitamin A and iodine are strongly related with child survival in this country and the supplementation programs are cost effective, However, the preventive interventions are reaching only a small proportion of the targeted populations (Kotecha and Lahariya, 2010). In a significant review, Patel *et al*. (2010) concluded that there is significant heterogeneity of responses to zinc supplementation and suggested the need to revisit and revise the strategy of supplementation in the treatment of children with acute diarrhoea in developing countries such as India.

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