

ZINC IN PAEDIATRIC HEALTH AND DISEASES

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ABSTRACT

The nutritional need of various micronutrients is realised within the last decade with the advent of newer better diagnostic techniques. Lower intake of animal foods which are the prime source of zinc, lower quality of nutrients intake, higher faecal loss of Zn during diarrhoea and inhibition of absorption of Zn by phytates present in the vegetables are some of the causes resulting in zinc deficiency in children of developing countries. Its importance in the management of persistent diarrhoea is gaining momentum with satisfactory results are being reported worldwide particularly when associated with severe acute malnutrition. Further the potential role and consensus guidelines for routine use of Zn in the prevention of infective diseases like acute respiratory tract infections, malaria, tuberculosis and particularly in intrauterine growth retardation babies is to be proven in time to come. Better dietary habits, food fortification and increased awareness and health education can prevent the Zn deficiency to a large extent.

Key-Words: Diarrhoea; Micronutrients; Pneumonia; Zinc (Zn)

Introduction

A number of micronutrients have gained attention of the researchers in the last decade because of their varied roles in normal physiology and biochemical processes. Of all the micro nutrients, iron is the most important and well known entity, having grave consequences in deficiency status. In addition to iron zinc is now increasingly realised to have wide public health impact. Zinc is required for effective functioning of multiple enzymes including enzymes of cell division, transcription and translation of genetic material. It is an important constituent of bio membrane and other proteins. Because of its role in cellular metabolism, its deficiency is manifested more in rapidly dividing cells, like for cells of immune system.^[1] Zinc deficiency also affects skin, respiratory, gastrointestinal, skeletal and reproductive system.

Main dietary source of zinc is animal source food, as the bioavailability of zinc is more in this type of food. High consumption of cereals and legumes, which contains inhibitors of zinc absorption^[2], low nutritive quality of food along with frequent enteric infections leading to faecal losses of zinc.^[3], contributes to zinc deficiency in growing children in developing countries. Effect of Zn in infections is studied in diarrhoea, pneumonia and other lower respiratory tract infections, upper respiratory tract infection, malaria and dengue.

Zinc in Infections

Zinc supplementation is associated with improved immune

response in diseases with frequent infections like sickle cell diseases^[4], HIV infections^[5] and Down syndrome^[6]. Zinc supplementation restores lymphocyte production, natural killer cell's function, wound healing and resistance to infections.^[1,7,8] Study by Bahl et al showed a positive correlation between low plasma zinc level and greater susceptibility to infections.^[9] However because of lack of proper cut off values and coexistence of other nutrients deficiency, Zn has not yet been used as a marker of increased risk for infections.

Zinc in Paediatric Diarrhoea

Worldwide diarrhoea accounts for annual death of 1.5 -2.5 millions in under five year of age.^[10,11] In India every year about 3.4 lakh children die of diarrhoea diseases.^[12] Centre for disease control -1992 made the first recommendation for use of zinc in acute diarrhoea.^[13] A joint statement by WHO and UNICEF reports decreased duration, severity and subsequent recurrence within next 2-3 months following use of Zn along with low osmolar ORS in acute diarrhoea.^[14] A pooled analysis of randomized control trials, reports 18% decreased incidence of acute diarrhoea in children aged 3 months to 3 years who received Zn supplementation as compared to those children who did not receive Zn.^[15] A study by Bhatnagar et al reported a 31% decreased in total stool output in Zn supplemented diarrhoea group as compared to placebo group.^[16] Total stool output is the most objective marker of severity of diarrhoea and also an indirect marker of dehydration.

A study by Bahl et al compared the efficacy of Zn in

diarrhoea comprising of 3 groups as Zn fortified ORS, Zn administered separately along with ORS and ORS alone acute diarrhoea.^[17] Zinc supplementation given separately with ORS solution was found to be most efficacious in reducing the duration of diarrhoea followed by zinc fortified ORS and then ORS alone.^[17]

A possible mechanism of action of Zn in diarrhoea is inhibition of basolateral potassium channels, which inhibits cAMP induced chloride dependent fluid secretion as studied in in-vitro study on rat ileum.^[18] It also improves the absorption of water and electrolytes by helping in early regeneration of brush border enzymes and also by enhanced immune response by improved cellular and humoral immunity.^[19,20]

