Recent advances in knowledge of zinc nutrition and human health

Sonja Y. Hess, Bo Lönnerdal, Christine Hotz, Juan A. Rivera, and Kenneth H. Brown

Abstract

Zinc deficiency increases the risk and severity of a variety of infections, restricts physical growth, and affects specific outcomes of pregnancy. Global recognition of the importance of zinc nutrition in public health has expanded dramatically in recent years, and more experience has accumulated on the design and implementation of zinc intervention programs. Therefore, the Steering Committee of the International Zinc Nutrition Consultative Group (IZiNCG) completed a second IZiNCG technical document that reexamines the latest information on the intervention strategies that have been developed to enhance zinc nutrition and control zinc deficiency. In particular, the document reviews the current evidence regarding preventive zinc supplementation and the role of zinc as adjunctive therapy for selected infections, zinc fortification, and dietary diversification or modification strategies, including the promotion and protection of breastfeeding and biofortification.

The purposes of this introductory paper are to summarize new guidelines on the assessment of population zinc status, as recommended by the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), the International Atomic Energy Agency (IAEA), and IZiNCG, and to provide an overview on several new advances in zinc metabolism. The following papers will then review the intervention strategies individually.

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Background

In 2004, the International Zinc Nutrition Consultative Group (IZiNCG) published a technical review [1] that was designed to provide an overview of current knowledge regarding zinc nutrition in relation to human health, to summarize the available information on assessing population zinc status, and to describe the range of programmatic options for controlling zinc deficiency. Since the publication of that document, recognition of the importance of zinc nutrition for human health worldwide has expanded dramatically, and more experience has been accumulated on the design and implementation of zinc intervention programs. Moreover, during the workshop on zinc supplementation and child mortality and morbidity held by the World Health Organization (WHO) in September 2006, it was concluded that "in view of the results of all the trials examining the impact of zinc supplementation on mortality, morbidity and growth, a consensus was reached on the need to develop new feasible approaches to improve the intake of zinc and its bioavailability in young children, in order to achieve adequate population coverage" [2]. Hence, the IZiNCG Steering Committee concluded that this would be an opportune time to reexamine the latest information on strategies to control zinc deficiency and to reassess the state of knowledge concerning interventions to enhance zinc nutrition.

Adequate zinc nutrition is essential for human health because of zinc's critical structural and functional roles in multiple enzyme systems that are involved in gene expression, cell division and growth, and immunologic and reproductive functions. As a consequence, zinc deficiency affects children's physical growth and the risk and severity of a variety of infections [1]. The results of multiple community-based intervention trials indicate

that zinc supplementation decreases the incidence of diarrhea and pneumonia among young children [3], and clinical treatment studies have shown that zinc supplementation during diarrhea reduces the severity and duration of such illnesses [4]. WHO and the United Nations Children's Fund (UNICEF) now recommend that zinc supplementation should be included as a component in diarrhea treatment regimens [5], and efforts are under way in a number of countries to scale up zinc supplementation during diarrhea.

In the above-mentioned report on the WHO workshop on zinc and mortality, the results of a meta-analysis of available trials of preventive zinc supplementation indicated that there was a statistically significant 9% reduction in overall mortality among young children who received zinc supplementation [2]. The recent *Lancet* series on maternal and child undernutrition concluded that zinc deficiency is responsible for ~4% of child mortality and disability-adjusted life-years [6]. Although the specific number of deaths that might be averted by zinc-related interventions can still be debated because of the numerous assumptions involved in such estimates, both of these foregoing analyses confirm that zinc deficiency is an important risk factor for child morbidity and mortality [7, 8].

In addition to the effects of zinc on morbidity and mortality, a number of studies indicate that preventive zinc supplementation increases linear growth and weight gain in previously stunted or underweight children [9]. Thus, interventions to prevent zinc deficiency also can reduce the overall rates of childhood malnutrition, as defined by anthropometric criteria. For all of these reasons, global commitment is urgently needed to implement policies and programs designed to control zinc deficiency.

