Zinc in human health

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SUMMARY

Malnutrition is a contributing cause of about half of the 10 million deaths annually worldwide, and contributes to a substantial proportion of the infectious disease morbidity among children in developing countries. Recent epidemiological and clinical evidence has shown that in most developing countries deficiencies of specific micronutrients are partly responsible for the severity of infectious disease morbidity and mortality in malnourished children. Efforts to improve micronutrient status have focused on iron, vitamin A and iodine. Supplementation with iron and vitamin A significantly reduces child mortality, while implementation of the universal salt iodization strategy reduces the incidence of iodine deficiency disorders. These strategies are considered to be among the most cost-effective health interventions in developing countries. A number of recent zinc supplementation studies in developing countries suggest that greater priority should also be given to the correction of mild to moderate zinc deficiency in children, pregnant women and lactating mothers. Some of these studies showed that zinc supplementation reduces the duration of malaria, and the severity of diarrhoea and respiratory infections (including pneumonia), and improves immunocompetence in susceptible children. The results of these studies indicate that zinc may be another specific micronutrient in which there is widespread deficiency in developing countries and that great benefits can be achieved by its supplementation.

Introduction

Childhood malnutrition is a major problem that can lead to long-term deficits in growth, immune function, and cognitive and motor development. It can also adversely affect children's behaviour and intellectual performance and presents an increased risk of morbidity and death from infectious diseases. In the past, these negative consequences of malnutrition were mainly associated with inadequate protein-energy intake (1). Malnutrition is, however, a more complex phenomenon, and often also involves deficiencies of one or more micronutrients (2,3). There is enough scientific evidence to justify the special attention being given to specific micronutrients such as iron, iodine and vitamin A in infant and maternal nutrition programs in developing countries (2-6). It is now known that lesser degrees of zinc deficiency are more common than was appreciated and that the subclinical deficiency of zinc can contribute to increased incidence and severity of infectious diseases in a susceptible population (7-10).

Recent scientific evidence suggests that zinc also deserves special attention, because zinc deficiency has been associated with lower birthweight, poor growth in childhood, reduced immunocompetence, increased susceptibility to infectious diseases, diarrhoeal disease and abnormal motor development in malnourished children (2,11-

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This review highlights the metabolic role of zinc, its bioavailability and implication in disease states with special focus on infant and maternal health.

Metabolic significance and biochemical functions of zinc

Zinc is one of the most essential trace elements in human nutrition because it is a component of over 200 metalloproteins with a wide range of biochemical functions, involving enzymes, structural proteins and hormones (17-19). The ability of zinc to participate in an impressive range of biochemical functions is partly due to its flexible and easily exchangeable ligand-binding with biomolecules (19). Zinc is a relatively safe element when compared with iron and copper, especially because of its lack of oxidant properties (17,18). This greatly facilitates the transport of zinc within the body and its metabolism in individual cells (19).

Zinc is absorbed by passive diffusion mainly in the jejunum. Metallothionein and other metalloproteins such as α_2-macroglobulin, where zinc is not exchangeable, albumin and transferrin, where zinc is exchangeable, and other oligopeptides play a regular role in the absorption, transportation and distribution of zinc (10,18,19). Muscle and bone have the highest concentrations of zinc, followed by skin, gastrointestinal tract, hair, nails, eyes and prostate gland (19). The relative size of the blood zinc pool is about 1% of the total body pool (19).

The ligand-binding properties of zinc are utilized effectively at the catalytic site of a wide range of enzymes (17,18). Zinc is involved in the regulation of blood sugar, thyroid and gonadal functions, adrenal hormone and prolactin production, acid-base balance and calcium metabolism (17-22). Zinc has structural roles in biological membranes, cell receptors (for hormones including testosterone) and other proteins,

such as gustin – a Zn-dependent polypeptide that is essential for normal development of taste buds and normal taste acuity (17,19). Zinc functions as an antioxidant and helps to stabilize cell membranes (14,19,22).

Zinc affects cell replication, growth and maturation because it influences the activity of multiple enzymes at the basic levels of replication and transcription (22). These include DNA polymerase (18,22), thymidine kinase (17,18), DNA-dependent RNA polymerase (18,22), terminal deoxyribonucleotidyl transferase (14,22), aminoacyl transferase, RNA synthetase (14,22), and a family of transcriptional regulators with a structure known as zinc-finger motif that are involved in sequence-specific DNA recognition and gene expression (14,17,18,22). Zinc is required for the expression of multiple genes regulating mitosis (14,18,22).

