Zinc and diarrhea

K Michael Hambidge

Department of Pediatrics, University of Colorado Health Sciences Center

Malnutrition is a major factor in the etiology, management and prognosis of persistent diarrhea in young children. Apart from inadequate energy intake, deficiencies of several specific nutrients have been implicated. Zinc is a micronutrient that appears to be of special interest, at least in some communities. Zinc deficiency has been documented in otherwise normal children. The risk of deficiency, however, is enhanced by diarrhea which is associated with variable but sometimes gross increases in zinc losses in the feces. These losses could contribute to a vicious circle, as there is now evidence that mild as well as severe zinc deficiency states can contribute to the duration and severity of diarrheal disease. During rehabilitation, impaired zinc nutriture could be responsible for slow growth, especially if the rehabilitation diet is high in phytate, a recognized inhibitor of zinc absorption. Research should be directed to a better understanding of zinc metabolism and homeostasis during diarrhea disease, to the consequences of zinc deficiency and to the benefits to be derived from zinc supplementation programs.


The interrelationships between nutrition and persistent diarrhea are both complex and important. In addition to the well documented significance of energy, protein, and major mineral deficiencies there is growing interest in the putative role of several specific micro-nutrients. Zinc is notable among these micro-nutrients of interest. This paper will include a brief review of the biological functions and clinical importance of this trace element. The major focus of the paper will be a critical review of the evidence that diarrhea can lead to zinc deficiency and that zinc deficiency can cause or contribute to diarrhea with apparent potential for a vicious circle to be established. Attention will be given to the specific role of zinc during early nutritional rehabilitation. Finally, future research directions will be highlighted.

Role of zinc in biology

The zinc atom has a unique combination of chemical properties that render it extraordinarily useful in biological systems (1). Because of this broad range of properties, zinc has many and varied biological roles, several of which still require further clarification. Even at this stage of our knowledge, however, it is apparent that the biological importance of this trace element is outstanding. In contrast to iron and copper, zinc does not change valency state and is therefore of no value in redox reactions. For the same reason, however, the body is not at risk of oxidant damage from zinc which allows this element to be transported and utilized much more readily. Zinc has an active role at the catalytic site of a variety of enzyme systems. Favourable properties for a catalytic role include the highly localized charge and electroinfinity, its ability for fast ligand exchange so that substrates can be readily passed along to the next stage of their metabolism and its flexible coordination geometry. Ligands vary in length and angle of attachment and can have a strained or 'entatic' arrangement which adds to the catalytic potential at the active site of these enzymes. The ability for fast ligand exchange also makes zinc a favorable element for participation at the receptor site for hormones, as has been demonstrated recently for the prolactin receptor for growth hormone (2).

In addition to its extensive role as a catalytic ion, zinc also has important biological functions as a structural ion. Zinc, for example, has structural as well as catalytic roles in some enzymes, e.g. alcohol dehydrogenase (3). Biological membranes (4) and nucleic acids may also utilize zinc as a structural ion. Zinc can form flexible multidentate cross links such as those at the base of the “zinc fingers” that characterize some transcription proteins (5). This is but one of many roles identified for zinc in intracellular growth. Zinc is, for example, necessary for the integrity of histones, proteins that are intimately involved with DNA, and is a component of DNA and RNA polymerases and of cytosolic enzymes involved in protein synthesis. It has been hypothesized that zinc may play a central role in the regulation of cellular growth (1). Zinc may also prove to be an important intracellular regulatory ion comparable in biological importance to calcium but very little is yet known about the details of this role.

Because of the extraordinary variety of biological
functions of this one micro-nutrient, correlating the biochemical chemistry of zinc with clinical features of zinc deficiency is a daunting task that keys behind our understanding of the biochemical correlates of copper, iron, iodide, or selenium deficiencies. However, it is quite clear that a lack of adequate quantities of this micronutrient can lead to deranged cellular function at many important sites. Indeed, it would be surprising if zinc were not found to be important for the functional integrity of the enterocyte and there are a variety of plausible biochemical explanations for the diarrhea that occurs secondary to zinc deficiency.

Physiology of zinc absorption and homeostasis

The small intestine has the central role in maintaining zinc homeostasis. In normal circumstances, the gastrointestinal tract adapts effectively to changes in zinc intake and zinc nutriture with compensatory changes in fractional absorption and in excretion of endogenous zinc via the feces (6). Moreover, very substantial quantities of endogenous zinc that are secreted into the lumen of the gastrointestinal tract post-prandially have to be reabsorbed to avoid negative zinc balance. For example, in one study employing a multi-lumen tube technique in normal adults, 8.7 mg of zinc was recovered at the ligament of Treitz, 6.7 mg zinc in the proximal duodenum, and 6.8 mg zinc in the distal duodenum after a meal that provided a total of 5.5 mg zinc (7). These data, if correct, imply that 3.0 mg of zinc had to be absorbed beyond the duodenum, where zinc absorption is generally considered to be maximal, in order to achieve even zero net absorption of this element! It is readily apparent then that any disturbance of normal gastrointestinal physiology could profoundly affect zinc homeostasis.

