REVIEW ARTICLE

The Role of Zinc in the Growth and Development of Children

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This review concerns the importance of zinc in growth, development, and cognitive function in children and the deleterious consequences of its deficiency on children's health. Possible strategies to overcome zinc deficiency and the results of some supplementation trials are discussed. *Nutrition* 2002;18: 510–519. ©Elsevier Science Inc. 2002

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INTRODUCTION

Marginal and moderate zinc deficiencies in children with impairment in their growth has been reported from developed and developing countries.[1] Severe zinc deficiency is less common among humans, but it has been useful to understand the seriousness of the consequences of zinc deficiency in animal experiments.[1] The effects of such a deficient state in humans can be devastating because zinc is essential for normal fetal growth and development and for milk production during lactation, and it is extremely necessary during the first years of life when the body is growing rapidly.[2,3] Intrauterine growth retardation, one consequence of zinc deficiency, increases the risk of morbidity and mortality of the newborn. Zinc is a metal with great nutritional importance and is particularly necessary in cellular replication and the development of the immune response.[4] Therefore, if the growing fetus and infant are at risk of developing zinc deficiency, then an adequate supply of it is essential for normal growth and development.[5] Zinc deficiency triggers an array of health problems in children, many of which can become chronic, such as weight loss, stunted growth, weakened resistance to infections, and early death.[3,6] There is evidence that zinc deficiency impairs immune responses of young children and that zinc supplementation can prevent and reduce the severity of common diseases such as diarrhea and lower respiratory tract infections. The severe negative effects of zinc deficiency on human health in developing countries have been recognized by the United Nations.[6] The United Nations Children's Fund and World Health Organization supported many studies designed to demonstrate the effect of zinc on growth, prevalence of diarrhea, and anemia by administering a combined oral supplement of iron and zinc to infants at age 3–6 mo for 6 mo.[7] The main cause of human zinc deficiency is a diet that is low in highly bioavailable zinc, but it also may be caused by illnesses that impair food intake, provoke catabolism or malabsorption, or increase zinc excretion.[8] Factors responsible for zinc deficiency in premature infants may also include high fecal losses and low body stores of zinc at birth aside from the increased zinc requirement during rapid growth.[1] Marginal zinc deficiency is associated with diets based on plant foods, especially those diets rich in phytate, a potent inhibitor of zinc absorption.[9,10] Zinc-rich foods tend to be expensive, so zinc fortification is an important consideration, especially because daily intakes appear to be more useful physiologically than intermittent doses.[6,11] On the one hand, a wide variety of foods in the United States are now fortified with zinc.[11] On the other hand, multivitamin and mineral supplements are used widely in industrialized countries, although there is no consensus on their effectiveness and no guideline on their composition.[7] Basically they contain iron, folic acid, zinc, and vitamin A and in some cases riboflavin, calcium, and magnesium. These kinds of supplements also may be considered for pregnant women in developing countries. However, potential interactions between components of the supplement that may reduce bioavailability of some micronutrients have to be investigated.[7] It seems clear that prevention of zinc deficiency among young children remains the best policy, not only on moral grounds, but also on economic ones. There is a great deal of work yet to be done to find an adequate way to prevent zinc deficiency, but it appears that zinc supplementation or food fortification with an adequate zinc compound may be the key to overcome such a worldwide nutritional problem.

ZINC AND GROWTH

Zinc plays an important role in growth; it has a recognized action on more than 300 enzymes by participating in their structure or in their catalytic and regulatory actions.[12] It is a structural ion of biological membranes and closely related to protein synthesis.[10] The concept of zinc fingers explains the role of zinc in gene expression and endocrine function, and mechanisms of action of zinc involve the effects of the metal on DNA synthesis, RNA synthesis, and cell division.[13] Zinc also interacts with important hormones involved in bone growth such as somatomedin-c, osteocalcin, testosterone, thyroid hormones, and insulin.[14] Zinc is intimately linked to bone metabolism, thus, zinc acts positively on growth and development. Zinc concentration in bone is very high compared with that in other tissues, and it is considered an essential component of the calcified matrix. Zinc also enhances vitamin D effects on bone metabolism through the stimulation of DNA synthesis in bone cells.[12] In a study conducted in our laboratory with growing animals, incorporation of zinc to bone resulted in greater zinc levels than in other organs. Conversely, when grown animals were evaluated,[12,16] incorporation of zinc to bone were lower than in young animals. This indicated that zinc in bone is very important during the stages of rapid growth and during

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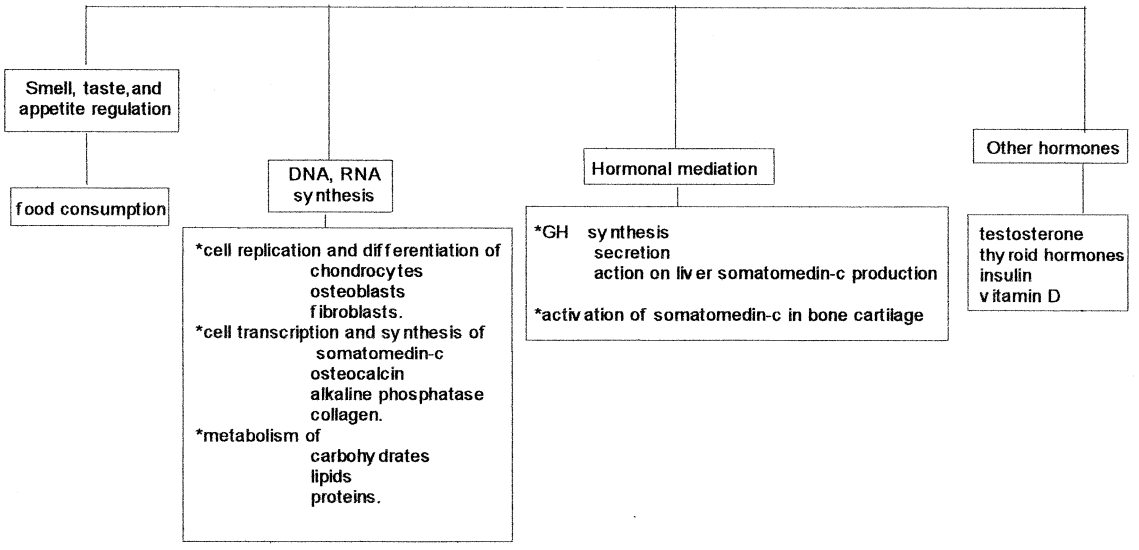

