The Role of Zinc in Health and Disease: Relevance to Child Health in Developing Countries

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The last few years have witnessed the earnest recognition of the vital role of micronutrients in human health. The pioneering work by Sommers et al[1] in Indonesia on the impact of vitamin A supplementation in young children with respiratoty infections, has led to a host of experiments evaluating the impact of both clinical and subclinical deficiency of micronutrients on child survival[2]. Of the micronutrients, in addition to vitamin A and iron, zinc stands out as the one with the greatest potential public health impact. Although, compared to other micronutrients, zinc status is considerably more difficult to assess in humans[3], its biological effects in malnourished children are diverse, ranging from a profound impact on growth[4], to a significant role in regulation of immunity[5]. This review will focus on cunent concepts of the biological effects of zinc, with special reference to its potential role in the paediatric age group in Pakistan.

Role of Zinc in iluman Growth

The importance of zinc in biological systems was recognized as early as 1869 by Raulin during studies on Aspergillus niger[6]. Although the importance of zinc in animals had been established[7,8], human zinc deficiency was first described by Prasad in 1961[9]. Since then, the importance of zinc in human metabolism and growth in both health and disease has become well established[10]. It is currently known that over 200 zinc metalloenzymes exist in the human body[11]. Of these, many e.g., carbonic anhydrase, alkaline phosphatase, carboxypeptidase A,B etc., perfonn a variety of vital functions. However, zinc deficiency does not exert its effects through deficient function of these enzymes alone. Zinc also performs a vital biological role in maintenance of biomembranes[12] and is also considered essential for DNA replication, transcription and translation[13]. Other important roles attributed to zinc include maintenance of adequate immune function[14] and brain development[15]. Our knowledge on the scope and contribution of zinc nutrition to paediatric physiology has widencd considerably since the initial limitation to six clinical 'syndromes'[16] and zinc is .now considered crucial to the maintenance of satisfactory growth in childhood. Zinc deficiency has been shown to effect the function of human growth hormone by modulating with the function of the polypeptide hormone-receptor 'zinc sandwich,[17] This could provide a mechanism to explain the close relationship between alteration in zinc nutriture and plasma insulin-like growth factors (Somatomedin C) [18,19]. A growth limiting mild zinc deficiency state has been described in young boys with short stature[20]. Although initial studies of zinc supplementation of the diet failed to show any significantly, greater effect on growth[21] and appetite[22], other studies of zinc supplementation have shown to significantly improve the linear ;rowth and weight gain of preschool children with stunting[3,24],

Role of zinc in intrauterine growth and lactation

The essential role of zinc in the maintenance of structure of biomembranes[12], DNA and RNA synthesis[13] and metabolism of essential fatty acids[25], makes it an extremely important micronutrient in pregnancy[26]. A close association has been found between zinc status and normal fetal growth[27-30] and abnormal zinc nutriture has also been associated with an increased rate of malformations[31,32] and premature rupture of membranes[33]. Ofparticularinterest is the association between low maternal levels of zinc and intrauterine growth retardation (IUGR)[34,35]. Although some studies have failed to show a

clear association between zinc and copper status and IUGR[36,37] others have found low maternal zinc levels to be the strongest predictor for low birth weight[38]. The effect of zinc depletion in pregnancy may be mediated through altered placental or maternal prostaglandin production[39] and the leucocyte zinc content has also been used to predict development of IUGR[40].

The zinc level of breast milk decreases progressively with the duration of lactation[41] and is also influenced by maternal zinc intake[42]. The malnourished mother with marginal zinc status may also produce zinc deficient breast milk[43] as a means ofconserving maternal zinc[44]. However, the breast milk content of zinc is higher than that of commercial formulae. It is thus possible that postnatal low zinc intake, especially associated with poorly fortified formulae, may lead to hypozincemia[45,46] and poor growth.