Thus, the requirement of zinc for normal cellular growth and differentiation may underlie the impairment of physical growth that is the hallmark of zinc deficiency in childhood (14,22).

Zinc and vitamin A metabolism

Adequate zinc status is partly necessary for the absorption, transport, metabolism, hepatic release and tissue utilization of vitamin A (22,23). Zinc is required for the biosynthesis of retinol dehydrogenase that catalyzes the oxidative conversion of retinol to retinaldehyde in various tissues, including the retina, where this process is involved in the visual cycle (22,23). Zinc regulates vitamin A absorption and is required for the biosynthesis of retinol-binding protein in the liver (22,23). This implies a regulatory role for zinc in mobilizing vitamin A within cells and in the liver.

Circulating zinc and vitamin A concentrations appear unrelated in well-nourished states but tend to co-vary in marginally nourished individuals with coexisting zinc and vitamin A deficiencies

(22,23). Thus, zinc deficiency could impose a secondary vitamin A deficiency on malnourished infants (23). Zinc deficiency might also limit the effectiveness of vitamin A supplementation programs.

Most studies regarding zinc-related vitamin A deficiency in humans are inconclusive (23,24). Data supporting the occurrence of vitamin A-related zinc deficiency in humans are very sparse. However, based on available research information, the metabolic functions of vitamin A are greatly enhanced in the presence of adequate zinc status (22-24).

Thus, given the critical role of both zinc and vitamin A in maintaining normal metabolic functions and resistance to infection, and in view of the dire lack of adequate information about the public health implications of a potential zinc–vitamin A interaction, there is an express need for more research in this direction, particularly in developing countries.

Sources and bioavailability of dietary zinc

Major sources of dietary zinc include milk, red meat, liver, poultry, fish, oysters, crabs, cereals, legumes, tubers, nuts and vegetables (2,19,22,25,26). Bioavailability of zinc is higher in milk, liver, red meat, fish, oysters and crabs; it is low in cereals, legumes, tubers and vegetables (2,19,22,25,26). The low bioavailability of zinc from plant sources is due to their content of phytate, lignin and fibre, which form insoluble complexes with the ingested zinc impairing intestinal absorption (2,22,25,26).

In most developing countries, because of economic constraints, the consumption of animal protein foods, which are rich sources of readily available zinc, is usually low (26,27). Staple foods in these countries are mainly cereals, legumes, tubers and vegetables, thus the bioavailability of dietary zinc is low because of the high content of phytate in the diet (26-29). Children in these

areas usually do not show obvious signs of zinc deficiency, but have often been found to have low plasma zinc levels compatible with subclinical zinc deficiency (2,6,8,28).

The phytate content in plant-based staple foodstuffs can be reduced by enzymatic and non-enzymatic hydrolysis (22,26,29). Some of the methods that enhance phytase-induced enzymatic hydrolysis of phytate include fermentation, sprouting and soaking (26,29). Endogenous phytase, which can be activated by soaking, is high in most cereals and in the microflora on the surface of grains (22,26). Soaking is particularly effective in non-enzymatically reducing the amount of water-soluble phytate in legumes and cereals (26,29). Zinc bioavailability can also be enhanced by citric acid, lactic acid, formic acid, vitamin C, high dietary protein, high levels of sulphur-containing amino acids (methionine, lysine and cysteine), lactose and pancreatic secretion (2,22,26,28). Some of these compounds enhance the absorption of zinc by preventing the formation of insoluble zinc-phytate complex in the gastrointestinal tract (22,27,28). The phytate-to-zinc molar ratio of a diet can be used to predict the inhibitory effect of phytate on zinc absorption (27,28,30).

The phytate-to-zinc ratio >12 found in some plant-based diets that contain low animal protein is considered to be a major factor contributing to zinc deficiency in developing countries (9,28). It is therefore important to reduce the phytate content during preparation of meals. Suboptimal zinc deficiency in humans has been associated with phytate-to-zinc molar ratios >15 (27, 28).

The bioavailability of zinc can be reduced by a high level of calcium in a diet that is high in phytate (28). The complex (Ca-Zn-phytate) formed in the intestine is less soluble than the Zn-phytate complex (28). The bioavailability of zinc can also be reduced by chemical food colourings (22,31). According to Ward (31), hyperactive children showed a significant reduction in serum zinc levels and an increase in urinary zinc output following

the consumption of beverages containing either the food colouring 'tartrazine' (code E 102) or 'sunset yellow' (code E 110).