FIG. 1.

development.[15] Zinc acts on growth at many levels, which are described in Figure 1.[12,16]

Zinc may alter appetite control by acting directly on the central nervous system, altering the responsiveness of receptors to neurotransmitters.[12] Zinc deficiency also is accompanied by alterations in smell and taste and by anorexia and weight loss.[12,17] At another level, zinc participates in DNA and RNA synthesis, which is ultimately related to cell replication; differentiation of chondrocytes, osteoblasts, and fibroblasts; cell transcription; and synthesis of somatomedin-c, collagen, osteocalcin, and alkaline phosphatase. Alkaline phosphatase is produced in osteoblasts and provides calcium deposition in bone diaphyses. Zinc acts on the synthesis of alkaline phosphatase, forms part of its structure, and is essential for its activity. Zinc also participates in the metabolism of carbohydrates, lipids, and proteins, which in turn leads to good food utilization. In another level, zinc plays an important role in hormonal mediation because it participates in growth hormone (GH) synthesis, secretion, and action on liver somatomedin-c production. In addition, zinc is involved in the activation of somatomedin-c in bone cartilage. Zinc deficiency and protein malnutrition are intimately related and both are associated with depressed synthesis and activity of somatomedin-c. However, zinc supplementation rather than protein supplementation could increase somatomedin-c levels in zinc-deficient animals.[12] Another animal experiment showed that the administration of bovine growth hormone to zinc-deficient animals with low somatomedin-c activity did not increase zinc concentrations to normal levels unless the animals were treated with zinc. Therefore, somatomedin-c synthesis depends not only on the stimulation of GH but also on the presence of zinc. Although the improvement in growth in response to zinc supplementation has been reported in humans, the relation between zinc and somatomedin-c action is not well understood because it has not been fully investigated. Zinc potentiates the action of GH in the liver because it stimulates somatomedin-c synthesis and action on bone cartilage, and it can increase GH binding to other receptors such as those present in adipocytes. At the last level, in addition to vitamin D, there are several hormones indirectly related to growth such as insulin, thyroid hormones, and testosterone. Among androgens, testosterone is one of the most potent anabolic agents; it increases weight and muscle mass and accelerates linear growth. There is a direct relation between blood levels of zinc and testosterone and changes in steroidogenesis provoked by zinc-deficiency caused hypogonadism. In fact, the first clinical manifestations related to zinc deficiency and its essential role in human nutrition were hypogonadism and growth retardation.[12,14,16–20]

However, it is important to remember that zinc has no pharmacologic effect on growth, so its improvements on growth rates are the result of the correction of a pre-existing zinc deficiency.[19,21]

In addition to affecting the growth of newborns, infants, and adolescents, zinc deficiency has an important role in intrauterine growth. Several studies have demonstrated the nutritional importance of adequate maternal zinc nutrition for normal fetal growth and development.[12]

PREGNANCY

Maternal nutrition status is an important determinant of perinatal and neonatal well-being. There are many nutrition programs designed to prevent iron-deficiency anemia during pregnancy, but in the case of zinc, which is also very important for maternal and infant survival, much less has been done. It is estimated that 82% of pregnant women worldwide usually have an inadequate regular intake of zinc and likely suffer health consequences of zinc deficiency.[20] In humans the research concerning maternal zinc status and birth weight has not provided consistent results.[20] The effect of maternal zinc deficiency on progeny growth on experimental animals is very clear. It results in late effects several months after birth such as decreased immunity and learning or memory disorders. In the case of humans, not all the studies found a link between maternal zinc status and birth weight.[16] However, consequences of maternal zinc deficiency are well known (Table I).[1,12,22,23]

Zinc deficiency leads to increased risk of maternal and neonate morbidity and mortality. Many studies have shown that pregnant women are at risk of zinc deficiency because their zinc intakes are very low compared with those recommended, and the diet consumed by most of these women has a high content of phytate.[14,24,25] Women with mature infants born by normal delivery had significantly higher serum zinc during pregnancy than did women with abnormal deliveries and/or abnormally developed infants. Teenage girls, women with multiple pregnancies, women with impaired intestinal absorption due to disease or drugs, and in particular women consuming a low-protein, high-phytate diet seem to risk developing zinc deficiency during pregnancy.[26]

TABLE I.

CONSEQUENCES OF MATERNAL ZINC DEFICIENCY

Spontaneous abortion
Congenital malformations
Low birth weight intrauterine growth retardation
Preterm and post-term delivery
Prolonged or inefficient first-stage labor
Protracted second-stage labor
Premature rupture of membranes
Pregnancy-related toxemia

Ortega et al. found that subjects with intakes lower than 50% of that recommended had significantly lower serum and mature milk zinc levels than did those with higher intakes (although all subjects had zinc intakes lower than those recommended).[27] In addition, mean dietary zinc intake of postpartum women was less than 42% of the recommended dietary allowances, as reported by Moser et al.[28] Anthropometric, biochemical, and dietary data evaluated by Huddle et al. indicates that zinc deficiency could be a factor limiting pregnancy outcome in rural Malawian women.[24] Vruwink et al. found that hair zinc concentration evaluated in pregnant women decreases significantly between 12 and 36 wk of gestation. In those subjects, mean zinc intake at 20 and 36 wk of gestation was about 60% of the recommended dietary allowance. Nevertheless, zinc nutriture was found to be adequate for normal growth and development of the fetus.[29]