Relationship of zinc and malnutrition

Although the close relationship of altered zinc hemostasis with growth in marginally nourished children, is well known[47,48], the most dramatic effects of zinc deficiency are seen in association with protein energy malnutrition. Serum albumin and pre-albumin metabolism are also closely dependent on zinc status[49] and have been suggested as useful parameters to monitor the health of children at a community level[50]. Low plasma and brain zinc levels have been found in children with protein energy malnutrition from all over the world, including South America[51,52]. Mexico[53], Egypt[54], Turkey[55], India[56], Nigeria[57], Jamaica[58] and among aboriginal children in Australia[59]. Zinc deficiency is especially associated withcertain special sub-types of malnutrition[60] and long standing PEM[61]. An association has also been found between zinc deficiency and supplementation on thymic regrowth and immune function[62-64]. In addition to effect on immune function, zinc supplementation of malnourished children has been shown to dramatically increase linear growth, weight gain and sexual maturation[65-67].

Zinc deficient diets have also been implicated in the delayed recovery from protein energy' malnutrition (PEM)[68]. The close relationship between zinc deficiency and the anorexia and reduced protein turnover of PEM is well known[69]. Golden et al[70] studied the prevalence of relative zinc deficiency in PEM and demonstrated reduced rates of weight gain during nutritional rehabilitation in zinc deficient children. It was also demonstrated that zinc supplementation led to decreased energy cost of tissue deposition[65-71]. However, there are very few studies analyzing the impact of zinc supplementation in malnutrition on changes in body composition, as such studies were difficult to perform in young children. The recent development and refinement of newer techniques of metabolic analysis in young children e.g. stable isotope (Doubly labelled water) estimation[72] and bio-impedance analysis[73], has made suchstudics widely possible. Such infonnation on the impact of different forms of nutritional rehabilitation on body composition is essential for optimal assessment of dietary therapy[74]. Thus, though zinc supplements are considered extremely important in the recovery phase of malnutrition[75], their exact role in nutritional rehabilitation requires further study, with improved assessment of body composition changes.

Relationship of zinc and vitamin A

There is a large body of experimental evidence suggesting a role for zinc in vitamin A metabolism[76]. It has been shown that zinc deficiency impairs synthesis of rctinol binding protein (RBP)[77,78] and that zinc has a regulatory role in RBP synthes is[79] . Zinc is thought to effect the release ofRBP from the liver and RBP levels have been shown to be lower in zinc deficient individuals[80]. Studies in India by Shingwckaret al[81] also provide supportive evidence for zinc-vitamin. A interaction in malnourished children[81]. They demonstrated an increase in plasma vitamin A and RBP in malnourished children after

only 5 days of zinc supplementation. Such zinc supplementation has been shown to improve vitamin A status inpreterm infants[82] as well as adults with alcoholic cirrhosis[83]. Although, a role for zinc in intercellulartransport of vitamin A is well established, recent experimental data also strongly suggest an essential role for zinc in intracellular transport of vitamin A[84]. Thus, in population with zinc deficiency and adequate stores of vitamin A, zinc supplementation may also improve vitamin A status concomitantly.

Role of zinc in diarrhoeal disorders

By virtue of its essential role in DNA replication and membrane synthesis[12,13] adequate supplies of zinc are important for intestinal regeneration and maintenance of mucosal integrity[85,86]. Zinc deficiency has been associated with ultrastructural changes and increased intestinal permeability[87]. Both short term and severe zinc deficiencyl is associated with alteration of intestinal brush border and disaccharidase activity[88,89] and altered mucosal glucose/electrolyte transport[90]. The role of zinc in sodium transport at a cellular level is only just being unravelled. Zinc supplementation has been shown to improve leucocyte sodium transport in children with protein energy malnutrition[91,92]. It is probable that zinc effects the red cell membrane calcium ATPase, in turn modulating intracellular transport mechanisms and membrane excitability[93]. Increased intestinal aminoacid losses have also been described after zinc depletion[94].

Although diarrhoea itself may be a manifestation of zinc deficiency[95], profound effect on zinc losses and balance have been described as a consequence of diarrhoeal illnesses. Profoundly increased fecal zinc losses and decreased blood levels of zinc have also been demonstrated after acute diarrhoea[96-100]. Similarly, increased endogcnous losses of zinc and decreased serum/glasma zinc have been described after chmnic diarrhoea[101,102]. A recent survey of zinc status in malnourished children has indicated profound depression of zinc levels[103]. Prolonged depression of serum zinc has also been described after post-measles diarrhoea[104] and such abnormalities are felt to be major determinants of the Hdiarrhoea_malnutrition cycle"[105].

