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ZINC AND THE RISK FOR INFECTIOUS DISEASE

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■ **Abstract** Zinc is an essential micronutrient for human growth, development, and immune function. Zinc deficiency impairs overall immune function and resistance to infection. Mild to moderate zinc deficiency can be best detected through a positive response to supplementation trials. Zinc supplementation has been shown to have a positive effect on the incidence of diarrhea (18% reduction, 95% CI: 7–28%) and pneumonia (41% reduction, 95% CI: 17–59%), and might lead to a decrease in the incidence of malaria. Zinc has also proven to decrease the duration of diarrhea by 15% (95% CI: 5–24%). Maternal zinc supplementation may lead to a decrease in infant infections. Studies assessing the role of zinc supplementation among persons with HIV, tuberculosis, and the common cold have not been conclusive. Two studies have shown zinc supplementation to decrease child mortality by more than 50%. Zinc clearly has an important role in infant and childhood infectious diseases; programs to increase the intake of zinc among deficient populations are needed.

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INTRODUCTION

Zinc is found in every cell of every living organism and is essential for DNA synthesis and for cell growth and differentiation (37, 83). Prasad et al. reported the first recognized cases of human zinc deficiency in 1963 among poorly growing adolescent boys in Egypt (74). The well-known consequences of human zinc deficiency, e.g., growth retardation and a decrease in immune function, are often difficult to attribute to this specific deficiency in persons who may also suffer from multiple macro- and micronutrient deficiencies (112).

There is no body store for zinc, thus bioavailable zinc from food or supplements must supply zinc on a regular basis (112). Supplementation trials assessing the benefits of zinc on the treatment and prevention of infectious diseases have been conducted in populations with likely zinc deficiency since 1988 (82). This review summarizes the results of published and unpublished studies that have assessed the efficacy of zinc for the prevention or treatment of infectious diseases and for overall mortality.

ZINC AS AN ESSENTIAL NUTRIENT

Zinc deficiency has been defined as a low total body zinc mass, calculated with zinc tracer studies (109). This is correctable by increased dietary zinc or supplementation. The most dramatic manifestation of zinc deficiency is acrodermatitis enteropathica (AE). Although symptoms vary by age, the most common conditions are dermatitis, intermittent diarrhea, recurrent infection, and growth retardation (108, 109). If left untreated AE can result in an overall mortality of 18% to 20% (108, 109). More common are milder forms of zinc deficiency that are more difficult to recognize, but can result in impaired immune function and increased susceptibility to infections or decreased ability to clear them.

ZINC AND IMMUNE FUNCTION

Dietary zinc deficiency impairs overall immune function and resistance to infection suppressing thymic function, T-lymphocyte development, lymphoproliferation, and T-cell-dependent B-cell functions (95). Although understanding of the role

of zinc in immune function has increased, specific mechanisms by which zinc acts for the prevention and treatment of infectious diseases in humans are still not clear.

Animal Models

Early studies on immune function in swine and rats discovered the key role of zinc in animal immune systems and led to speculation that zinc is a critical micronutrient for overall human health, specifically immune system development and maintenance (61, 101). Prasad et al. conducted early studies on baby pigs and rats, which showed zinc deficiency to cause growth retardation and a decrease in overall enzyme activity in the tissues (75, 76). The mouse has been used frequently as a model for the role of zinc in the human immune system (31). Zinc studies on mice have shown that 30 days of a zinc-deficient diet can lead to a decrease in cell-mediated immunity and a subsequent inability to fight infections (39). Further studies have shown that supplementary zinc administered to zinc-deficient mice can prevent the impairment of the immune system and can improve the overall resistance to infections (31).

Human Immune Function Studies

Micronutrient deficiencies have the potential to negatively affect humans at multiple levels of immune function (54). The impact of zinc deficiency on innate immunity has been well studied among severely zinc-deficient patients with skin lesions as a result of AE (previously discussed) (109). Zinc supplementation has been shown to improve immunologic indexes among persons suffering from sickle cell anemia (2). Sazawal et al. (90) randomized 86 children to receive zinc or placebo for the treatment of diarrhea. After 120 days of supplementation, cell-mediated immune response was tested using a multiple antigen skin test. The zinc-supplemented children showed a decrease in the percentage of children anergic or hypoanergic, whereas the placebo-supplemented children showed no change ($p < 0.05$). Zinc-supplemented children also had a rise in geometric mean CD_4 cell count when compared to the control group (ratio 1.45, 95% CI: 1.03–2.01).