In some cases, the iron and folate supplements routinely prescribed significantly decreased the oral bioavailability of zinc in pregnant women despite dietary intakes.[5] The combined dietary and supplementary intake of iron in some subjects provided total dietary intakes of over 200% those recommended. Those subjects showed significantly lower serum and mature milk zinc levels than did those with lower iron intakes.[30] A study performed with stable isotopes demonstrated that zinc absorption in women who do not receive iron supplement from the third trimester of pregnancy to the lactation period is higher (20% to 31%) than in those receiving 18 mg of iron daily (18%).[31] In contrast, Tamura et al. found no evidence of an adverse effect of folic supplementation on maternal zinc nutriture and pregnancy outcome.[32] It seems preferable to provide multisupplements balanced in minerals and vitamins because iron supplements alone resulted, in some cases, in zinc deficiency. Zinc requirements and interactions are also important to consider when designing mineral supplements for preterm babies, infant formulas, and food fortification.[5]

There are few data available on whether prenatal zinc supplementation improves maternal and neonatal zinc status.[22,33] Therefore, the nutrition status of pregnant women should be monitored carefully and supplementation should be tailored to the needs of each individual.[30] Pregnancy outcome is related to incidence of fetal growth retardation, maternal infections during the perinatal period, birth weight, and Apgar score. Although a weak association was found in some studies between umbilical cord blood zinc levels and anthropometric measurements of newborns,[34] there is no consensus in the literature as to whether maternal zinc nutriture is associated with pregnancy outcome or fetal growth.[35] The lack of a reliable method to estimate zinc nutrition status may be one of the problems in finding such an association. Nonetheless, in a study performed in 1997 with 289 women in Birmingham, Alabama, neither the concentrations of serum zinc nor those of vitamins A and E and proteins showed a significant correlation with measures of pregnancy outcome.[36] Tamura et al. also reported that plasma zinc concentrations decline as gestation progresses and, when adjusted for gestational age, are not significantly associated with any measure of pregnancy outcome or neonate condition.[35] Thus, plasma zinc during the late first trimester to the early third trimester is not a predictor of pregnancy outcomes.[35] Caulfield et al. reviewed zinc supplementation trials in pregnant women and its effects on birth weight and concluded that, although the increase in the average birth weight of infants of supplemented mothers is small, it is comparable to the effects observed in energy and protein supplementation.[33] A possible explanation for the increased birth weights of babies of zinc-supplemented mothers may be that zinc affects the duration of pregnancy rather than fetal growth per se.[14,20] Caulfield et al. reported that 15 mg of zinc prenatally added to iron and folate improves maternal and neonatal zinc status, although zinc concentrations in both cases remained lower than values reported for well-nourished populations.[33] Goldenberg et al. found that supplementation with 25 mg of zinc daily in early pregnancy is related to greater infant birth weights and head circumferences in some cases.[37] Women who were supplemented with 45 mg of zinc orally daily from the day of reporting pregnancy until delivery showed significant increases in serum zinc and their babies had higher birth weights and gestational ages than did subjects in the control group. Garg et al. reported that those results were obtained in women supplemented for more than 3 mo and were related to the duration of the treatment.[38] Goldenberg et al. also reported that daily zinc supplementation in women with relatively low plasma zinc in early pregnancy had beneficial effects on birth weight and head circumference.[37] In this way, zinc supplementation with 25 mg of zinc from 19 wk until delivery resulted in greater birth weights and head circumferences in infants, predominantly in women with a body mass index below 26.[37]

Mild maternal zinc depletion has been strongly associated with intrauterine growth retardation.[5,39] Prematurity and intrauterine growth retardation have been associated with low serum zinc and insulin-like growth factor-I.[40] Zinc supplementation may be beneficial to women at risk of delivering small-for-gestational-age babies.[5] However, George et al. in a prospective study found no differences in plasma, red blood cells, and white blood cells zinc across 65 women with small-for-gestational-age babies and 51 women with appropriate-for-gestational-age babies.[39] Perhaps another factor was the cause of the condition in that population. Serum zinc decreases during pregnancy, but the range of individual values at the end of normal gestation may be rather large. Zapata et al. suggested that high levels of maternal serum zinc in healthy women at delivery may be related to maternal tissue distribution that could favor diffusional components of maternal-to-fetal transfer of zinc.[41] Studies in animals have suggested that, with inadequate zinc intakes, pregnant rats mobilize zinc from metabolically active pools for transfer to the fetus, and deposition of zinc into non-mobilizable maternal pools is reduced to preserve zinc for essential functions. Therefore, adjustments in zinc metabolism maintain embryogenesis even when zinc intakes are marginal, whereas gross developmental defects occur in humans and animals with severe zinc deficiency.[42] Studies have shown that the proportion of zinc bound to albumin increases in pregnant women who are marginally deficient in zinc. On the one hand, zinc bound to albumin is more labile than that bound to α_2-macroglobulin; thus zinc is more available to be supplied to the placenta in humans or transferred to the fetus.[42] On the other hand, even in marginal zinc deficiency, there is a fall in food consumption; thus, tissue catabolism is increased in these cases and pregnant dams may mobilize tissue zinc and deliver apparently normal pups.

Earlier studies in animals have suggested that diets that increase catabolism reduce the teratogenic effects of zinc deficiency because of the possibility that zinc is released from body tissues when the metabolic state is altered. There are two major pools of zinc in the organism: bone and muscle. Masters et al. reported that most of the specific activity (^{65}Zn) in fetuses of zinc-deficient or zinc- and calcium-deficient dams came from breakdown of maternal muscle with a relatively small contribution of bone zinc. In contrast, specific activity of zinc in fetuses from zinc- and calcium-

adequate dams was less than 30%, indicating that most of the zinc came from the diet.[43] Lowe et al. concluded that in marginal zinc deficiency, the flux of zinc to the maternal hepatic pool or to other, more slowly turning over tissue is reduced.[42] This situation in addition to a reduction in food consumption and tissue catabolism in late gestation support a normal pregnancy outcome.[42] In addition to the clinical manifestations of zinc deficiency cited in Table I, the main teratogenic effect of maternal zinc deficiency during pregnancy seems to be a defective closing of the neural tube. Numerous studies have shown a high prevalence of zinc deficiency in populations where this defect is frequent. Favier reviewed this hypothesis and concluded that zinc is lower in children with neural tube defects, not as a result of the total absence of a carrier but perhaps of a non-optimal structure.[23] Thus, zinc deficiency reduces the activity of numerous enzymes in the brain, which may lead to a cessation in cell multiplication at a crucial period of morphogenesis.[23] Velie et al., in more than 430 fetuses or infants with neural tube defects and 429 controls, associated increased total preconceptional zinc intake with a reduced risk for neural tube defects.[44] The quality of the food source of zinc was very important because zinc-rich foods such as animal products were related to a reduced risk of neural tube defects.[44] In contrast, Hambidge et al. studied 27 women with a pregnancy-associated neural tube defect and found no differences in serum zinc compared with matched controls. They also concluded that folic supplements do not alter zinc status of the mother or the embryo.[45]