It is therefore natural that the potential of zinc supplementation during diarrhoeal disorders has intrigued researchers and has been recommended as a fortification measures against malnutrition[106]. However, the available data on supplementation studies is scanty and conflicting. In a controlled trial of oral zinc supplementation in acute diarrhoea, Sachdev et al[107] were able to demonstrate some shortening of diarrhoea duration and frequency. Prelliminarry data from similar studies at ICDDRB also demonstrated significant clinical, nutritional and immunological benefits of zinc supplementation during diarrhoea[108]. A subsequent study of oral zinc sulfate (20 mg twice daily) supplementation by Sachdev et al[109] in two small groups of infants with persistent diarrhoea showed improvement in zinc status and some effect (though insignificant) on diarrhoea duration and frequency. An additional crucial question in studies of oral zinc suppleinentation is of zinc bioavailabilitv. It is unclear if the total body zinc status regulates intestinal absorption of zinc[110,111]. Other micro-nutrients such as copper may also interfere with zinc absorption[112] and dietary constituents such as phytates[113] may be important in determining zinc availability for absorption. This is particularly important when evaluating dietary management of diarrhoea and malnutrition with traditional, cereal-based. Thus studies of dietary zinc replenislunent must also evaluate issues such as bioavailability and endogenous losses[118,119].

Monitoring zinc nutriture and problems in assessment

One of the major limitations in our understanding of zinc "status" and its role in human nutrition, has been the difficulty in assessing zinc "deficiency" and the impact of "supplementation" studies. It is now clear that zinc behaves biologically as a "type II nutrient"[120] i.e., its tissue concentrations may not var considerably with a deficient state, although there may be a significant diminution or cessation of

growth. Even in very severe zinc deficiency the quantitative reduction in total zinc is small. Conversely. clinical features of zinc deficiency may only be clearly evident in very severe cases and milder deficiencies may not be recognizable. Sometimes, the clinical features are non-specific e.g., although growth retardation is one of the earliest and best documented forms of mild zinc deficiency. it is not specific. Urinary excretion of zinc, though a sensitive indicator and index of zinc intake, is difficult and tedious to monitor accurately. There has been recent interest in measuring zinc content of rectal biopsy specimens. However, such measurements are technically difficult, with a significant risk of contamination and the clinical applications of this particular diagnostic tool are naturally very limited.

There has been recent interest in the measurement of metallothionein I (MT) as a zinc specific metabolic buffer pool[121,122]. Increased hepatic metallothionein I (MT) synthesis is the main mechanism by which zinc is redistributed in the body in response to stress etc i.e., in zinc deficiency states, zinc bound MT is reduced, whereas, MT levels are increase in response to infection or stress provided the subject is zinc sufficient[123]. However, there are a number of technical problems in metallothionein radioirnrnunoassay but a recent red cell MT ELISA test seems much more promising[119].

In summary. despite a wide understanding of the status of zinc nutrition in man[124], satisfactory methods of assessment of zinc remain elusive[125]. Blood levels, both plasma and semm, may vary greatly and are also effected by a host of factors. Hypozincaemia e.g., as in pregnancy[126], does not necessarily reflect a zinc deficiency state and may be adaptive. Although alternatives such as measurement of leucocvte zinc status[127] or hair analysis have been suggested, their usefulness as indices of zinc status has been questioned. However, despite limitations, plasma or serum zinc remain very useful in confinnation of moderate to severe zinc deficiency[128,129] especially when used in conjunction with oilier tests such as, measurements of zinc dependent metalloenzymes such as. alkaline phosphatase or a metabolic buffer such as metallothionein. Additional dynamic information can also be obtained from zinc metabolic balance studies[126] although these are technically difficult to perfonm The recent introduction of stable zinc radioisotopes has made investigation qf zinc absorption, endogenous secretion and body zinc exchange, possible[130,131].