Zinc in Respiratory Disorders

In India, under five mortality of 1.7 million children were reported in 2010, with major causes as pneumonia (24%) and diarrhea (13%).^[21] Zinc supplementation in young children has demonstrated variable effects. Two recently published randomized control trials from Bangladesh and India, studied the effect of zinc supplementation along with antibiotics, in reducing the severity of ARI or pneumonia in children less than 2 year of age.^[22,23] A 30% reduction in duration of severe pneumonia as evidenced by reduced fast breathing, chest in-drawing and hypoxia were reported by study in Bangladesh.^[22] Another trial from Kolkatta reported significantly increased recovery rate by 2.6 times in comparison to controls.^[23] Study by Aggarwal et al reported reduced risk of developing pneumonia in children supplemented with zinc.^[24] However some double blind trials have suggested no beneficial effects of zinc supplementation in ARI with respect to duration of severity of pneumonia, tachypnoea, chest in drawing or hypoxia.^[25-27]

Study by Rerksuppaphol et al reported decreased duration of cough, rhinorrhoea and other symptoms of upper respiratory tract infections in 8 to 13 year old school going children supplemented with zinc, with no effects on incidence of common cold or URTI.^[28]

Zinc in Malaria

Zinc supplementation as an adjuvant to standard anti-malarial treatment in plasmodium falciparum malaria in preschool children were shown to reduce the number of visits to health centres, as per a randomized control trial in Papua New Guinea by Shankar et al.^[29] Another RCT as published in American Journal of clinical Nutrition -2002, evaluated effect of zinc as an adjuvant to standard anti-

malarial drugs, across five countries in Africa and found no effect on duration of fever, parasitemia or change in Hb concentration in the initial 72 hours or during the 4 weeks follow up period, though serum Zn level showed a rise.^[30]

Zinc in Dengue

One study has correlated low serum zinc level with higher severity of Dengue and higher liver enzymes level indicating more liver cell injury.^[31] However till today no clinical trial has been published regarding zinc supplementation of Zn in Dengue.

Zinc in Human Growth and Lactation

Zinc is present as a prosthetic group in a number of metalloenzymes for example, carbonic anhydrase, alkaline phosphatase, carboxypeptidase, catalyzing various key biochemical reactions in human body. Zinc is an essential micronutrient, involved in maintaining adequate immune response^[32], DNA replication, transcription and translation^[33], as a component of cell membrane^[34], and also required for proper brain development^[35]. Zinc has an effect on normal functioning of growth hormone, by modulating the function of polypeptide hormone receptor zinc sandwich.^[36]

This mechanism explains the close relationship between altered zinc level and plasma insulin like growth factor (somatomedin C).^[37,38] Zinc deficiency in antenatal life has a negative influence on physical and intellectual development in humans.

Zn is essential in maintaining the proper structure of biomembrane^[34], for DNA and RNA synthesis and metabolism of essential fatty acids^[39] and hence is an essential micronutrient in pregnancy^[40]. Zn deficiency has been associated with an increased rate of foetal malformation^[41], premature rupture of membrane^[42], and also IUGR^[43]. Conflicting results have been published about association between levels of Zn deficiency and IUGR.^[44-46] The effects of Zn deficiency in pregnancy may be mediated through altered placental or maternal prostaglandin production.^[47]

In a clinical trial supplementation of 15 mg of daily zinc, along with iron and folate during pregnancy, reported an increased range of foetal heart rate and improved foetal activity, both indicating better foetal well-being and subsequent development of the foetus, as compared to the foetus of non-zinc supplemented pregnant women.^[48] Zinc content of breast milk is dependent on maternal serum zinc level.^[49] Mothers with deficient Zn status, secrete Zn

deficient breast milk, in an attempt to conserve maternal Zn level.^[50] Formula milk has lower Zn content as compared to breast milk and so babies fed with formula milk are more prone to have lower Zn level and consequent impaired growth.^[51]

Different studies on effect of Zn on physical growth have published inconsistent results. A meta-analysis by Brown et al.^[52], reviewing 33 different studies, found a small positive impact on linear growth and weight gain in Zn supplemented prepubertal children. Another randomized control trial has shown no effect on human growth with similar doses of zinc used.^[53]