RISK OF INFECTIOUS DISEASE

The role of zinc in human immune function has led to observational studies assessing zinc status and susceptibility to infectious disease. Bondestam and colleagues (18) studied 28 children between 10 months and 10 years of age and observed serum zinc levels to be significantly lower among children who were more susceptible to infections when compared to healthy controls. In a study of zinc status among pregnant Malawian women, low hair zinc status was associated with malaria morbidity after controlling for the number of pregnancies ($p < 0.05$) (43). In a study of Indian children age 12–59 months, low initial plasma zinc was associated with an increased risk of diarrhea and acute lower respiratory infection (ALRI) episodes

(8). Although zinc status cannot be accurately assessed with plasma zinc or hair zinc measures, observational studies have suggested the need for zinc supplementation trials for the treatment and prevention of numerous infectious diseases. Improvements in response to zinc supplementation may be the best way to assess subclinical zinc deficiency.

Diarrhea

Diarrhea increases the rate at which endogenous zinc is lost from the gut mucosa. A study by Castillo-Duran and colleagues observed zinc losses during acute diarrhea in hospitalized infants in Brazil (23). Increased zinc losses along with dietary insufficiency may increase susceptibility to diarrhea pathogens and resulting damage may establish a cycle of infection and deficiency (105). Zinc was first studied as a treatment for diarrhea and then observed to decrease the incidence of additional diarrhea episodes.

In a pooled analysis of nine randomized controlled trials, zinc supplementation was reported to lower the incidence of diarrhea by 18% (95% CI: 7–28%) compared to the children not supplemented (103). This report assessed both short-course supplementation trials, with zinc given as a 14-day therapy for diarrhea, and continuous supplementation, with zinc given as a daily supplement for at least several months. Five continuous trials reported a decrease of 27% (0.42–1.06) in the incidence of persistent diarrhea and three trials reported a decrease of 13% in dysentery (0.64–1.19). Among the three short-course trials there was a 34% decrease in diarrhea prevalence in the two to three months following supplementation (0.52–0.83). A later randomized controlled trial published after this pooled analysis found that the incidence of diarrhea among 12- to 35-month-old children in Bangladesh was lower in the zinc-supplemented groups (RR 0.89, 95% CI: 0.79–0.99) (77). In a recent trial Gupta et al. (47) supplemented 280 children 6 to 41 months of age with 10 mg zinc five times a week, 50 mg zinc once a week, or placebo for 16 weeks. Children receiving zinc (both daily and weekly) had significantly lower rates of diarrhea during the supplementation period (0.68 and 0.69 episodes/year in zinc-supplemented groups versus 1.67 episodes in the placebo group, $p < 0.05$).

Pneumonia

The Zinc Investigators' Collaborative Group (103) performed a pooled analysis of four randomized controlled trials of zinc supplementation on the incidence of pneumonia. The zinc-supplemented groups had a 41% (95% CI: 17–59%) reduction in the incidence of pneumonia. In a recent trial Bhandari et al. (14) also found a reduction in the incidence of pneumonia. After correcting for multiple episodes of pneumonia in the same child, zinc-supplemented children had a relative risk of pneumonia of 0.74 (95% CI: 0.56–0.99) compared to those receiving placebo. The revised pooled analysis of all five trials estimates a 34% reduction in the incidence of pneumonia episodes (95% CI: 17–47%).

Two short-course zinc supplementation trials assessed the incidence of pneumonia among 3- to 36-month-old children in Bangladesh and Pakistan (103). Children in these trials received zinc or placebo for 14 days after an episode of diarrhea; ongoing surveillance surveys assessed the incidence of pneumonia for two to four months. The pooled analysis showed no statistically significant effect, although the point estimate (0.74) was similar to that seen in the continuous supplementation trials, but the sample size was much smaller. In a cluster randomized trial by Baqui et al. (9), children in communities receiving zinc for the treatment of diarrhea had a 19% decrease in ALRI hospitalization rate. Although this decrease was not statistically significant, it may have public health significance if replicated in the future. One study was found that assessed the potential interaction between vitamin A and zinc in the prevention of ALRI. Rahman et al. (77) reported an increased relative risk of ALRI in the zinc-supplemented children (RR 1.62, 95% CI: 1.16–2.25) and in the vitamin A–supplemented children (RR 1.06, 95% CI: 0.74–1.53) when compared to placebo. There was a decrease in the incidence of ALRI for those supplemented with both vitamin A and zinc (RR 0.75, 95% CI: 0.46–1.20). The results of this trial are not easy to explain because they are inconsistent with other vitamin A and zinc trials.