LACTATION

The lactation period poses a different threat to maternal zinc homeostasis because zinc requirements during this period are very high.[46] The nearly two-fold increase in zinc absorption during lactation likely was in response to the demand for zinc to synthesize breast milk.[2] In some cases, plasma zinc concentrations increased from the time of delivery to 1 mo postpartum, possibly to meet lactating zinc demands, whereas erythrocyte zinc concentrations decreased.[28] There is a common consensus that bioavailability of zinc from human milk is higher than that from cow's milk or formulas. Casey et al. evaluated plasma zinc response with human milk, cow's milk, and formulas and corroborated that consensus.[47] This difference can be attributed to the existence of a citrate-rich fraction, the presence of lactoferrin, and the lower casein or phosphorous content of breast milk.[16] Colostrum, which is rich in proteins and zinc, is gradually replaced by mature milk. As lactation proceeds, there is a gradual increase in milk output and a substantial drop in zinc concentration.[48,49] After the first month of lactation, human milk zinc concentrations are low in comparison with cow's milk concentrations and declines further as lactation progresses. Perrone et al. reported a time-dependent decline of copper, zinc, and selenium in human milk, with similar 10 d half-times.[50] Fung et al. reported that the amount of zinc in breast milk averages 2 mg/d at lactation 7 to 9 wk postpartum.[2] Walravens et al. reported that the zinc content of human milk declines from 40 μM/L at 1 mo to 10 to 15 μM/L at 6 mo.[19] Krebs reported that, in the early weeks postpartum, zinc excretion in milk is 30 to 40 μM/d (2 to 3 mg) and declines to 15 μM/d (1 mg) by 2 to 3 mo postpartum.[46] Krebs also reported that the zinc level in breast milk is about 3 mg/L at 2 wk postpartum.[49] Therefore, breast milk may provide only a small percentage of the zinc requirements of infants after the age of 6 mo.[51]

Nevertheless, although mechanisms of zinc excretion in milk are not well understood, high zinc concentrations in milk may be associated with low zinc intakes. This may be due to a greater secretion by the mammary gland of zinc bound to stress-mediated carrier proteins such as α_2-macroglobulin, which may bind zinc, and it was detected in high concentrations in women of low socioeconomic status.[46]

Although evidence suggests that zinc bioavailability from human milk is very high, the fact that zinc concentrations decline as lactation proceeds has led to concerns about the risk that fully breast-fed infants may have suboptimal zinc intakes after the early months of lactation.[16,52] Krebs also concluded that zinc concentrations in human milk decline sharply during the early months postpartum, regardless of maternal zinc intake or adequate zinc status, but zinc requirements of the fully breast-fed infant are easily achieved because of the high bioavailability of zinc in human milk.[52] This situation is optimal; however, up to 5 to 6 mo thereafter, infants may become marginally zinc deficient if breast-feeding continues.[52] Further, if this period is accompanied by potentially increased losses of zinc, such as the presence of diarrhea, zinc supplementation should be considered. At this time, decline in weight gain is often a sign of marginal zinc deficiency.[19] Therefore, among breast-fed infants, growth faltering in comparison with reference growth curves may be common in developing and developed countries.[19] Decreased growth rates in breast-fed infants become apparent after 4 to 6 mo of nursing. In developing countries, growth velocity decreases earlier, from about 12 wk of breastfeeding.[19] Walravens et al. found that growth faltering may be due in part to inadequate zinc intake in infants breast fed for longer than 4 mo.[19]

A major determinant of postnatal survival is the ability of the infant to resist infection and respiratory and diarrheal diseases.[20] Newborns are at particularly higher risk for infections during the first 6 mo of life because adaptive immunity is not fully functional and exposure to pathogens is significant. Therefore, because zinc has a central role in immunity and health development, its deficiency might be a previously unrecognized cause of decreased vaccine efficacy in infants.[20] Exclusive breast feeding is protective, so the introduction of complementary foods is not encouraged before age 5 to 6 mo; after that age, the choice of high-quality complementary food is very important and beneficial in providing an adequate amount of the essential nutrients and energy.[46,49]

Krebs et al. studied healthy infants who were fed human milk exclusively for at least 5 mo and then evaluated at ages 2 wk and 3, 5, and 7 mo and found that zinc intakes (mean $\pm$ standard error of the mean) from breast milk were 2.3 $\pm$ 0.68, 1.0 $\pm$ 0.43, 0.81 $\pm$ 0.42, and 0.52 $\pm$ 0.31 mg/d, respectively.[53] They concluded that, although zinc intake seemed to be adequate on average through 5 mo, it is advisable to consider the introduction of weaning foods at this point to avoid possible future marginal zinc deficiency.[53] Whatever the type of feeding, zincemia in the newborn decreases during the first 2 mo after birth. This decrease lasts longer in premature babies born with lower reserves of zinc, because zinc mainly accumulates in the liver during the last week of gestation.[16] Therefore, the term infant's zinc status is not a concern during the first months of life because the infant can use zinc from hepatic thionein reservoirs, which are high and provide an adequate amount to cover the infant's requirements, to supplement zinc derived from milk. However, in the case of preterm infants, caution must be used because zinc thionein and hepatic reservoirs may be not adequate since the reservoirs are completed or formed during the last days of gestation.[16] The possibility of suboptimal zinc status has to be considered after age 6 mo, when zinc milk concentrations begin to decline. Krebs et al. factorially estimated zinc requirements in infants and found that calculated requirements for retention and for urine and sweat losses, and thus for apparent absorption, are approximately 10% lower in girls. That finding could explain the observed sex differences in the growth response of infants to dietary zinc supplements.[54] Krebs et al. also determined that male infants of non–zinc-supplemented mothers cannot meet zinc requirements after the 7 mo of lactation even considering 100% absorption of dietary zinc. Although female requirements are consistently low, the estimated net absorption necessary to meet their zinc requirements after 7 mo of lactation would have to be higher than 90%.[54]