Zinc in Neurodevelopment and Intelligence

Zinc acts as neurotransmitter and as an essential component for cell division, DNA and RNA synthesis and integrity of cell membrane; it is required for proper development of nervous system and intelligence in later life. Studies on role of micronutrients in cognitive development has suggested its role in development of cognition, intelligence, behavioural response to stress, emotion and also on motor activity.^[54,55]

Zinc is also found to be beneficial in treatment of attention deficit hyperactivity (ADHD) disorder when prescribed along with methylphenidate.^[56] A study done by Mahmoud et al. have reported a lower Zn level in ADHD patients^[57] and another study reported improvement in symptoms on Zn administration^[58]. Behavioural disease like autism, has also been reported to be associated with lower zinc level^[59], whereas some other studies published in conclusive results^[60,61].

Zinc in Oral Health

Study on relationship between zinc deficiency and children's oral health, reported increased incidence of dental caries, gingivitis, and bleeding gums in zinc deficient children with improved symptoms on zinc supplementation.^[62] Compromised oral health is a reflection of role of zinc in general immune response, lower quality of the food ingested and personal hygiene.

Zinc in Malnutrition

Protein energy malnutrition (PEM) patients show low plasma and brain zinc levels, reported from all over the world.^[63-67] Nutritional rehabilitation of PEM slows down in associated zinc deficiency as reported by Golden et al.^[68] These studies suggest rapid recovery of PEM in zinc supplemented diet, however to decode exact role of zinc

during rehabilitation, it requires further studies.

Zinc in Oral Health

Zn plays a regulatory role for RBP (Retinol Binding Protein) synthesis in the liver^[69,70] and also for intracellular transport of vitamin A^[71]. Lower RBP levels are seen in Zn deficient individuals.^[72] A study in India has demonstrated an increase in serum vitamin A and RBP in malnourished children after only five days of Zn supplementation.

Miscellaneous Effects of Zinc

Large doses of Zn inhibit copper absorption from the gut and hence it has been approved by US food and drug administration (USFDA) in 1997 for lifelong treatment of Wilson's disease^[73,74] along with Penicillamine.

A recent study in patients with acute Leukaemia on chemotherapy has shown reduced incidence & severity of chemotherapy induced adverse effects in patients who were given Zn supplementation along with chemotherapy.^[75] The logical explanation for the same is improved immune response and its role in cell division & DNA & RNA synthesis.

Monitoring Zn Level and Associated Problems

Biologically Zn behaves as a type II nutrient. Its tissue concentration may not vary considerably with a deficient state, although there may be a significant cessation of growth.^[76] Even in very severe Zn deficiency, quantitative reduction in Zn level may remain small. Hence clinical features of Zn deficiency become evident only in very severe cases and may remain undetected and unreported in milder deficiency. Moreover most of the time the clinical presentation are nonspecific like growth retardation, increased risk of infection, poor weight gain etc. making the diagnosis of Zn deficiency more difficult. Metallothionein I (MI) is measured as a Zn specific buffer pool.^[77,78] MI-I synthesis by liver is induced during stress, however in Zn deficient status MI bound Zn level is decreased.^[79] Metallothionein I is measured as an indicator of body store of Zn.^[77] Serum Zn level varies considerably with Zn status and is also affected by a number of confounding factors, hence alternatives like leukocyte Zn level,^[80] hair analysis and measurement of Zn dependent metallothionein like alkaline phosphatase are the other available options to study the Zn status of an individual. Additionally Zn metabolic balance studies to analyse its absorption, endogenous secretion and metabolism can be done by use of stable Zn radioisotopes.^[81,82]

Conclusion

Zinc deficiency is frequently encountered in third world countries closely associated with protein energy malnutrition and low quality of diet ingested. Zn is required for proper immune response and hence its deficiency is reflected as an increased incidences and severity of childhood infections in the form of diarrhoea, pneumonia and ARI.

Recent Cochrane database review published in June 2012, does not support Zn supplementation in diarrhoea, however multiple RCTs are in favour of Zn supplementation.^[83] No recommendations has been made for its use in pneumonia, ARI, ADHD, autism and other learning disorders, however clinical experiences in developing countries where people's buying capacity is low and Zn deficiency is seen as a component of widespread multiple nutrients deficiency, zinc supplementation in the form of fortification in different day to day foods, improves growth and resistance to and recovery from infections.

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