Malaria

Interest in nutritional modification for the prevention of malaria began before 1950 (93). Animal studies have shown low plasma zinc concentrations to lead to an increased mortality from malaria and have demonstrated a protective effect of zinc supplementation (25). Cross-sectional studies have shown relationships between low zinc status and increased incidence of malaria (42, 43). In randomized zinc supplementation trials the data have been mixed. Shankar et al. (94) and Bates et al. (11) both found daily zinc supplementation to decrease the incidence of febrile clinic-based illnesses with confirmed *Plasmodium falciparum* parasitemia. There was an overall pooled reduction of 36% (95% CI: 9–55%) in the incidence of malaria (11, 94). In contrast, Muller et al. (65) did not find a significant difference in the incidence of malaria between the daily zinc and placebo groups. However, this study assessed malaria incidence through daily household surveillance, which may not have been the best measure of clinical episodes of malaria.

Skin and Wound Infections

There have been few studies conducted showing evidence of zinc supplementation reducing skin infections in diverse populations. Castillo-Duran et al. (22) supplemented 32 infants in a nutrition recovery unit in Chile with zinc (2 mg/kg) or placebo daily for 90 days and observed a significant reduction in episodes of pyoderma among zinc-supplemented infants (three infants in the zinc group versus ten infants in the placebo, $p < 0.03$). Osendarp et al. randomized mothers to receive zinc or placebo during pregnancy and found a decreased number of impetigo infections among infants of mothers taking zinc compared to those taking placebo

($p < 0.005$) (68). There have been a limited number of studies on additional skin problems, such as acne, but the data are not strong and are typically from extremely small populations, thus conclusions are difficult to draw (87).

Zinc was first used for skin healing and wound repair by ancient Egyptians in the form of calamine (72). Zinc deficiency is now recognized to have adverse effects on the healing process and may increase the time for tissue repair (17, 72, 81). Wounds have also been shown to heal faster with both oral zinc supplementation and topical treatment. Pories et al. (72) randomized 20 patients to oral zinc sulfate or placebo and observed the duration of wound healing. Zinc-supplemented patients healed in 45.8 days compare to 80.1 days for placebo recipients ($p < 0.02$). In a study of topical zinc for the treatment of incisional wounds, more patients showed a decrease in wound size among the zinc treatment group than among the placebo group (73% versus 42%, $p < 0.05$) (70). Brodribb & Ricketts (19) found that oral zinc sulfate decreased the mean healing time for superficial burns by 21% compared to placebo and the mean healing time for deep burns by 19% compared to placebo. In a study by Fox et al. (38), topical zinc sulfadiazine was compared to the standard of care (silver sulfadiaze cream) in 80 burn patients and was found to be just as efficacious at preventing infection; zinc sulfadiazine is 24 times less expensive than silver sulfadiaze.

HIV/AIDS

HIV-positive persons are at risk for micronutrient deficiency due to decreased consumption of food, increased malabsorption, and increased losses of zinc from an increased incidence of diarrheal infection (62, 78). Zinc is a necessary component of basic immune function, thus a deficiency may lead to faster progression to more advanced stages of disease (62). Zinc is also a necessary component for HIV binding for the production of proviral peptides (71) that theoretically could lead to increased viral replication (78).

Siberry et al. (96) reviewed studies published to date on zinc in HIV-infected individuals. In this review, 10 studies assessed zinc deficiency among HIV-positive individuals; the prevalence of deficiency ranged from 4% to 57%. This review found inadequate intake of dietary zinc to be a problem in both adults and children, although adults more frequently took supplements containing zinc. Tang et al. (100) assessed the zinc intake of HIV-positive men in the United States by dietary surveys and found that those with the highest zinc intake (consuming 20.2 mg/day) had a relative hazard of 2.06 for progression to AIDS, i.e., a doubling in the rate of progression, when compared to those in the lowest quartile (consuming less than 11.7 mg/day); those with any intake of zinc supplementation had a relative hazard of 1.52 for progression to AIDS when compared to those with no supplementation. Because the zinc consumed in supplements by these men was self-determined, the association could have been due to the use of more zinc in those who were developing symptoms. In another study of zinc intake by food frequency and dietary recall, the progression of HIV, measured by declining CD_4 cell count, was enhanced with either very low or very high reported zinc intake (12).