These estimated percentages of zinc absorption necessary to meet zinc requirements in females and males are much higher than

published values of zinc absorption from human milk; thus, after the 7 mo of lactation, infants could be at risk of zinc deficiency and its consequences.[54] Therefore, although the bioavailability of zinc in maternal milk is high, even a well-nourished mother may provide only 7 to 10 μM of zinc daily. Thus, zinc absorption would have to approach 80% to 100% to meet zinc requirements of nursing infants to allow zinc deposition in soft tissues and especially in bone.[19,54] However, growth velocity, which is the main determinant of zinc requirements, also declines as infants age, so the decline in zinc concentrations of human milk could be a control mechanism to prevent an unnecessary burden to maternal zinc status.[54] In another study, Krebs et al. concluded that the needs for dietary zinc are adequately met by most fully breast-fed infants despite relatively low zinc intakes in relation to estimated requirements.[55] This may result from the combination of a high fractional absorption and the efficient conservation of intestinal endogenous zinc.[55] Although a diet of breast milk can in rare circumstances cause insufficient zinc intakes,[56] there are several case reports of exclusively breast-fed infants who presented clinical evidence of zinc deficiency with symptoms such as erosive skin changes, alopecia, a failure to thrive, irritability, and diarrhea. Zinc supply was low in all these cases, but different zinc supplementation strategies resulted in the normalization of laboratory values of zinc deficiency and the amelioration of symptoms.[56–59] Although the cause of inadequate zinc concentration in breast milk is not known, there may be a defect in the transfer of zinc from maternal serum to breast milk related to the alteration of a zinc transporter. There are reports of severe zinc deficiency, fatal in most of the cases, in pups born of mothers with a mutation in ZnT-4, which is expressed in the mammary gland. A mutation in a gene of the zinc transporter ZnT-4 may account for abnormally low milk zinc concentrations associated with severe zinc deficiency in breast-fed infants.[52,60]

INFANCY

Marginal zinc deficiency is a common nutritional problem around the world, especially in children of developing countries where diets have less available zinc. Nevertheless, zinc deficiency remains difficult to identify because of the lack of a reliable laboratory index to estimate zinc nutrition status.[13] This is the reason zinc supplementation trials have become the best source of information about zinc nutriture around the world and especially in risk groups such as children.

The existence of marginal zinc deficiency among children produces serious consequences for health such as retarded growth, an increase in infectious diseases, and the impairment of cognitive function.[10]

Diet

The high intakes of phytate relative to zinc in the diet of children from many countries, but predominantly developing countries, suggest that these children are at great risk for inadequate zinc nutriture, with all the consequences that this may provoke for child health.[61–64] However, it is important to remember that high cereal intake is not exclusive to diets of developed countries.[65] Thus, it is noteworthy that mild, growth-limiting zinc deficiency might be prevalent in healthy children and in developed countries.[65,66] Due to dietary modifications including the intake of cereals, vegetables, and the frequent use of soy formulas instead of breast milk, children from developed and developing countries may suffer from zinc deficiency.[21,67] It is estimated that 10% to 15% of the formulas fed to US infants currently is soy formula.[68] With regard to feeding strategies in premature infants, studies have demonstrated that feeding with human milk is better than with any other strategy. In the case of fortified human milk, the data suggest that its properties compared with those of formula are more beneficial in the improvement of health, and some investigators have proposed the promotion of feeding preterm infants with fortified human milk.[69]

The use of zinc-fortified formulas has been demonstrated to improve growth and immune function in children recovering from malnutrition. Schlesinger et al. reported higher linear growth together with increased salivary concentrations of immunoglobulin A.[70]

Lönnerdal et al also evaluated various types of infant formulas and weaning foods in the suckling rat pup model and found that regular, preterm, hydrolisate, and weaning formulas have high bioavailabilities of zinc comparable to human and cow's milk. However soy-, rice-, and cereal-based formulas had very low zinc bioavailabilities (45% to 55%) because of the presence of phytate.[71]

