Editorial

The Role of Zinc in Child Health in Developing Countries: Taking the Science where it Matters

The role of zinc in human health has been recognized for almost half a century with the discovery of the syndrome of zinc deficiency, delayed sexual development and growth failure among adolescents in Iran(1). Following the discovery of this association however, despite sporadic studies of zinc supplementation in malnourished children and the recognition of the association between zinc deficiency, malnutrition and prolonged diarrhea(2), systematic evaluation of the role of zinc in child health and policy relevant research has been relatively slow.

Zinc is widely recognized as an essential micronutrient with a catalytic role in over a 100 specific metabolic enzymes in human metabolism(3). These include all major enzyme-classes (oxidoreductases, transferases, hydrolases, lysases, isomerases and ligases). Zinc also chelates with the amino acids cysteine and histidine, forming 'zinc fingers' that are important for protein transcription. Additional processes that are regulated by zinc include expression of the metallothionein gene, apoptosis and synaptic signaling. Zinc is one of the most ubiquitous of all trace elements involved in human metabolism and plays multiple roles in the perpetuation of genetic material, including transcription of DNA, translation of RNA, and ultimately cellular division. It is thus critical to understand the role of zinc in health and disease, especially during the vulnerable periods of growth and development(4).

Unlike other essential micronutrients such as iron and vitamin A, there are no conventional tissue reserves of zinc that can be released or sequestered quickly in response to variations in dietary supply. It is recognized that the equivalent of approximately one-third (~450 mg) of total body zinc exchanges between the blood stream and other tissues(5). The major source of zinc intake is through diet, with the transcellular uptake occuring in the distal duodenum and proximal jejunum, potentially facilitated by specific transporters, such as zinc transporter protein-1 (ZnTP-1) (6). The intestine also serves as the major conduit for zinc elimination from the body with almost 50% of the daily zinc losses occurring in the gut. However, much of the zinc that is secreted into the intestine is subsequently reabsorbed, and this process serves as an important point of regulation of zinc balance. Other routes of zinc excretion include the urine, which accounts for approximately 15% of total zinc losses, and epithelial cell desquamation, sweat, semen, hair, and menstrual blood, which together account for approximately 17% of total zinc losses(7).

Given the diverse array of biological functions of zinc, it is not surprising that multiple physiological and metabolic functions, such as physical growth, immunocompetence, reproductive function, and neurobehavioral development are all affected by zinc status. When the supply of dietary zinc is insufficient to support these functions, biochemical abnormalities and clinical signs may develop. The potential benefit of zinc on the immune system can be mediated via a variety of pathways including stabilization of the epithelial barrier, and function of neutrophils, natural killer cells, monocytes,

and macrophages. In addition zinc status may affect lymphocyte counts and function occur, as well as alterations in the balance of T helper cell and TH1 and TH2 cytokines(8,9).

Growth and Development

Given the multiple metabolic roles of zinc and the earlier reports of the clinical association of zinc deficiency, there has been considerable interest in the potential growth benefits of zinc. Although the primary mechanisms whereby zinc influences growth are uncertain, there is a large body of literature indicating that zinc depletion limits growth and development. These include several studies of zinc supplementation among low birth weight infants (LBW) in developing countries indicating significant benefits on weight gain and some benefit on linear growth(10-12). Subsequent trials in Bangladesh (13, 14) have likewise found greater weight gain among severely malnourished inpatients who received supplemental zinc (10 mg/kg/day up to a maximum of 50 mg/day) during the course of nutritional rehabilitation.

However, there have been relatively fewer reports of a positive effect of zinc supplementation on children's linear growth during recovery from severe malnutrition perhaps related to the duration of supplementation and pre-existing zinc status. A recent meta-analysis of 33 randomized intervention trials evaluating the effect of zinc supplementation on the growth of pre-pubertal children(15) concluded that zinc supplementation produced highly significant positive responses in linear growth and weight gain (mean effect sizes of 0.30-0.35 SD units), with comparatively greater growth responses in children with low initial weight-for-age or height-for-age Z-scores.