Randomized trials assessing zinc supplementation in HIV-infected individuals have been few. Although these data are scarce, they do not suggest a negative effect of zinc supplementation on the course of HIV/AIDS as suggested by the food intake observational studies described above (62, 51). Supplementation trials of HIV-positive patients have shown zinc supplementation to decrease opportunistic infections (62) and improve weight gain and CD_4 cell count (51). Further research in this area is warranted.

Tuberculosis

Only one study to date has been found to assess zinc for the treatment of tuberculosis. Karyadi et al. (52) randomized 80 persons age 15 to 55, with newly diagnosed tuberculosis, to receive 15 mg Zn and 5000 IU vitamin A or a placebo daily for six months. In the first two months, patients supplemented with Zn + vitamin A eliminated bacilli from sputum quicker than those receiving placebo ($P < 0.01$). No adverse effects were apparent.

Maternal and Fetal Infections

The global prevalence of maternal zinc deficiency is unknown (16, 28). Although precise estimates are difficult to make (16), it can be assumed that the percentage is high given the known zinc deficiency in developing countries (24) and the increased demand of daily zinc in the diet during pregnancy (99). Maternal plasma zinc concentrations decrease as the pregnancy progresses (48). This may be because of the high demands of fetal growth and development. Observations such as this have led to a number of supplementation trials that have assessed both maternal and fetal outcomes of zinc supplementation during pregnancy.

Supplementation trials have assessed the impact of maternal zinc supplementation on hypertension, preterm/postterm labor, premature rupture of membranes, maternal infection, postpartum hemorrhage, perinatal mortality, congenital malformations, fetal growth, and gestation (92). Evidence for zinc supplementation to increase infant birth weight and improve most infant and maternal health outcomes is inconclusive; the largest potential benefits will likely be seen in infant neurobehavioral and immune function (27, 92).

Osendarp et al. (68) followed up 383 Bangladeshi infants of mothers who were randomized to receive zinc or placebo daily for six months, from 12 to 16 weeks gestation until delivery. Fewer episodes of acute diarrhea (RR 0.84, $p < 0.037$) and fewer episodes of dysentery (RR 0.36, $p < 0.019$) were noted among infants of mothers who received zinc supplementation during pregnancy as compared to infants of mothers who did not receive zinc supplementation.

In a recently published review by Osendarp et al. (69), eight trials were reviewed assessing the benefit of zinc supplementation on neonatal immune status, early morbidity, and infant infection. Data have been presented here from only two of the five studies available with infant morbidity as the outcome. The preliminary findings show lower rates of infectious diseases among infants born to the zinc-supplemented mothers and suggest potential for further study.

THERAPY FOR INFECTIOUS DISEASES

Diarrhea

Data supporting the efficacy of zinc for the treatment of childhood diarrhea are extensive. The Zinc Investigators' Collaborative Group reported a pooled analysis of seven published and unpublished studies in children under five years old (103). Children with acute diarrhea had a 15% (95% CI: 5–24%) lower probability of continuing the episode of diarrhea if treated with zinc versus placebo. Children with persistent ($\geq$14 days at the time of treatment) diarrhea had a 24% (95% CI: 9–37%) lower probability of continuing the episode of diarrhea if treated with zinc than with placebo. Children with persistent diarrhea treated with zinc had a 42% lower rate of treatment failure or death than children given placebo (95% CI: 10–63%). In a World Health Organization meeting report, 12 published and unpublished zinc supplementation studies were assessed; 11 of the 12 studies confirmed a decrease in diarrheal duration after zinc supplementation (104). All five studies that looked at the proportion of episodes lasting more than seven days showed a decreased proportion among zinc-supplemented children. Although studies have been done with various supplementation doses (one to four times the recommended daily allowance), the data support a 20-mg/day dose as both safe and efficacious (7). Al-Sonboli et al. (6) randomized children three months to five years of age to receive zinc (22.5 mg for three to six months of age, 45 mg for seven months to five years of age) or placebo for the treatment of diarrhea. Children receiving zinc had fewer stools (4.1 versus 10.0, $p < 0.01$) and fewer days of diarrhea (1.2 versus 2.5, $p < 0.001$) than did children receiving placebo.