Assessment of the risk of zinc deficiency

Because of the serious consequences of zinc deficiency, it is essential to quantify the risk of deficiency in those populations that are most likely to be affected by this problem. Regrettably, there are as yet very limited national-level data on the prevalence of zinc deficiency. To promote the inclusion of zinc status assessment in the context of national health and nutrition surveys, guidelines on the assessment of population zinc status were recently published following a consensus conference convened by WHO, UNICEF, the International Atomic Energy Agency (IAEA), and IZiNCG [10]. The three main types of zinc status assessment that were considered included biochemical, dietary, and functional methods.

Serum or plasma zinc concentration is considered the best available biomarker of the risk of zinc deficiency in populations [11]. Methods for collecting, processing, and analyzing samples for determining serum zinc concentration have been comprehensively reviewed [1, 12]. The prevalence of zinc deficiency should be expressed as the percentage of the population with serum zinc concentration below the specific lower cutoffs in relation to reference data for age, sex, time of day, and fasting status of the individuals examined [13, 14]. When the prevalence of low serum zinc concentration is greater than 20%, the risk of zinc deficiency is considered to be elevated and should be addressed through public health nutrition interventions to improve zinc status. This same indicator also can be used to assess the impact of an intervention program, by comparing the percentage of individuals with low serum zinc concentrations before and after initiation of the intervention. Because serum zinc concentration falls during the acute-phase response to infections, it is advisable to include biochemical indicators of infection, such as C-reactive protein or α_1-glycoprotein, to avoid the possibility of overestimating the prevalence of low serum zinc concentration due to concurrent infections [15, 16].

Inadequate dietary intake of absorbable zinc is one of the major causes of zinc deficiency. Therefore, assessment of the adequacy of zinc intakes through the use of 24-hour recalls or weighed dietary records is an important component in evaluating the risk of zinc deficiency in a population [11]. Dietary assessment can be used to identify subpopulations that have an elevated risk of zinc deficiency and to characterize dietary patterns that contribute to inadequate zinc intakes, thus informing on the appropriate design of food-based interventions. The prevalence of the population with zinc intakes less than the Estimated Average Requirement (EAR) [1, 17] can be used as the specific indicator of the risk of zinc deficiency in the population. Assessment of the adequacy of zinc intakes should take into account dietary zinc bioavailability, preferably through quantification of the phytate:zinc molar ratio of the diet [18] or by using available equations to predict zinc absorption based on dietary zinc and phytate contents [19]. The risk of zinc deficiency is considered to be elevated and of public health concern when the prevalence of inadequate intakes is greater than 25%, in which case an intervention to increase dietary zinc intakes is recommended [11]. The change in prevalence of inadequate zinc intakes can be used to assess the impact and effective targeting of food-based interventions.

Although there are several adverse functional consequences of inadequate zinc intake, these outcomes are not specific to zinc deficiency. For example, the incidence of some types of infections can be reduced by providing supplemental zinc [3, 20], but the disease rates are more closely linked to the level of exposure to specific pathogens. Thus, a high incidence or prevalence of particular infections, such as diarrhea, may suggest that the population could benefit from interventions including zinc, but the illness rates would

not be very useful in quantifying the extent of zinc deficiency in the population. Similarly, low height-for-age is not specific to zinc deficiency and could be attributable in part to maternal short stature, frequent infections, and other nutritional deficiencies. Thus, providing zinc alone should not be expected to fully reverse childhood stunting. Nevertheless, a previous meta-analysis of randomized, controlled trials among prepubertal children found that the severity of stunting in the study populations predicted the response to zinc supplementation [9]. Thus, the percentage of children under 5 years of age with height-for-age z-score (HAZ) less than −2.0 SD with respect to the reference population [21] has been recommended as the best functional indicator to assess the likely risk of zinc deficiency in a population [11]. This risk is considered to be elevated and of public health concern when the prevalence of low height-for-age is greater than 20%, in which case nutrition intervention strategies should include a means to improve zinc status.