Effect of persistent diarrhea on zinc nutriture

The results of several studies have indicated an association between diarrhea, especially persistent diarrhea, and abnormalities of zinc status including increased fecal zinc losses, negative zinc balance, hypozincemia and low tissue zinc concentrations. For adults maintained on total parental nutrition, intravenous zinc required to achieve positive zinc balance averaged 13 mg zinc per day in patients with on-going gastrointestinal fluid losses compared with a mean of 2.5 mg intravenous zinc per day in patients without any continuing gastrointestinal losses (8). This high intravenous requirement is greater than an average oral dietary zinc intake for adults in this country of which only about 25% would be absorbed. In these patients, ongoing zinc losses by the gastrointestinal tract were found to correlate with fecal mass (8). A similar correlation has been observed by Castillo-Duran in infants with diarrhea in Chile (9, 10). He also demonstrated the negative zinc balance that occurred in the early stages of treatment of acute diarrhea. Ruiz, too, has demonstrated the variable but sometimes very high fecal losses of endogenous zinc that occur during oral rehydration therapy of acute dehydrating diarrhea (11).

What effect can these excessive fecal loses of zinc have on zinc nutriture? At one extreme it appears that protracted diarrhea may eventually result in clinically severe zinc deficiency mimicking acrodermatitis enteroxopathica (12, 13). Generally, however, reports have been limited to low plasma, serum or tissue zinc concentrations. Naveh, found serum zinc to be depressed slightly in Israeli infants with acute diarrhea and markedly in those with diarrhea of more than ten days' duration (14). Serum zinc was found to be depressed but only temporarily in young Bangladesh children with acute diarrhea, while there was prolonged depression of serum zinc following post-measles diarrhea (15). In Chile, Castillo-Duran observed a strong negative correlation between fecal zinc losses and plasma zinc (9). Earlier studies in Chile had found depression of plasma zinc in acute diarrhea with normalization of levels during recovery (16) and both hypozincemia and low-hair zinc in children in chronic diarrhea (17). Despite the extensive documentation of hypozincemia in acute and persistent diarrhea it is important to recognize that this is not an inevitable association. It a study in Italy, children with chronic post-enteritis diarrhea had normal plasma zinc concentrations (18). Zinc nutriture is expected to depend not only on the extent of excessive fecal zinc losses, but on previous zinc nutritional status and the current dietary intake of this micro-nutrient.

Though the serum, or preferably plasma, zinc concentration remains the most extensively evaluated and accepted laboratory index of zinc status it lacks adequate sensitivity and has several other limitations (19). For example, allowing time for clot retraction before separating serum results in an increase in zinc concentration in the serum that is linear over a 2 h period (20). The concentration is also dependent on the time since the meal and the size of the previous meal (21). On the other hand, post-prandial zinc concentrations are more sensitive than post-absorptive concentrations to changes in zinc nutriture (22). At best, these and other factors introduce considerable 'noise'. For these and other reasons, many attempts are being made to identify other useful assays, including measurements of zinc concentrations in other tissue and measurements of the activity of zinc metallo enzymes (19). In general, none of these alternative or additional approaches have withstood the test of time and become clearly established as useful indices. Perhaps the most promising alternative index for children with diarrhea is the concentration of zinc in rectal mucosa. Sachdev has found this to provide a more sensitive index than serum zinc and has reported low-
Zinc deficiency as a cause of diarrhea

Diarrhea is one of the cardinal features of acrodermatitis enteropathica, the phenotypic expression of which is attributable to a severe zinc deficiency state (24). This rare, autosomal recessively inherited disease corresponds closely to Lethal Trait A-46 or Adema disease in cattle, in which diarrhea is also a prominent feature (3). Though a cardinal feature in most cases of acrodermatitis enteropathica, diarrhea does not occur in about 10% of subjects. The precise cause of the diarrhea associated with zinc deficiency has not been elucidated satisfactorily. Mild histological and ultrastructural changes have been documented in intestinal cells (3), but the integrity of junctional complexes has been reported to be preserved (25). Zinc is important for the integrity of the immune system (26). The potential importance of changes in gut immunity secondary to zinc deficiency merits research. The activity of several brush-border enzymes, including disaccharidases, has been reported to be depressed in zinc-deficient rats when expressed on a gram protein basis (27). However, in one study, disaccharidase activity was found not to be disproportionately affected by zinc deficiency (28). In a study using a rat model, Ghishan found that zinc deficiency causes significant reduction in net transport of sodium and water in the small and large intestine (29). That this observation may be relevant to the human is suggested by the results of a study on a small number of malnourished infants in Jamaica by Golden and Golden (30). In that study, zinc supplementation of a soy-protein diet used for the recovery stage from severe protein-energy malnutrition appeared to prevent diarrhea from occurring during late stages of recovery. The diarrhea that occurred in infants who did not receive the zinc supplement had a high sodium content. The results of this and of an earlier small study by the same investigators (31) indicate that relatively mild human zinc deficiency can also cause diarrhea with beneficial effects accruing from zinc supplementation.