Baqui et al. (9) implemented a community-based trial of zinc supplementation during a diarrhea episode in Bangladesh; 30 health workers were randomly allocated to a zinc intervention or to a control group. Three- to 59-month-old children received either 20-mg zinc tablets to be taken daily for 14 days plus oral rehydration solution (ORS) (intervention) or ORS alone (control) when mothers sought care for the diarrhea episode. Ongoing cross-sectional surveys and follow-up visits for current episodes were used to obtain information on length of diarrhea episode, prevalence of diarrhea and ALRI, and mortality in a two-year observation period. The duration of all episodes decreased by 23% (95% CI: 14–31%) and prevalence of all diarrhea by 15% (95% CI: 4–24%) among the children living in areas randomized to receive zinc (9).

Pneumonia

One study to date has assessed the impact of zinc on the clinical course of pneumonia. Brooks et al. (20) randomized 270 Bangladeshi children age 2 to 23 months to receive 20 mg/day zinc or placebo in addition to antibiotics for the treatment of severe pneumonia. Children receiving zinc had a shorter duration of chest indrawing, elevated respiratory rate, and hypoxia. The overall duration of pneumonia in children treated with zinc was four days as compared to five days among

placebo-supplemented children ($p < 0.05$), and overall hospitalization was five days among zinc-supplemented children as compared to six days among placebo-supplemented children ($p < 0.05$).

Malaria

One study to date has assessed zinc for the treatment for *P. falciparum* malaria. In that study, 1087 children between the ages of 6 and 60 months in Ecuador, Ghana, Tanzania, Uganda, and Zambia who presented to a health center with a fever and $\geq 2000/\mu l$ *P. falciparum* were randomized to receive zinc or placebo in addition to chloroquine (102). No differences were found between the zinc or placebo groups in the main outcome measures: (*a*) the length of time to fever reduction, (*b*) the proportion of children with a 75% reduction of parasitemia in the first 72 hours, and (*c*) the change in hemoglobin concentration during the three days of hospitalization or after the four-week follow-up.

Measles

Only one study to date has assessed the benefit of zinc supplementation for the treatment of measles. Mahalanabis et al. (59) randomized children nine months to 15 years of age who were hospitalized in India for measles. Although more than half of the children in both the zinc and placebo groups had low plasma zinc concentration, zinc supplementation did not decrease the time to recovery or the proportion of children judged to be cured by day six.

Common Cold

Zinc for the treatment of the common cold was first investigated in the early 1980s with the use of zinc gluconate lozenges. Although zinc has been found to inhibit the replication of several rhinoviruses in vitro (41), the same effect in vivo has not been observed; the exact mechanism for how zinc may work in humans is not known. Three systematic review articles summarizing the effects of the first eight clinical trials found that zinc gluconate lozenges have an inconsistent effect on the severity and duration of the common cold (40, 46, 60). Beneficial effects were found in three trials (34, 45, 64), and no benefits were found in five trials (5, 33, 35, 111). Many trials have been criticized for study design problems (34, 111) and small sample sizes (5, 35).

Since these reviews were published there have been mixed results in trials of the use of zinc as a treatment for the common cold. Macknin et al. (58) did not find a difference between the time to resolution of cold symptoms between children receiving 10-mg zinc gluconate lozenges five to six times a day and those receiving placebo for the treatment of the common cold. In a study by Turner (106), prevention and treatment of rhinovirus infection with intranasal zinc gluconate did not prove to be effective ($n = 91$).