The validity of these indicators and proposed cutoffs is still provisional, so they should be evaluated further when opportunities become available during national assessment surveys. As more experience is gained, these recommendations will need to be reviewed and revised as necessary.

Quantifying the risk of zinc deficiency

As with other micronutrient deficiencies, three main factors are responsible for the development of zinc deficiency in lower-income countries: inadequate dietary zinc intake or absorption from predominantly plant-based diets, as discussed above, or suboptimal breastfeeding practices; disease states that either induce excessive losses or impair utilization of zinc; and physiological states that increase zinc requirements, such as periods of rapid growth during childhood and pregnancy. These issues are reviewed in more detail elsewhere [1, 10, 22].

Because so little information is available from nationally representative surveys on the prevalence of low serum zinc concentration or inadequate dietary zinc intake, current estimates of the extent of zinc deficiency must rely on the prevalence of stunting among children under 5 years of age [11]. Fortunately, relevant information is available at the national level for most countries **(fig. 1)** [23]. Approximately 30% of children under 5 years of age worldwide are stunted (HAZ < −2 SD with respect to the distribution of the reference population data). WHO recommends a prevalence of stunting greater than 20% of the population to indicate a public health concern [24]. The highest prevalence rates of stunting (> 30%) are observed in countries in sub-Saharan Africa, South Asia, Southeast Asia, and Central America. Intermediate prevalence rates (20% to 30%) are found in the Andean countries, some Central American countries, Southern Africa, and some countries in North Asia. As zinc deficiency is not the only factor affecting children's growth, assessment of dietary zinc intake and serum zinc levels can be used to confirm the risk of zinc deficiency in these countries [11]. These assessments should be incorporated into existing public health and child nutrition monitoring programs whenever possible.

New advances in zinc metabolism

Although this document focuses primarily on the recent progress that has been achieved with regard to the role of zinc nutrition in public health, some of the advances that have occurred in our understanding of zinc metabolism and the factors that govern zinc homeostasis are also worth noting. A comprehensive review of new research on zinc metabolism is beyond the scope of this paper, but several new discoveries concerning zinc transport proteins will be described briefly, because they provide some insight into the complexities of zinc homeostasis, and this knowledge eventually may yield useful information for estimating dietary zinc requirements and for developing new methods to assess zinc status.

The efficiency of zinc absorption from the diet usually ranges from about 15% to 35% in adults, depending on the amount consumed and the presence of other dietary factors, such as phytate, that may inhibit absorption [25]. Active transport dominates at low or normal intake, whereas passive diffusion contributes more significantly at high intake [26]. The extent of the homeostatic regulation of zinc metabolism in humans is not well known, but both absorption and excretion appear to be involved. Studies in experimental animals suggest that zinc homeostasis is closely regulated, although not to the same extent as for iron. The mechanisms underlying the regulation of zinc absorption have long remained elusive.

Understanding of the mechanisms regulating zinc absorption and homeostasis has progressed considerably because of the discovery of two families of zinc transporters: the so-called ZIP proteins and the ZnT proteins. Members of the ZIP family of proteins (which are also referred to in the literature as Zrt-like proteins and Irt-like proteins, with systemic designation "SLC39") transport zinc from the extracellular space and intracellular organelles into the cytoplasm [27]. Thus, the net effect of these transporters (or "zinc importer proteins") is to increase cytoplasmic zinc. There are 14 known members of the ZIP family encoded by the human genome [28], but only a few of them have been characterized or evaluated with regard to physiological significance. ZIP-1 is expressed ubiquitously in human tissues but is only localized to the