Zinc nutriture in infants

The first six months of life are a period of rapid growth, and zinc intake varies with the mode of feeding (22,32). The relatively high zinc requirements during this period can be met satisfactorily by breastmilk alone for most healthy infants (19,22,32). The infant is able to utilize zinc from hepatic zinc thionein for several weeks postpartum to supplement zinc derived from breastmilk (32,33). The bioavailability of zinc in breastmilk is very high (80%) compared to whey-adjusted cow's milk (35%), even though the concentration of zinc in breastmilk is lower than in cow's milk (19). This difference in bioavailability is due to higher levels of citrate and the presence of lactoferrin in breastmilk, and high levels of phytate, calcium and casein in cow's milk (19,22).

Healthy infants, fed exclusively on breastmilk for four to six months, usually do not develop zinc deficiency within this period (32,33). Several researchers (32,34,35) have documented the possibility of suboptimal zinc status in breastfed infants after six months of age. This is partly related to the fact that zinc content of breastmilk falls with the duration of lactation (32).

From six months to two years of age, adequacy of zinc intake becomes highly dependent on the amount and bioavailability of zinc from complementary foods (35-39). Thus, prolonged breastfeeding without adequately prepared complementary foods may reduce an infant's zinc intake, thereby increasing the risk of zinc deficiency (35-39).

The breastfed, low-birthweight infant is usually at risk of developing zinc deficiency because of increased requirements, potentially lower intake and/or lower absorption efficiency (22,35). Zinc deficiency may also occur in children fed with cow's milk, because of the high levels of phytate, calcium and casein in cow's milk, which impair the absorption of zinc (32,35). The same is true for soymilk because of its high phytate content (19).

Zinc supplementation (between 10 and 20 mg Zn/day) enhances linear growth and significantly reduces the incidence of anaemia (13,22,32,35). Stunted children benefit more than non-stunted children; children of up to 24 months of age benefit more than older children (19,32,35). Another benefit of zinc supplementation reported in a recent study by Albert et al. (40) is that supplementation with zinc improves seroconversion to vibriocidal antibody and, hence, has the potential to improve the efficacy of oral cholera vaccine in normal and malnourished children.

These findings clearly indicate the need to develop strategies for improving the zinc status of infants and children in developing countries. An important factor is to ensure adequate bioavailability of zinc and other micronutrients in the diet of infants. There are a number of commercially prepared adequately fortified complementary foods that can be used for this purpose. However, these products are too expensive for widespread use in low-income communities. A more viable option there is to increase aggressive advocacy of awareness of zinc deficiency and to educate people on the benefits of fortification of the already available locally prepared complementary foods. Fortification of home-made complementary foods can be achieved by addition of locally available foodstuffs that are rich in zinc, such as powdered forms of whole grains, dry beans, nuts, adequately prepared and minced seafood, poultry, pork and red meat (36-38,41,42). Gibson et al. (26) have used a similar community-based dietary intervention strategy in rural southern Malawi with some success.

The safe upper limits of zinc intake adjusted for body weight proposed by the World Health Organization (WHO) (3,15,28,34,43) are as follows: 13 mg/day for

infants from 6 to 12 months of age; 23 mg/day for children from 1 to 6 years of age; 32 mg/day for girls from 10 to 12 years of age; and 34 mg/day for boys from 10 to 12 years of age.

For young children, zinc supplementation should be considered in cases of malnutrition, low dietary zinc bioavailability, severe stunting, low plasma zinc, persistent diarrhoea and severe infections. Since zinc is only one of several nutrients that are necessary for adequate growth in infants and young children, the deficiency of other nutrients may negatively affect the linear growth response to zinc supplementation (41,42). Thus, it is better to use a micronutrient mix containing zinc in the rehabilitation of such children. Zinc supplementation to improve stunted growth is more effective when zinc is the primary growth-limiting nutrient in the diet (41,42).

According to Gibson (42), caution must be observed when selecting the dose for zinc supplements, especially for catch-up growth in children with severe protein-energy malnutrition and an already compromised immune system. High doses of zinc supplements without the required general nutritional rehabilitation including other micronutrients may cause increased morbidity and mortality in this group of children (42,44).