Turner & Cetnarowski (107) assessed the efficacy of zinc acetate and zinc gluconate lozenges among 273 persons challenged with a rhinovirus and among 281

natural cold patients. Among those with artificially induced colds, zinc gluconate significantly reduced the duration of the cold [2.5 days compared to 3.5 days among placebo ($p = 0.035$)]. No effects on duration were observed among zinc acetate–treated persons, and no effects on severity were observed with either zinc acetate or gluconate. Among those presenting with a natural cold, no effect was observed on duration or severity with zinc acetate or gluconate treatment. Prasad et al. (73) found zinc acetate lozenges to shorten the mean overall duration of cold symptoms (4.5 days in zinc-treated patients compared to 8.1 days in placebo, $p < 0.01$) and a decreased overall severity of symptoms based on patient scoring. Mossad (63) studied the efficacy of zincum gluconicum nasal gel and found that zinc-treated patients had a significantly shorter duration of illness (4.3 days versus 6.0 days) when compared to placebo ($p < 0.005$). Zinc may or may not be efficacious for a decline in the severity of, or the complete resolution of, common cold symptoms, but it does not appear to cause any significant adverse effects if used as a lozenge or nasal spray for the treatment of the common cold.

INTERACTIONS WITH OTHER MICRONUTRIENTS

Deficiencies of zinc, vitamin A, and iron are common in low-income populations and have important health consequences. Although copper deficiency is uncommon, estimates of population copper deficiency are not known. (79). Some minerals can compete for absorption in the body and an abundance of one micronutrient might lead to a deficiency in the other (1, 86) Because public health programs may provide additional ways to increase intake of these micronutrients, it is important to consider potential interactions.

Iron

Iron and zinc are essential micronutrients for growth and maintenance of human health. Iron deficiency impairs psychomotor development, decreases physical activity and work capacity, and lowers resistance to infection. Iron and zinc have chemically similar absorption and transport mechanisms, and therefore may limit each other's bioavailability. (86) Studies assessing joint supplementation have thus far been conducted in pregnant and nonpregnant women and in children under the age of five.

Many studies have assessed potential interactions by looking at biochemical indicators. Several trials have not found an adverse effect of dual iron and zinc supplementation (26, 29, 32, 66, 67, 113), whereas others have seen a negative effect of zinc supplementation in iron status (50, 55, 91, 115).

Three trials to date have assessed the impact of iron and zinc supplementation on common childhood morbidities. In a study by Rosado et al. (80), both the Zn- and the Fe + Zn–supplemented children had significantly fewer total illness episodes (3.9 and 3.7, respectively, versus 4.6, $p < 0.035$) and diarrhea episodes per child (0.7 and 0.8, respectively, versus 1.1, $p < 0.01$) than did children who received placebo (80). In another study Bangladeshi infants were supplemented

weekly from 6 to 12 months of age with (*a*) 20 mg Fe and 1 mg riboflavin, (*b*) 20 mg Zn and riboflavin, (*c*) Fe, Zn, and riboflavin, (*d*) riboflavin alone, or (*e*) micronutrient mix; *a–d* are reported here (10). At the six-month follow-up no supplement was significantly associated with the risk of acquiring diarrhea. When assessing only severe diarrhea (defined as episodes requiring ORS with $\geq$ five loose stools in 24 hours), the Fe + Zn group had a 19% lower rate when compared to the control group among all infants ($p < 0.05$), and a 30% lower incidence rate among infants < -1 weight-for-age Z score (WAZ) ($p < 0.01$). Infants < -1 WAZ supplemented with Fe + Zn also had a 40% lower rate of severe acute lower respiratory infections than the control group ($p = 0.015$).

Vitamin A

Vitamin A is an essential micronutrient for overall vision and specifically dark adaptation (97, 101, 110). Christian & West (30) reviewed the interactions of vitamin A and zinc in cross-sectional, observational, and supplementation clinical trials and concluded zinc deficiency could impose a secondary vitamin A deficiency in protein-energy deficient populations.

One trial that assessed the incidence of diarrhea randomized 12- to 35-month-old children in Bangladesh to receive zinc, vitamin A, both, or placebo (77). The incidence of diarrhea was lower in the zinc-supplemented (RR 0.89, 95% CI: 0.79–0.99) or vitamin A–supplemented (RR 0.84, 95% CI: 0.74–0.94) groups; there was no interaction between zinc and vitamin A. Three studies were found that assessed the interaction of zinc and vitamin A for the treatment of diarrhea. In each of these studies children younger than five years of age were randomized to four treatment groups: zinc, vitamin A, both vitamin A and zinc, or placebo (36, 53, 98). In each of these studies, zinc decreased the duration and severity of diarrhea regardless of the vitamin A supplementation status. Vitamin A did not affect the duration or severity of diarrhea.