Despite the limitations of currently available laboratory assays and investigations, trials of dietary supplementation with zinc in suspected individuals offers the best opportunity of assessing the biological and nutritional significance of such trace element supplementation. It is thus appropriate to quote Hambidp from a recent review of assessment of zinc status[125]..“If supplementation is associated with a physiological or clinical response. this approach may provide the most convincing evidence obtainable of a pre-existing specific trace element deficiency state. Moreover, such a response would indicate that the deficiency was of physiological or clinical significance or both”.

Potential impact of zinc deficiency among children in Pakistan

The exact magnitude of clinical and subclinical zinc deficiency among children in Pakistan is unknown. However, most of the risk factors including maternal malnutrition, intrauterine growth retardation, PEM and diarrhoeal episodes are very common. The incidence of low birth weight among newborn infants in Pakistan exceeds 22%[132] and zinc deficiency has been frequently noted in such circumstances[35,37]. Low level of zinc have also been noted among Asian pregnant women in UK[36] It is also not uncommon to encounter severn clinical zinc deficiency such as, acrodermatitis enteropathica in malnourished children with diarrhoea, but milder degrees of zinc deficiency are often unrecognized (ZA Bhutta and AM MolIa, unpublished observations). Given the myriad effects of zinc on immune function, zinc deficiency in malnourished children could precipitate a variety of intercurrent infections, further delaying clinical recovery from diarrhoea[133].

Despite the lack of specific data from Pakistan, there is sufficient regional information to indicate that clinical and sub-clinical zinc deficiency may be prevalent. Some of the earliest cases of clinical zinc deficiency were described from a westerly neighbour, Iran[134] in growth retarded adolescents. A number of studies in Bangladesh in malnourished children[75] and in those with diarrhoea[107] have identified both low blood levels of zinc as well as noticeable clinical improvement after zinc supplementation.

A closer and comparable population would be that of North India. In a series of studies from Delhi, Sachdev et al have reported serum levels of zinc as well as rectal mucosal measurements in children withacute and PD[108,110]. They were able to identify 30- 40% reduction in serum and rectal mucosal zinc levels in children with PD, in comparison to normal age and nutritionally matched controls. It is therefore, logical to assume that similar incidence of zinc deficiency exists in Southern Pakistan. Although wheat is a traditional staple in many parts of the country and has a comparatively higher zinc content[135], many of the other traditional weaning foods, particularly rice based diets, are relatively low in zinc content and have high phytate content, effecting zinc bioavailability.

In our previous studies employing a traditional khitchri and yogurt diet in the nutritional rehabilitation of PD" 117, the estimated daily zinc intake was a mere 0.02 rug per 100 KCa1 consumed. This would have been insufficient to replenish diminished body stores in deficient states and could potentially lead to increased energy cost of growth. We did observe slowing of weight gain in many children fed the khitchri-yogurt diet alone during the second week of nutritional rehabilitation and it is possible that in addition to other factors, micronutrient deficiencies may have played a role in this observed nutritional "dip". Another question which remained unanswered, was the nature of the dramatic initial weight gain observed during nutritional rehabilitation, as no other measure of body composition was used. It has been suggested that the weight gain in such children on cereal based diets may be related to the accumulation of fibre or water in the bowel. rather than tissue deposition[136], The nature of weight gain and tissue accretion during and after rehabilitation requires further investigation.

We believe therefore, that the question of micronutrient deficiency during PD, merits further exploration in Pakistan. Two recent regional studies suggest that zinc supplementation may have a significant role in susceptible populations.

Sazawal et al provided 20 mg elemental zinc daily in a double-blind randomized controlled trial to children with acute diarrhoea in India and were able to convincingly demonstrate a 23% reduction in the risk of continued diarrhoea[137]. Similarly, Roy in studies of zinc supplementation of zinc deficient children with PD in Bangladesh[138] demonstrated a significant reduction in stool output as well as the rate of intestinal mucosal regeneration[139]. These regional supplementation studies suggest that zinc replacement may play an important role in recovery from diarrhoea. If a role of zinc deficiency in PD and malnutrition could be demonstrated in our paediatric population, appropriate pharmacological interventions and/or dietary manipulations could be recommended for nutritional rehabilitation and would have a considerable public healthbenefit.

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