When casein hydrolysate formula was compared with cow's milk formula with respect to zinc absorption, Krebs et al. found that net zinc absorption from casein hydrolysate is higher.[72] Protein digestibility was higher from ultrahigh-temperature–treated formula than from conventionally heat-treated formula. When whey-predominant, ultrahigh-temperature–treated formula with 13 or 15 g of protein per liter was evaluated, using breast-fed infants as controls, iron, zinc, and copper status were satisfactory in all groups.[73] Knowing which factors in infant formulas negatively affect trace element absorption would be helpful when making dietary choices of weaning foods and for possible changes in the composition of these foods to improve mineral bioavailability.[71] In the case of soy formulas, soy protein was thought to have an inhibitory effect on zinc bioavailability, but Lönnerdal et al. demonstrated that it is the high phytate content that reduces zinc bioavailability from these formulas.[68] Lönnerdal et al also demonstrated that there is no threshold level of a phytate:zinc ratio that needs to be exceeded to observe the inhibitory effect, but there is a linear negative correlation between zinc absorption and phytate content.[68] Therefore, although soy formulas have been designed to meet the nutrient requirements of human infants, their high phytate content may negatively affect trace element absorption. However, reducing the phytate content and partially hydrolyzing the protein in soy formula had a beneficial effect on zinc absorption in many cases.[74] Zinc absorption was higher from low-phytate soy formula than from regular soy formula in rhesus monkeys (36% versus 22%) and rat pups (78% versus 51%).[74] Infant formulas in the United States are supplemented with zinc to 5 to 7 mg/L.[68] Tyrala et al. reported that a formula that provides 12.5 mg/L of zinc allows a positive zinc balance for preterm infants.[75] In the case of iron, the recommended level is 12 mg/L.[76] There has been some concern as to whether the increased intake of iron via food-fortification programs could have a negative effect on the absorption of zinc. Studies in humans have shown that high concentrations of iron interfere with zinc absorption when the minerals are administered in an aqueous solution but not when given in a meal; this result may be due to an alternative absorption pathway for zinc bound to low-weight ligands formed during digestion.[77,78] Whittaker, with reference to Lönnerdal et al.,[68] suggested that, when infant formulas contain 7 mg of iron per liter, the relation of iron to zinc would be 1:1, with satisfactory hematologic indexes and the exclusion of possible interactions between these minerals.[77] Metabolic studies to determine the effect of iron fortification in infant formulas on zinc absorption demonstrated that iron:zinc ratios of 5.4:1 and 1.3:1 do not alter zinc absorption.[77] Fairweather-Tait et al. did not find an adverse effect from adding iron to an infant formula on zinc absorption. However, they used reduced iron for which bioavailability is variable and its gastric solubility is low.[79] A solution providing 10 mg of zinc and 25 mg of iron per 0.5 mL would supply the child's requirement for iron and zinc, with no interference by iron on zinc absorption or by zinc on copper absorption.[51] Many experiments evaluating the interaction between iron and zinc suggest that, when dietary ligands are present, there is little or no interaction between the absorption of zinc and

TABLE II.

ZINC SUPPLEMENTATION EFFECTS ON DIARRHEA IN CHILDREN

Reference	Subjects ages	Supplementation	Observations
89	3–24 mo	20 mg Zn for 2 wk	Shorter recovery period from diarrhea or malnutrition
90	3–24 mo	20 mg Zn for 2 wk	Reductions in diarrhea and respiratory morbidity
83	6 mo–2 y	14.2 mg Zn acetate or 40 mg Zn acetate for 15 d	Substantial reduction in the rate of prolonged diarrhea and its duration
84	6–9 mo	10 mg Zn sulfate for 7 mo	Median incidence of diarrhea was reduced by 22% and 67% fewer children had one or more episodes of persistent diarrhea
81	6–35 mo	20 mg Zn	Reduced severity and duration of diarrhea; fewer watery stools per day and fewer days with watery stools
91	4–36 mo	10 mg Zn for 5 mo	Fewer episodes of diarrhea and respiratory infections
92	LBW babies	5 mg Zn for 8 wk	Reduced prevalence of cough and diarrhea
93	18–36 mo	20 mg Zn methionine or 20 mg Fe sulfate or 20 mg Zn+20 mg Fe for 12 mo	Zinc-supplemented children of both groups had fewer episodes of disease, including diarrhea

LBW, low birth weight

iron.[78] With the recognition of the impact of zinc deficiency on human health and especially in children, there was the need to develop programs to combat this deficiency, preferably by incorporating zinc into pre-existing micronutrient intervention strategies, as in the case of iron-fortification programs.[6] Allen suggested that serious consideration should be given to the simultaneous inclusion of iron and zinc in children's supplements, although one limitation of dual supplementation is that zinc stores could become depleted relatively soon after supplements are withdrawn, whereas iron stores can last for some years.[51]

Diarrhea

Chronic diarrhea causes zinc deficiency, and zinc deficiency in turn can contribute to diarrhea.[61,80] Zinc loss during bouts of diarrhea is comparable to the daily absorption requirement.[31] Duration and severity of diarrheal illnesses among infants from developing countries suffering from malnutrition and impaired immune status are greater than in well-nourished children. All these factors may be associated with zinc deficiency because zinc supplementation has resulted in amelioration of these episodes. In addition, the impact of zinc supplementation on recovery from diarrhea was greater in stunted children, which is also related to zinc deficiency.[81]

Black reported that the duration of diarrhea is 9% to 23% shorter in zinc-supplemented children and that the incidence of diarrhea in zinc-supplemented groups is reduced by 8% to 45%.[82] Zinc supplementation accelerated regeneration of the mucosa, increased levels of brush-border enzymes, enhanced cellular immunity, and elevated or augmented secretory antibobodies.[21] Thus, zinc supplementation can reduce the incidence and severity of childhood infections and may lower child mortality in impoverished areas.[80] Zinc supplementation was associated with a substantial reduction in the rate of prolonged diarrhea and on its duration, suggesting that it may be beneficial in children with diarrhea in developing countries.[83] Ruel et al. found that supplementation with 10 mg of zinc sulfate for 7 mo in children can reduce the median incidence of diarrhea by 22%.[84]

Patients with chronic inflammatory bowel disease also showed low serum zinc and an altered response to oral zinc load.[85] In those cases, zinc supplementation was also beneficial in the resolution of small bowel mucosal damage, suggesting a role for zinc in the treatment of shigellosis.[86] Golden et al. suggested that, for children recovering from severe malnutrition, it is advisable to administer zinc supplements, especially to prevent diarrhea and if a soy-based formula is contemplated.[87] They associated zinc supplementation with a decrease in the energy cost of tissue deposition and regrowth of the thymus.[87] Chevalier et al. used zinc with a pharmaceutical purpose, e.g., an immunostimulator in the recovery period of children suffering from severe protein-energy malnutrition, and found that this treatment allows coincidental nutritional and immune recovery in these children, with a reduction in the duration of hospitalization prevention of frequent relapses, for only one additional US dollar per month of hospitalization.[88]

Table II lists many supplementation trials performed in children and their effects on diarrheal prevalence and morbidity.[81,83,84,89–93]