One study thus far has assessed the potential interaction between vitamin A and zinc in the prevention of ALRI. Rahman et al. (77) reported an increased relative risk of ALRI in zinc-supplemented children (RR 1.62, 95% CI: 1.16–2.25) when compared to placebo, but saw no effect on the incidence of ALRI in children receiving vitamin A supplementation or vitamin A and zinc supplementation. These results are puzzling and should be repeated before conclusions can be drawn.

Children under age five in vitamin A–deficient areas are routinely supplemented with vitamin A because of evidence that this reduces mortality (13). Assessment of joint supplementation trials indicates that vitamin A and zinc are both critical to health in different capacities, and generally no adverse interactions result from dual supplementation.

Copper

Copper is an essential micronutrient involved in numerous biochemical interactions in the body, including iron mobilization, the maintenance of the electron

transport system, and the formation of collagen (37). Copper deficiency can occur in humans and may result in depressed growth, abnormal bone development, alopecia, achromotrichia, neonatal atoxia, impaired reproduction, cardiovascular disorder, anemia, increased low-density lipoprotein cholesterol and decreased high-density lipoprotein cholesterol (37, 84). Although population-level copper deficiency is unknown (79), it is biologically plausible that increases in zinc intake through supplementation or fortification could limit the absorption of copper, thus resulting in deficiency (3). Trials assessing the impact of zinc supplementation on copper levels are few. Abdulla & Suck (4) randomized 83 adults in India and Pakistan to receive daily zinc supplementation and assessed copper levels through fasting blood samples. After six weeks of supplementation, copper levels decreased from 1.01 $\pm$ 0.11 mg/L to 0.86 $\pm$0.04 mg/L ($p < 0.001$) in the highest zinc supplement group. The levels returned to normal six weeks after supplementation ended. Sazawal et al. (89) assessed a subsample of 115 infants who were randomized to receive 10 mg zinc or placebo for 120 days. After the supplementation period there was no significant difference in copper concentration among zinc-supplemented or control infants (2.5 μg/dl and 5.5 μg/dl, respectively).

RELATIONSHIP WITH CHILD MORTALITY

Only two studies thus far have had the power to detect a difference in child mortality. Baqui et al. (9) found a 51% reduction in overall child mortality (95% CI: 6–75%) among children living in clusters who received zinc for the treatment of diarrhea when compared to children not receiving zinc. Sazawal et al. (88) randomized infants who were small for their gestational age to receive either zinc or nonzinc in a four-cell design (riboflavin alone; riboflavin + 5 mg zinc; riboflavin, calcium, phosphorus folate, and iron; or riboflavin, zinc, calcium, phosphorus, folate, and iron) from 30 to 284 days of life. Zinc was associated with a 68% reduction in mortality among these infants. Reductions in mortality are not surprising given the impact zinc has been shown to have on diarrhea and pneumonia, the two most common causes of death in children under age five. Additional trials are under way in Zanzibar and Nepal to assess the impact of zinc supplementation on child mortality.

RECOMMENDED ZINC INTAKES AND PREVALENCE OF DEFICIENCY

The World Health Organization's recommended daily allowance for zinc intake in children less than one year of age consuming a diet with low bioavailability of zinc is 5 mg/day; for children more than one year of age 10 mg/day is recommended (111). Research in the past 10 to 15 years has attempted to quantify the prevalence

of zinc deficiency through population-based methods. Countrywide estimates of the percent of the population with inadequate zinc intake have been developed by assessing the zinc available in the diet and the fractional absorption of zinc (21). According to this method, an estimated 23% of the world's population is zinc-deficient (K.E. Brown, personal communication).

POSSIBLE INTERVENTION PROGRAMS

Increasing zinc intake among deficient populations may be done through supplementation, improved quality of overall diet, fortification of staple foods, and plant breeding for greater zinc bioavailability (15). For prevention of common morbidities and overall improvement in zinc status, supplementation programs may need to determine the optimal dose and dosing schedule (15). Adding zinc to already existing supplementation programs, such as those targeted toward pregnant women, may be a sustainable way to reach target populations (15).