Maternal zinc nutriture

The non-availability of well-defined biochemical indicators of maternal zinc status, and the lack of consensus on appropriate indicators of zinc status for pregnant women are partly responsible for the inability of policy-makers to recognize the public health significance of maternal zinc deficiency and its consequences for pregnancy and neonatal survival and well-being (45,46).

There is paucity of data on the contribution of maternal zinc deficiency to maternal and infant morbidity and mortality rates in developing countries (45). In addition, research in developed countries relating to maternal zinc status and birthweight of neonates has not produced consistent results (45-47). However, several reports have indicated that women are at increased risk of zinc deficiency during pregnancy, because of the high fetal requirement for zinc (45,46). Severe maternal zinc deficiency has been associated with spontaneous abortion and congenital malformations (45). Mild to moderate zinc deficiency has been associated with prolonged gestation, intrauterine growth retardation, preterm delivery, complications of labour and delivery, and low birthweight (45,47).

According to Caulfield et al. (45), the question as to whether maternal zinc deficiency increases the likelihood of labour and delivery complications is critical for developing countries, where women have little access to essential obstetric services. It is therefore necessary to provide zinc supplementation for pregnant women in developing countries (47).

Effect of zinc on immune function

Zinc plays a crucial role in the development and maintenance of the immune system (14,20,22,48). It is involved in multiple aspects of the immune system, from the barrier of the skin to the regulation of genes within lymphocytes (11,14,15,22,48).

Zinc is important for the normal function of cell-mediated immunity through neutrophils, macrophages and natural killer cells (14,22,48). It also affects the development of acquired immunity and immunoglobulin production (14,22,48). It plays a significant role in the biological activity of a thymic hormone (thymulin) and in the synthesis and release of various cytokines, such as interleukins (IL-1 and IL-2) (10,22,48,49). Zinc deficiency can cause impaired immune function and increased susceptibility to bacterial, viral and fungal infections (11,14,22,48). Mild to moderate zinc deficiency affects the development and/

or function of most cells of the immune response, T cells, B cells and macrophages (14,20,48). Zinc deficiency causes depressed thymic hormone activity, decreased natural killer cell activity, a specific CD4+ T-cell population depression, and decreased production of IgA, IgM and IgG (14,20,48,49).

According to Shankar and Prasad (14), the effect of zinc on some major components of the immune system is due to the many roles that zinc plays in basic cellular functions, such as DNA replication, RNA transcription, gene expression, cell division, cell activation and maintenance of cell membrane integrity.

Effect of zinc on HIV/AIDS

There is substantial research information indicating the significance of micronutrient supplementation in improving the nutritional status of HIV+ patients. However, the effect of zinc supplementation on HIV/AIDS patients is a controversial issue.

Zinc has been reported to act as an antiviral agent (20,50,51), as an antioxidant and as immune-modulator in HIV infection (20,49). Zinc is capable of enhancing and inhibiting the activity of the HIV protease enzyme (20). Integrase, a Zn-dependent enzyme that requires 'zinc-finger protein' for optimal activity, catalyzes the integration of viral DNA with host DNA (20). Zinc, therefore, has a dual role as a major component of viral replication and an inhibitor of replication. Low levels of zinc in plasma and in serum have been reported in HIV+ patients in the asymptomatic state (20,52) as well as in AIDS patients (53). Some studies (20,54) did not observe any reduction in serum zinc level in HIV+ patients. Other studies (20,52,55) reported declining zinc levels in plasma and serum of patients as the disease progresses. Studies to evaluate the impact of zinc supplementation in AIDS patients show an apparent reduction in infectious complications in zinc-supplemented patients compared to placebo (20,56). Results of some studies (20,56) showed significant

increase in mean CD4+ cells and in the absolute counts of CD3+ lymphocytes after 10 weeks' supplementation with 0.45 mg/kg/day of elemental zinc. Zinc supplementation studies using oral zinc in HIV+ children have been documented (48,57). Significant increases in the CD4+ count were recorded in some of the patients in the studies. However, a study by Tang et al. (58) showed an association between increasing zinc intake and increasing disease progression. Yet other epidemiological and clinical studies of zinc intake, serum zinc levels and their relationship to progression to AIDS found no association between increasing zinc intake and increasing disease progression (20,52,59).

Zinc plays an important role in HIV replication. Therefore, the effect of zinc intake on AIDS patients is complicated and may have more impact on the virus than on the immune response of the patient (20, 48). While there is an urgent need for more intensive controlled studies of zinc in HIV/AIDS, the adverse effect of zinc deficiency on the immune system requires that normal plasma levels of zinc be maintained through supplementation.