Further evidence to support a role of mild-zinc deficiency in the severity and duration of some cases of diarrhea has been provided by a study by Sachdev in Bangladesh (33). In a controlled randomized study, 50 infants with acute dehydrating diarrhea were given 40 mg zinc per day or a placebo starting when rehydration had been accomplished. There was a trend for the zinc-treated group to have a reduced frequency of stools and a shorter duration of diarrhea. When data from a subgroup with low rectal mucosal zinc concentrations were analyzed separately and retrospectively, these differences were statistically significant. Thus, there is evidence, though still quite limited, that mild human zinc deficiency can contribute to the severity and duration of acute diarrhea and that correction of the zinc deficiency can have a favorable impact on the recovery from diarrhea.

Zinc during early nutritional rehabilitation

Several studies of different populations have demonstrated increases in physical growth velocity in infants and young children in response to dietary zinc supplementation (34–38). For example, significantly greater increases in weight-for-age Z scores were documented in zinc-supplemented infants and toddlers in Denver, Colorado compared with placebo-treated controls over a six-month study interval (34). The main criterion for inclusion in this study was a decline in weight-for-age percentile that crossed at least two major percentile lines and resulted in a weight-for-age less than the 10th percentile. As zinc supplements have no effect on growth when added to a diet that already has an adequate level of this micro-nutrient (39), the results of these studies are important in that they provide strong evidence for the occurrence of a growth-limiting mild zinc deficiency state. A similar growth response to zinc supplementation has been reported in young children during recovery from severe protein-energy malnutrition (40). Though a major focus of these studies has been on physical growth rates, which provide a relatively simple clinical marker, other consequences of mild to moderate zinc deficiency, especially impairment of T-cell function and other deficits in host defense mechanisms (26), are of greater potential concern. These observations on young children who were selected on the basis of poor physical growth are also likely to be of practical importance during rehabilitation of young children with persistent diarrhea and malnutrition in whom increased fecal losses of zinc must add to the risk of inadequate zinc retention.

Future research directions

(a) Zinc nutritional status: As new and promising approaches to the laboratory assessment of zinc status are identified, these should be applied to the assessment of zinc nutriture in young children with diarrhoea. One assay that appears to have potential is the determination of rectal mucosal zinc (23). Pilot
studies in our laboratories (Hong et al. unpublished observations) suggest that the use of zinc stable isotopes to measure the size of a pool of zinc that readily exchanges with zinc in plasma may provide useful information on zinc nutritional status. Such measurements could be undertaken as a component of more comprehensive kinetic studies (see item 2 below). Among other potentially useful indices of zinc status is the measurement of zinc uptake by erythrocytes in vitro (41).

(b) Zinc metabolism: Application of recent technical progress with the use of zinc stable isotopes in studies of human metabolism offers the potential for new insights into changes in zinc metabolism and nutriture in young children with acute and persistent diarrhea. An example is the quantitative measurement of zinc absorption and of fecal losses of endogenous zinc in children who are rehabilitated on diets that utilize locally available food staples many of which may be high in phytate. Phytate is a dietary constituent that can have a substantial negative impact on zinc absorption (42). Differences in the fractional absorption of zinc from different diets are as important as total dietary zinc in determining zinc absorption and may well lead to regional differences in zinc status during recovery from diarrhea.

(c) Zinc supplementation: Well-designed, randomized, placebo-controlled and blinded zinc supplementation studies of adequate size are an essential and key aspect of any research programs designed to evaluate the role of zinc in the pathogenesis and management of persistent diarrhea. These supplementation studies will also serve to define the importance of zinc during recovery from diarrhea including, for example, the relationship of this micro-nutrient to physical growth velocity and immune status. Zinc nutriture is expected to vary in different populations depending on local diets and other environmental factors. Extrapolation of either positive or negative results of studies in one location therefore requires caution and there is a need for parallel studies of zinc metabolism and supplementation in multiple centers.

References
23. Sachdev HPS, Mittal NK, Yadav HS. Serum and rectal mucosal zinc levels in acute and chronic diarrhea. Indian Pediatr 1990;27:125-33