Growth

Decreased growth rate in children has been associated with increased morbidity, reduced scholastic achievement, and long-term negative effects on physical work capacity and reproduction performance.[94,95] In some populations, growth stunting was not related to health or micronutrient status.[94] However, growth stunting can occur in association with marginal deficiencies of several micronutrients. Consequently, in these cases, supplementation with single nutrients will produce little or no beneficial effects on linear growth, so it is advisable to supplement with multiple micronutrients, although the increment in length can be less than expected.[95] Two minerals have been found to be critical during infancy and childhood, when the period of rapid growth takes place: iron and zinc. Supplementation studies have shown that these minerals are related to birth weight and weight and height increases in children, but it has often been difficult to characterize the exact role of these micronutrients on growth.[96]

Despite ample food supplies, growth stunting or underweight in children remains high. The role of low zinc intake in these children should be explored.[97]

Although zinc deficiency delays growth and development, the benefits of zinc supplementation on incremental growth are controversial.[95] Chinese children of short stature have demonstrated a prevalence of sparse hair and low plasma zinc. Zinc supplementation improved growth and caused the disappearance of anorexia in those suffering from it.[9] Zinc supplementation was also beneficial for inducing growth in short Japanese children without endocrine abnormalities, as reported by Nakamura et al.[98] Zinc may mediate growth by affecting the activity of insulin-like growth factor-I.[8] Ninh et al. associated the increase in growth velocity resulting from zinc supplementation in growth-retarded

TABLE III.

ZINC SUPPLEMENTATION EFFECTS ON GROWTH IN CHILDREN

Reference	Subjects ages	Supplementation	Observations
97	55.8 ± 11.2 mo	10 mg Zn sulfate for 6 mo	Increased mid–upper arm circumference and weight gain but no influence on height; lower infection rates
100	81.5 ± 7.0 mo	10 mg Zn amino acid chelate for 90 d	Increase in median triceps-skinfold *Z* score and a smaller deficit in median mid–arm circumference *Z* score
101	29.0 ± 2.9 wk (LBW)	11 mg/L formula for 6 mo	Higher plasma zinc, improved linear growth velocity, higher maximum motor development scores
102	Preadolescent and adolescent	10 mg Zn for 12 mo	Male schoolchildren and adolescents of short stature increased growth velocity, with no differences among females
103	SGA babies	3 mg Zn acetate for 6 mo	Greater weight gain and better linear growth; additive effect with exclusive breastfeeding after 4 mo
91	4–36 mo	10 mg Zn for 5 mo	Increased plasma concentration of insulin-like growth factor-I
104	11–17 y	30 mg Zn or 50 mg Zn for 12 mo	Affected weight gain and *Z* scores for weight for age and arm muscle area for age after only 3 mo of supplementation; thereafter, the effects vanished
105	6–24 mo	5 mg Zn for 12 wk	Reduced hospitalizations but did not improve growth; no effects on length, height, or head circumference
106	22–66 mo	70 mg Zn alone or with vitamin A for 6 mo	No effect on weight or height; improvement in serum zinc concentration
89	3–24 mo	20 mg Zn for 2 wk	Prevented possible decrease in body weight and serum zinc concentration
90	3–24 mo	20 mg Zn for 2 wk	Reduced growth retardation
107	4–11 y	12.5 mg Zn or 12.5 mg Zn and 12 mg Fe	Iron plus zinc supplementation improved growth rates in all children and zinc supplementation alone improved rates only in children with ferritin levels >20 ng/L before the study

LBW, low birth weight; SGA, small for gestational age

children with increased plasma concentrations of insulin-like growth factor-I.[91] In another experiment in stunted children, zinc supplementation enhanced catch-up growth via higher levels of insulin-like growth factor-I.[21] Penland et al. evaluated growth and neuropsychological functions of Chinese children after supplementation with zinc (20 mg), zinc (20 mg) and micronutrients, and micronutrients alone. Their results confirmed the essentialness of zinc for growth, neuropsychological functions, and repletion with many other nutrients that could affect those functions.[99]

Table III shows the results of supplementation trials performed in children and their effects on growth.[89–91,97,100–107]

Behavior and Brain Function

Several studies around the world have reported that children with a history of malnutrition attain lower scores on intelligence tests than do those who are properly nourished.

Undernutrition in early life can limit long-term intellectual development.[3] Factors such as income, education, and other aspects of the environment apparently can protect children against the harmful effects of a poor diet or exacerbate the results of malnutrition.[3]

Zinc is a critical nutrient for the development of the central nervous system:[8,20,108,109]

1. zinc-dependent enzymes are involved in brain growth
2. zinc-finger proteins participate in brain structure and neurotransmission
3. zinc-dependent neurotransmitters are involved in brain memory function
4. zinc is involved in the precursor production of neurotransmitters
5. metallothionein-III is one protein that binds zinc in neurons

Most supplementation studies in children have not reported effects on behavior; however, studies in animals have shown that severe zinc deficiency during the period of rapid growth of the brain altered emotional development, lethargy, and learning; attention and memory also were affected.[110,111] There is evidence associating zinc deficiency with deficits in activity, attention, and motor development and thus interfering with cognitive performance in humans; however, there is no clear explanation of the mechanisms underlying this relation. In humans, severe zinc deficiency can cause abnormal cerebellar function and impair behavioral and emotional responses.[108] Test learning and memorization difficulties have been discovered in pups born of zinc-deficient animals. These findings are related to those of other researchers on the effect of zinc deficiency during the first weeks of life, when a drop in neurons has been noted.[20,23] Moreover, maternal zinc status during midpregnancy may be particularly important for ensuring optimal central nervous system development because rapid neurogenesis and structural development occurs before the third trimester.[20] Sandstead et al. found that Chinese children supplemented with 20 mg of zinc with micronutrients improved their neuropsychological performances.[8] Zinc deficiency also may reduce activity. Bentley et al. found that, after 7 mo of zinc supplementation with 10 mg/d of zinc as oral zinc sulfate, independent of limiting factors such as age, motor development, sex, maternal education, family socioeconomic status, and nutrition status at baseline, zinc-supplemented as opposed to control children were much more likely to sit than lie down, play more, and whine or cry less.[112] Penland et al. evaluated growth and neuropsychological functions of Chinese children after supplementation with zinc (20 mg), zinc (20 mg) and micronutrients, and micro-

nutrients alone and confirmed the essentialness of zinc for growth, neuropsychological functions, and repletion with many other nutrients that could affect these functions.[99] Penland suggested that reduced activity in preschoolers and adolescents could help to conserve zinc for continued growth; thus, growth stunting could be an adaptation that allows a continued supply of zinc for behavioral adaptation.[113] Nevertheless, more research is needed to determine the long-term developmental importance of such differences in activity patterns during zinc supplementation (for a review of the behavioral data and methodologic issues in studies of zinc nutrition in humans, see Penland[113]).