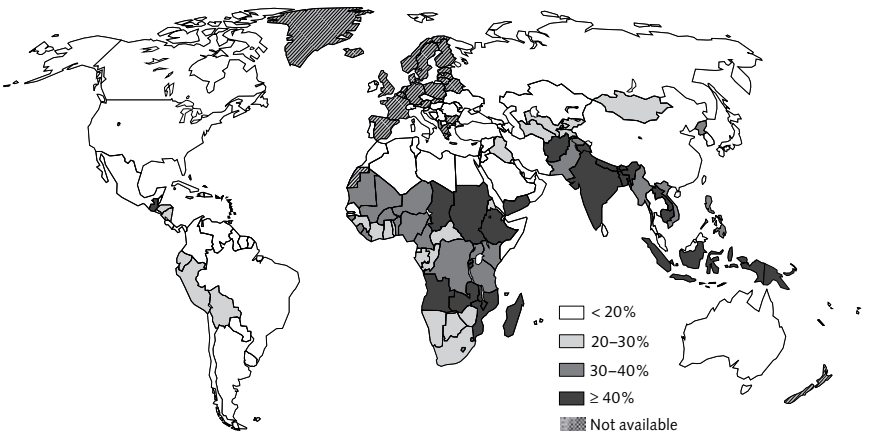

FIG. 1. Prevalence of nutritional stunting in children under 5 years of age. Source: IZiNCG [23]

plasma membrane in some cell types, possibly because of zinc-responsive regulation of its subcellular localization [29, 30]. In zinc-deficient cells, ZIP-1 migrates to the plasma membrane, whereas in zinc-replete cells, it is associated with intracellular compartments [31]. To date, ZIP-1 appears to be mostly involved in zinc uptake by erythroleukemia (K562) cells and prostate cells [29, 32]. ZIP-2 and ZIP-3 have also been shown to be involved in zinc uptake by some cell types, the latter in mammary epithelial cells [33].

The ZIP-4 transporter has been shown to be a key zinc importer in the intestinal cell. This transporter was discovered when mutations in the ZIP-4 gene were linked to the human genetic disorder acrodermatitis enteropathica [34]. Acrodermatitis enteropathica is due to an autosomal recessive mutation of the gene that codes for ZIP-4, causing disrupted transport function and impaired zinc absorption. Patients with acrodermatitis enteropathica need daily zinc supplements throughout life [35]. Because such supplements alleviate the problems of patients with acrodermatitis enteropathica, it is obvious that there are other, but less efficient, zinc transport mechanisms in the enterocyte. The ZIP-5 protein is expressed on the basolateral membrane of the enterocyte [36], where it may be responsible for zinc transport from the systemic circulation into the enterocyte, possibly as a means of drawing zinc into the intestinal cells when dietary zinc is low [27].

Recently, ZIP-14 has been shown to be involved in the uptake of zinc by the liver in response to acute inflammation and infection [37]. Serum zinc concentration falls during these conditions, whereas liver zinc concentration increases, possibly in an attempt to withhold zinc from pathogens. Liver ZIP-14 expression rises in response to the cytokine interleukin-6 (IL-6) during the acute-phase response [37], suggesting that induction of ZIP-14 may be responsible for the hypozincemia associated with infection.

The ZnT ("SLC30") family of zinc transporters has nine members in the human genome. These zinc transporters are primarily involved in cellular efflux of zinc and in uptake of zinc by intracellular organelles. Thus, the net effect of these transporters is to decrease cytoplasmic zinc concentration. ZnT-1 expression in the intestine is regulated by dietary zinc [38] and has been implicated in the regulation of whole-body zinc homeostasis by controlling zinc efflux from the enterocyte. ZnT-2 and ZnT-4 are involved in the flux of zinc in the endosomes, possibly regulating intracellular trafficking of zinc. These membrane transporters all have six transmembrane-spanning domains and a conserved histidine-rich region predicted to have a cytoplasmic loop that is likely to bind zinc [39, 40]. Experiments showing zinc sequestration by endosomal vesicles during overexpression of ZnT-2 suggest that this transporter may be important for controlling intracellular transport of zinc by the enterocyte [41]. All three transporters are found primarily in intestinal villus cells, and much less frequently in crypt cells.