Effect of zinc on diarrhoea in children

In developing countries, the use of both oral rehydration solution (ORS) therapy to correct fluid and electrolyte abnormalities, and appropriate antimicrobial drugs to treat selected diarrhoeal diseases have led to a drastic reduction in mortality and morbidity among children (43,60). However, the poor nutritional status of children in most developing countries puts them at further risk of diarrhoea-associated morbidity and mortality, regardless of the ORS therapy (43,61). Appropriate strategies to improve the nutritional status of affected children and to reduce the frequency of stool passage have been the prime focus of research studies (10,62,63).

Several studies, including clinical trials, have shown that diarrhoea is associated with

an increased loss of zinc and that zinc supplementation holds substantial promise as an adjunct to the treatment of diarrhoea (15,62-65). According to Castillo-Duran and co-workers (66), marked faecal zinc loss occurs during diarrhoea, thus a low serum zinc level can be considered as a reflection of acute zinc loss.

Zinc supplementation studies carried out in a number of developing countries reported significant reduction in the duration and severity of episodes of acute watery diarrhoea in infants, especially those whose initial plasma zinc levels were low (64,67,68). Similar results have been reported for children with persistent diarrhoea (69,70). Zinc supplementation was also more useful in cases of severe or prolonged diarrhoea episodes than in short-lasting or milder episodes (15,65,67,68,70).

Studies by the Zinc Investigators' Collaborative Group (65,71) indicated that zinc supplementation (10 to 20 mg elemental zinc), given for 14 days during and after diarrhoea, reduces the incidence of diarrhoea in the subsequent two to three months without additional zinc supplementation. A double-blind placebo-controlled study by Rahman et al. (72) showed that combined zinc (20 mg elemental zinc daily for 14 days) and vitamin A (200000 IU orally on day 14) supplementation is more effective in reducing persistent diarrhoea and dysentery than either vitamin A or zinc alone.

The benefit of zinc supplementation in all cases of diarrhoea was not limited to stunted children, acutely malnourished children or to children in any particular age group (61,63,65,71,72). In addition, the benefit of the supplementation was not affected by the aetiology of the diarrhoea episodes in the children, as both virus-associated and virus-free diarrhoea episodes responded well to therapy (64,65).

The issue of dose regimen for zinc supplementation and the frequency with which it should be given is still contentious (43). The effectiveness of the dose strongly depends on the age and zinc status of each individual (15,43,63,68). However, clinically important benefits have been reported when supplements containing 10 mg Zn/day as sulphate (15), 20 mg Zn/day as methionate (15), and more than 20 mg elemental Zn/day were administered to children under three years who presented with acute diarrhoea (43,63,68). Fuchs (43) has suggested that a dose adjusted for body weight might be necessary to ensure the efficacious and safe therapeutic use of zinc in the treatment of acute infectious diarrhoea.

Thus, current research reports strongly suggest that zinc supplementation may represent an important therapeutic advance in the treatment of acute and persistent diarrhoea in developing countries. This new strategy may successfully complement ORS and other therapies of proven benefit, such as continued breastfeeding of infants and general nutritional rehabilitation.

Effect of zinc on acute lower respiratory tract infections in children

According to Bahl et al. (15) the prevalence of acute lower respiratory tract infections was about 3-fold higher in children (12 to 59 months of age) with low plasma zinc (≤ 8.4 µmol/l) compared to children with normal plasma zinc (>8.4 µmol/l). In addition, boys with low plasma zinc had a 4-fold higher risk of suffering from acute lower respiratory tract infections than girls. The authors noted the possible involvement of coexisting deficiencies of other micronutrients in plasma that were not measured in the study.

Scientific reports on the effect of zinc supplementation on acute lower respiratory tract infections in children in developing countries are still unclear. In a double-blind, randomized controlled trial, Sazawal et al. (73) showed a 45% reduction in the incidence of acute lower respiratory infections in children (6 to 36 months of age) receiving 10 mg elemental zinc supplementation daily for six months.

The Zinc Investigators' Collaborative Group (71) found that the incidence of pneumonia in children was reduced by 41% after pooled analysis of 10 randomized controlled zinc supplementation trials in nine developing countries. These trials used between 10 and 20 mg elemental zinc for at least two weeks. The researchers (71) concluded that the substantial benefits of either short- or long-term zinc supplementation for the prevention of pneumonia is an important means of improving child survival in developing countries.