Effect of Zinc on Diarrhea

Given the association and biological plausibility of the role of zinc in intestinal mucosal injury and recovery, a number of randomized controlled trials have demonstrated significant reduction in the incidence and duration of acute and persistent diarrhea in zinc-supplemented children compared to their placebo-treated counterparts (16,17). A pooled analysis of randomized, controlled trials of zinc supplementation performed in nine low-income countries in Latin America and the Caribbean, South and Southeast Asia, and the Western Pacific, demonstrated that supplemental zinc led to an 18% reduction in the incidence of diarrhea and a 25% reduction in the prevalence of diarrhea (18). While the pooled analysis did not find differences in the effect of zinc by age, baseline serum zinc status, presence of wasting, or sex, the relevance of zinc supplementation to various geographic regions of the world remained unclear. Recent studies from Africa using zinc supplementation in young children indicate significant benefit on diarrhea burden indicating that the effect may be consistent across various geographical regions(19,20) and even if zinc is administered with oral rehydration solution(21). Recent studies in Bangladesh of using zinc in the treatment of diarrhea in a community setting have also demonstrated substantial reduction in concomitant use of antibiotics by health-care providers(22), thus suggesting that there may be additional benefits to the use of zinc in the treatment of diarrhea. It is also anticipated that the forthcoming World Health Assembly will also ratify a joint UNICEF WHO statement that will strongly endorse the use of zinc supplements in young children with diarrhea.

Respiratory Infections

Despite advances in the recognition and management of acute respiratory infections (ARI), these account for over 20% of all child deaths globally(23). In preventive trials of zinc supplementation, a significant impact has been

shown on the incidence of acute lower respiratory infections(24-26). The recent pooled analysis of trials conducted in India, Jamaica, Peru and Vietnam indicated an overall 41% reduction in the incidence of pneumonia among zinc-supplemented children(27). More recently, the administration of zinc to children hospitalized with pneumonia in Bangladesh has been shown to reduce the severity and length of hospitalization (Brookes A, *et al.*, Lancet 2004 in press).

Malaria

The benefits of zinc supplementation on the severity of disease and outcome of malaria are less straight forward. Bates, *et al.*(28) administered 70 mg zinc twice weekly for eighteen months to children in Gambia and were able to show 32 % reduction in clinic visits due to *P. falciparum* infections. Similarly a trial undertaken in Papua New Guinea among pre-school children(29) indicated a 38% reduction in clinic visits attributable to *P. falciparum* parasitemia as well as heavy parasitemia. In contrast a recent trial in Burkina Faso did not find any reduction in episodes of falciparum malaria among children who received daily supplementation with 10 mg zinc for six months(19). This variable effect of zinc in malarial areas may be related to an impact on the severity of disease rather than the incidence.

Programmatic challenges: Atwater memorial lecture (King)

The aforementioned evidence indicates the potential role of zinc for improving child health in public health settings(30). While much of the data derives from efficacy trials, they are largely restricted to well-controlled experimental situations, even in community settings. What is needed however, are large effectiveness trials in representative settings that may help understand and develop mechanisms for the use of zinc in health systems in a replicable and sustainable manner. The Bellagio child survival group estimated that the introduction of zinc in prophylactic and therapeutic public health programs could save as much as 9% of all under-5 deaths globally(31). Given the emerging evidence of the scale and magnitude of zinc deficiency in south Asia(32), it is important that these interventions be evaluated at the earliest.

There is an additional unfinished research agenda that must also be pursued without holding zinc interactions back. It is also important to unravel several unanswered questions such as interactions with iron and multiple micronutrient deficiencies in susceptible populations, optimal delivery systems for zinc and frequency of administration as well as potential adverse effects(33). However, given the overwhelming evidence of the potential benefit of zinc for treatment of at risk children in susceptible populations, it is important to introduce this intervention in public health systems as soon as possible.

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