As described for the ZIP proteins, individual members of the ZnT family of transporters are located in specific cell types. For example, in rats ZnT-1 is found mostly in the ileum, ZnT-2 is located primarily in the duodenum and jejunum, and ZnT-4 is found throughout the small intestine [42]. ZnT-5, ZnT-6, and ZnT-7 have been found to be involved in zinc homeostasis in the pancreas, brain, and prostate, respectively [43–45]; these transporters seem to be involved in zinc uptake in the Golgi apparatus [45, 46]. ZnT-3 is localized to synaptic vesicles in some types of neurons [47], and ZnT-8 is associated with the secretory granules of pancreatic beta-cells [48]. Thus, it is evident that the ZnT family is involved in multiple aspects of zinc homeostasis.

Several zinc transporters are involved in zinc secretion. ZnT-4, for example, has been shown to be involved in the secretion of zinc by the mammary gland, and mutations of the gene cause the defect *lethal milk* in mice [49]. The milk of these animals has very low

zinc concentration, resulting in severe zinc deficiency and high mortality among their pups. Several studies have also shown that healthy, well-nourished lactating women can have abnormally low concentrations of zinc in their breastmilk [50]. Supplementation of these women did not increase milk zinc concentrations, suggesting a defect similar to that observed in mice with the *lethal milk* defect, who are unable to secrete zinc into milk. A recent study of a family of women with low milk zinc contents, causing transient neonatal zinc deficiency in their infants, showed that milk zinc secretion was impaired because of a mutation in ZnT-2 [51]. It is not yet known how common this type of mutation is in lactating women or how often it causes zinc deficiency in breastfed infants.

The zinc transporters respond to conditions of low or excessive zinc exposure and changes in zinc status, presumably in an attempt to modulate their effects on particular tissues and biological functions. For example, during zinc deficiency, the abundance of ZnT-1 protein in the small intestine is reduced, decreasing endogenous zinc losses, and the localization of ZIP-4 is changed to the entire villus, maximizing zinc uptake. In the liver, ZnT-1 protein abundance is increased during zinc deficiency, most likely in an attempt to increase zinc in the systemic circulation; however, liver zinc decreases, as has been shown in animal studies [52]. Other tissues, such as the pancreas, muscle, and mammary gland, also respond to alterations in zinc status, but our knowledge regarding homeostasis in these tissues is more limited. Furthermore, little is still known about the regulation of zinc homeostasis and how different tissues contribute to this regulation in humans. It may be possible in the future, however, to combine results from animal models with data from compartmental modeling obtained in humans to unravel relevant information for understanding human zinc requirements and developing new methods to assess zinc status.

As discussed in the first IZiNCG technical document [1], the recommended strategies to control zinc deficiency include supplementation, fortification, and dietary diversification and modification. The present document reviews the current state of knowledge and information gaps regarding each of these intervention strategies. In particular, two papers discuss the available evidence regarding preventive zinc supplementation among infants, preschoolers, and prepubertal children [53] and among pregnant and lactating women [54]. A third paper examines zinc supplementation as adjunctive therapy in the treatment of diarrhea and other diseases [55]. Another paper reviews the current state of knowledge concerning zinc fortification [56], and three separate papers describe the information available on dietary diversification and modification strategies. One of these latter papers focuses on general principles and approaches to dietary diversification and modification [57], another describes the specific contribution of breastfeeding to maintaining adequate zinc intakes among infants and young children [58], and the third covers the potential of recently developed biofortification approaches to improve zinc status [59]. The general conclusions of these reviews, their related programmatic implications, and the most critical remaining research needs are summarized in the last paper [60].

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