In another study (72), zinc was associated with a significant increase in acute lower respiratory tract infection in children, 12 to 35 months of age, receiving 20 mg elemental zinc for 14 days. This adverse effect was reduced when a vitamin A capsule (200000 IU) was administered to a similar group of children on day 14 of the trial (72). These results indicate that zinc alone might increase lower respiratory illnesses, but interaction between zinc and vitamin A reduces the adverse effect (72). The authors, however, emphasize the need for further studies using lower doses of elemental zinc. This finding further stresses the significance of combined micronutrient supplementation in combating acute lower respiratory tract infections and other diseases in children in developing countries.

In a double-masked, randomized placebo-controlled trial in an Indian urban slum (74), infants were given 10 mg and older children 20 mg elemental zinc or placebo daily for four months. On enrolment all the children received a single dose of vitamin A (100000 IU was administered to infants and 200000 IU to older children). Substantial reduction in the incidence of pneumonia was observed in both infants and older children receiving zinc supplementation compared to the placebo, thus indicating that routine zinc supplementation in children (6 to 30 months of age) can reduce the incidence of pneumonia. In addition, routine administration of zinc was shown to be effective in preventing severe (rather than mild) respiratory infections (74).

In a recent double-blind, randomized controlled trial, Mahalanabis et al. (75) evaluated the effect of zinc supplementation in children (9 months to 15 years of age) with clinically severe measles accompanied by pneumonia. Children were assigned randomly to receive 20 mg elemental zinc as acetate twice daily for 6 days, or a placebo. All the children received a single oral dose (100000 IU) of vitamin A together with a full course of antibiotics (75). The time taken to achieve a clinically improved status was not different between the two groups of children. In addition, after 6 days of treatment, the improvement in zinc and retinol concentrations in serum was similar in both groups. The results indicate that zinc supplementation showed no additional benefit to severely ill children with measles accompanied by pneumonia, treated with vitamin A and appropriate supportive therapy (75). In the opinion of the authors, long-term zinc supplementation can prevent pneumonia in children, because of improved immune responses. However, in an acute illness such as measles-associated pneumonia, there probably is insufficient time for mounting an adequate immune response to favourably modify such acute illness.

Inconsistency in the reports on the effect of zinc supplementation in children with lower respiratory tract infections in developing countries is a clear indication that further appropriately designed studies are urgently warranted in this area. However, given the findings to date, there is the need to include appropriate zinc supplementation in the treatment of lower respiratory tract infections in infants and children with low plasma zinc levels.

Interactions of zinc with copper and iron

The uptake of both zinc and copper occurs in the small intestine, where zinc can interfere with copper bioavailability as they compete

for absorption via intestinal cell metallothionein (19,22). Copper, however, does not affect the bioavailability of dietary zinc (22,43). Metallothionein has a higher affinity for copper than for zinc, but zinc, not copper, induces synthesis of intestinal metallothionein (19,22,43).

High intake of zinc increases the biosynthesis of metallothionein in enterocytes, which then bind with copper. The copper-metallothionein complex is excreted in the faeces after desquamation of the enterocyte (19,22,43). It is therefore possible that zinc supplementation can aggravate marginal copper deficiency (22,43) in malnourished children. Thus, there is a need to ensure that zinc supplementation is accompanied by an adequate intake of copper and other micronutrients. However, clinical signs of copper deficiency have been reported only with large daily doses of zinc (150 mg) given for prolonged periods (22,43).

Several studies have also shown that the efficiency of absorption of both zinc and iron depends on the ratio in which they are present in the diet or supplement (22,34,76,77). Negative effect of iron on zinc absorption in the gastrointestinal tract occurs only when the Fe:Zn ratio in the diet or supplement is greater than 2:1 (34,76).

Effect of zinc on malaria

Morbidity and mortality in malaria-endemic regions in developing countries are very high among malnourished children (78-81). A number of studies have associated vitamin A deficiency in children with *Plasmodium falciparum* parasitaemia (78,82). Zinc is known to be essential for a variety of lymphocyte functions implicated in resistance to malaria (78). These functions include synthesis of IgG, interferon-gamma, tumor necrosis factor and microbicidal activity of macrophages (14,78).