POSSIBLE STRATEGIES TO OVERCOME ZINC DEFICIENCY

Supplementation of children with zinc and with other micronutrients may be beneficial during periods of greatest vulnerability such as pregnancy and early childhood and when the diet is low in animal products and based on high-phytate cereals and legumes.[51] Adolescents also have very high zinc requirements to maintain skeletal maturation, especially in females after menarche and during pregnancy.[114] However, it can be difficult for infants and young children to meet their zinc requirements during the transition from milk to solid foods.[51]

The forms of zinc used in many supplementation trials are zinc acetate, zinc gluconate, amino acid chelates such as zinc methionine, zinc carbonate, zinc chloride, and the most frequently used forms, zinc oxide and zinc sulfate.[6,51] There are five zinc salts listed as generally recognized as safe by the US Food and Drug Administration (FDA): zinc sulfate, zinc chloride, zinc gluconate, zinc oxide, and zinc stearate. However, no zinc compounds have been approved as safe by the FDA for direct addition to food. Nevertheless, the total quantity of zinc salts used has notably increased since 1970, and the compounds used most are zinc sulfate and zinc oxide.[77]

The main disadvantages of these zinc salts are their unacceptable taste and resulting nausea and dyspepsia. The solubility of these compounds is very important and strongly associated to their absorbability.[6,51] Zinc sulfate and zinc chloride are very soluble; zinc acetate is freely soluble; and zinc carbonate and zinc oxide are insoluble and thus poorly absorbed.[6,51] Another important factor influencing the solubility of zinc compounds, especially of those poor solubility in water, is the intragastric pH, which may be a limiting factor in their absorption.[6,51] This is very important to take into account, especially in developing countries, where there is a high prevalence of zinc deficiency and of *Helicobacter pylori* infection (about 80% to 90%), which causes 30% to 40% of achlorhydria cases. Therefore, when a zinc supplementation or fortification program is promoted or the effectiveness of a treatment with a zinc compound is evaluated, the prevalence of *H. pylori* infection and its consequences also must be considered in the analysis.[6,115–117]

An integrated approach using targeted supplementation, fortification, and dietary strategies should be used to eliminate zinc deficiency in developing countries. Zinc salts that are readily absorbed and at levels that will not induce antagonistic nutrient interactions should be used. There are three common strategies to combat nutrient deficiencies: supplementation, fortification, and dietary modification and diversification. Supplementation is appropriate for populations where zinc status must be improved over a relatively short period and the requirements cannot be met from habitual dietary sources. The current recommended doses in such cases are 5 mg/d for children younger than 5 y, 10 mg/d for children older than 5 y, 20 to 25 mg/d for pregnant women, and 4 $mg \cdot kg^{-1} \cdot d^{-1}$ for children with protein-energy malnutrition and persistent diarrhea. In a study of pregnant adolescents, Wolfe et al. showed that the form of zinc is important when considering the impact of a supplement.[114] They found that mean plasma zinc concentrations were higher in subjects consuming zinc sulfate than in those consuming zinc oxide.[114] This finding is very important because bioavailability of the zinc source has to be considered not only in this kind of study but also when considering a possible food-fortification program.[114]

Food fortification with zinc is recommended when its deficiency is endemic or when it is targeted in specific regions or for certain high-risk groups within a country. One critical factor in developing a food-fortification program is the choice of the food product to be fortified, which has to be widely or preferentially consumed by the risk groups. Another important aspect is the bioavailability of the fortificant considered, which has to be readily absorbed and utilized; resistant to any dietary inhibition of zinc absorption; safe, stable, and acceptable; and have no effects on the organoleptic properties of the food vehicle. To calculate the optimal fortification level for a food product, the toxic threshold level for zinc for normal individuals must be taken into account. The US daily reference dose, which is based on a lowest observed adverse-effect level of 1 mg/kg, is about 0.3 mg/kg. Foods in the United States frequently enriched with zinc and iron include flour, bakery goods, breakfast cereals, cereals, macaroni, infant formulas, and infant foods. The third strategy involves changes in food-selection patterns or traditional household methods for preparing and processing foods with the aim of enhancing the availability, access, and utilization of foods with a high content and bioavailability of zinc. They include (for reviews, see Gibson et al.[6] and Gibson and Ferguson[118]):

1. improved cereal varieties
2. addition of enhancers of zinc absorption
3. modified milling practices
4. soaking to reduce phytic acid content
5. germination to increase phytase activity
6. fermentation to increase microbial phytase activity
7. combined strategies

A combination of some of these strategies according with the characteristics of the risk populations may be the key to overcoming such an important nutritional problem.

CONCLUSIONS

Zinc deficiency is a serious nutritional problem among children of developed and developing countries; the consequences to children's health are retarded growth and development and the impairment of cognitive functions. There are some possible nutritional strategies to overcome zinc deficiency, although the FDA has not approved any zinc compound as safe for direct addition into food. Nevertheless, zinc supplementation has demonstrated beneficial effects on children health all around the world.

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ERRATUM

In the Conference Summary by Barry S. Kendler, PhD, that appeared in the January 2002 issue of *Nutrition: The International Journal of Applied and Basic Nutritional Sciences* [2002;(1):115–117], the degrees of one of the presenters at the conference was published incorrectly as "MD," whereas the correct title should have been ND (Doctor of Naturopathy). The sentence in question (top of page 117, immediately following the title of the presentation) should have correctly read:

Lyn Patrick, ND, associate editor of *Alternative Medicine Review:* HIV and Nutrient Supplementation.

We deeply regret this error and extend our apologies to Lyn Patrick, ND.

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