Long-term changes in dietary intake and the bioavailability of zinc are the ideal way of improving population zinc status. Further studies are needed to assess potential dietary changes that will affect the bioavailability of zinc and the acceptance of these changes within a population (49). These changes may include the adaptation of food preparation and processing methods that reduce the content of zinc-inhibiting phytates (56). Fermentation is one example whereby the phytate-to-zinc ratio is reduced, thus increasing the bioavailability of zinc (44). The genetic engineering of plants to increase the concentration of bioavailable zinc may be another way to improve zinc in the diet (113).

Fortification of staple foods with zinc is an option for increasing daily zinc intake (57). Before fortification can be realized, target foods and a target population must be identified. The food to serve as the fortifying vehicle must be digested in a predictable quantity to ensure the micronutrients are reaching the target population in an adequate quantity and quality. In addition, the process of fortifying must not change or alter the food itself or increase the price such that consumers are not willing to buy it (79).

Short-term zinc supplementation for the treatment of diarrhea and possibly pneumonia has proven effective in numerous randomized trials. Incorporating zinc tablets as part of a simple treatment regime for diarrhea is safe and effective and may decrease the unnecessary use of antibiotics for nondysentery diarrhea (7, 15). Zinc in addition to antibiotics for the treatment of pneumonia may prove to be an effective way to decrease the duration of the episode. Short-term supplementation has the added benefit of improving health and overall immune status in the weeks following treatment. This simple treatment regimen may be an effective way of improving zinc status and decreasing childhood morbidity and mortality.

The options for improving zinc status among deficient populations are many. Consideration must be made for which program best fits the community and the people the program is trying to reach.

CONCLUSION

The human body requires a daily intake of zinc to maintain immune function and normal growth and development. Severe zinc deficiency, manifested as acrodermatitis enteropathica, is rare, whereas mild to moderate zinc deficiency is widespread in developing countries, especially among women and children. The existence and consequences of this level of deficiency are well demonstrated by the response to supplementation.

Data supporting the use of zinc for the treatment and prevention of diarrhea in children under age five are robust. Zinc supplementation decreases the duration, severity, and incidence of diarrhea episodes. Further studies are being conducted in India, Pakistan, and Mali to assess the best way to promote zinc along with oral rehydration solution for the treatment of diarrhea. Zinc has been shown to prevent pneumonia, and in a recent trial was shown to be an effective treatment for severe pneumonia (20). Additional treatment trials are currently being conducted in India, Nepal, and Tanzania. Zinc decreases the incidence of skin infections among infants, increases the rate of healing among surgery patients, and decreases infection rates among burn patients.

Although data thus far show potential for a beneficial effect of zinc supplementation on the incidence of malaria, additional studies are needed to confirm this. It is doubtful that zinc supplementation is beneficial in the treatment of a current malaria episode. Although some studies of HIV have shown a negative effect of excess zinc intake on HIV/AIDS progression, the few supplementation trials to date have not shown a negative effect on AIDS progression or overall immune status in HIV-positive patients.

Numerous investigators have researched the use of zinc for treatment of the common cold. Although this use is not harmful, the data do not conclusively show a benefit. There is also inconclusive evidence on the effects of zinc supplementation during pregnancy for the prevention of early infant infections, but additional trials are needed.

As supplementation programs become more widespread, understanding the potential clinical consequences of micronutrient interactions becomes increasingly important. Although iron and zinc compete for absorption sites and negative interactions have been shown when assessing biochemical indicators, the data are not consistent when assessing clinical outcomes. Negative effects have not been shown on copper status in the few trials that have assessed copper concentration after zinc supplementation, despite known biological plausibility. Vitamin A and zinc have separate health benefits and seem to act independently of one another within the body. Zinc supplementation has been shown in some trials to improve vitamin A status in zinc-deficient populations.

Given the evidence that zinc supplementation decreases the severity, duration, and incidence of diarrhea and decreases the incidence of pneumonia, the results in two studies of reduced child mortality are not surprising. The burden of disease related to zinc deficiency was assessed by Caulfield & Black (24). Based on the

observed impact of supplementation trials on infectious disease, zinc deficiency is estimated to cause 779,000 deaths each year (24). The widespread benefits of zinc supplementation and overall improved zinc status among children under age five have been shown. Further work is urgently needed to develop practical supplementation programs for children suffering from subclinical zinc deficiency. The data are not yet conclusive with regard to improved zinc status of pregnant women. The potential benefit that zinc supplementation might have on infant morbidity in the first few months of life should encourage additional research in this field.

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