Studies on the possible efficacy of zinc supplementation in reducing childhood morbidity from malaria are contradictory

(14,81,83,84). A cross-sectional study among school-age children in Papua New Guinea showed an inverse association between zinc status and *P. falciparum* parasitaemia (14, 84). In another study in The Gambia, children receiving zinc supplements had 32% fewer clinic visits for malaria due to *P. falciparum* than children receiving placebo (83).

A placebo-controlled trial to assess the effects of zinc supplementation on malaria morbidity among preschool children in a malaria-endemic region of Papua New Guinea was carried out by Anuraj Shankar et al. (84). The results indicated that zinc supplementation reduced the frequency of health centre attendance due to *P. falciparum* malaria by 38%. Moreover, a 69% reduction was observed for malaria episodes accompanied by high levels of parasitaemia (>100,000 parasites/µl), suggesting that zinc may preferentially protect against more severe malaria episodes (84). These authors reported that zinc supplementation had no effect on densities of *P. vivax* parasitaemia. According to Shankar et al. (84), zinc does not reduce the incidence of malaria but reduces the number of parasites that cause illness, and thus its severity. This is because insufficient zinc levels affect the development and functioning of most immune cells, and inhibit cell-mediated immune responses (78,84).

A randomized double-blind placebo-controlled trial designed to test the hypothesis that zinc supplementation reduces morbidity from *P. falciparum* was carried out in African children in a malaria-endemic region of Burkina Faso by Müller et al. (81). The results of this study reported no evidence of zinc supplementation being effective against *P. falciparum* malaria in a population of African children with a high prevalence of malnutrition and zinc deficiency (81). Children receiving zinc supplements were no different in the number of episodes of *P. falciparum* malaria, or any other malariometric parameters, from the recipients of placebo (81). The finding was for all age

groups, and was consistently seen during both the longitudinal study and the cross-sectional surveys. The authors concluded that their inability to show the effect of zinc supplementation on morbidity from malaria may provide evidence that cell-mediated immunity is less important in the case of malaria in humans. Such a hypothesis would be supported by the overwhelming evidence of malaria not behaving as an opportunistic infection in African children with HIV infection or AIDS (81,85).

The opposite views expressed by these authors (81,84) create an urgent need for more placebo-controlled studies to elucidate the effect of zinc and other micronutrients on the morbidity and mortality of malaria in endemic regions in developing countries.

Assessment of zinc status

The non-availability of acceptable sensitive, specific and low-cost indicators for assessing the zinc status of an individual or a population at risk of developing zinc deficiency is partly responsible for the slow implementation of appropriate intervention programs in developing countries (10,15,28).

Zinc has a dynamic metabolic state that is regulated by strong homeostatic control of absorption and excretion (10,19,22). When absorption of zinc is low, the body reduces the rate of excretion of zinc in an effort to preserve zinc store (10,19,22). However, results from several studies strongly support the use of mean plasma zinc concentration as the most practical biochemical method for assessing zinc status of an individual and at the population level (2,6,10,15,19).

Factors militating against using plasma zinc for assessing zinc status of an individual include hypoalbuminaemia, time of sampling in relation to meals, diurnal variations and nonspecific decrease in plasma zinc concentration as a result of an acute phase response following infection in adults (2,10,15,19,22).

Despite the limitations of using plasma zinc as an indicator of zinc status for an individual, plasma zinc can serve as a useful method for assessing zinc status in epidemiological studies. Zinc status can also be assessed by determining whether the growth rate of a child is affected by appropriate zinc supplementation (22,28).

Dietary zinc intake data can also be used to assess zinc status of a population (28). This would include estimating the amount and sources of zinc, phytate and fibre in the diet (86,87) and calculating the diet Zn:phytate molar ratio (28,29).

Conclusion

It is clear from the information presented in this review that the public health significance of zinc deficiency cannot be overemphasized. Those in the high-risk group for zinc deficiency include low-birthweight infants, children with either frequent or persistent diarrhoea, malnourished children, pregnant women and lactating mothers, particularly in developing countries. The available data indicate that either adequate dietary zinc intake or zinc supplementation, together with other micronutrients and appropriate clinical management, enhances the recovery of children suffering from diarrhoea, infectious diseases, malaria and malnutrition. Not only can mild to moderate zinc deficiency in children enhance the development of these conditions, but these conditions can cause an increase in the children's requirement for zinc. It is therefore very important to improve the zinc status of individuals in the high-risk group by integrating a zinc intervention into ongoing primary health care programs and/or existing nutrition and public health programs in developing countries.

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