

Zinc and Health: Current Status and Future Directions

Human Zinc Deficiency¹

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ABSTRACT The objective of this paper is to provide a current overview of the significance of zinc in human nutrition. To achieve this, the following issues are addressed: (1) the biochemistry and biology of zinc in the context of their relevance to zinc in human nutrition and to our understanding of the complexity and practical importance of human zinc deficiency; (2) the history of our understanding of human zinc deficiency with an emphasis both on its brevity and on notable recent progress; (3) the clinical spectrum of severe zinc deficiency; (4) the lack of ideal biomarkers for milder zinc deficiency states, with the consequent dependence on randomized, placebo-controlled intervention studies to ascertain their prevalence and clinical consequences, including growth delay, diarrhea, pneumonia, other infections, disturbed neuropsychological performance and abnormalities of fetal development; (5) the public health significance of human zinc deficiency in the developing world; (6) reasons for concern and unanswered questions about zinc nutrition in the United States; (7) the need for better understanding of human zinc metabolism and homeostasis (including its limitations) at a molecular, cellular, organ-system and whole body level and of factors that affect zinc bioavailability; and (8) potential strategies for the prevention and management of human zinc deficiency. This review concludes with an emphasis on the immediate need for expanded research in directions that have become increasingly well demarcated and impelling as a result of recent progress, which is summarized in this overview. *J. Nutr.* 130: 1344S–1349S, 2000.

KEY WORDS: • *humans* • *zinc deficiency* • *zinc bioavailability* • *zinc biomarkers*

Zinc is one of the essential trace elements and, as such, a member of one of the major subgroups of the micronutrients that have attained such prominence in human nutrition and health. The convening of the workshop “Zinc and Health: Current Status and Future Directions” in November 1998 by the National Institutes of Health, organized and principally sponsored by the Office of Dietary Supplements, attests to the recent rapid growth in respect for the importance of zinc in human health. In turn, this timely recognition, together with our expanded knowledge base, has enhanced our sensitivity to the many unanswered questions and to priority directions for research.

The biology of zinc

The exceptional ability of the zinc atom to participate in strong but readily exchangeable ligand binding, together with

the notable flexibility of this metal’s coordination geometry, has proved to be extraordinarily useful in biological systems (Williams 1989). In retrospect, this is anything but surprising, although it is only very recently that adequate scientific appreciation of the implications of these properties has emerged. The incorporation of this trace element into mammalian biological systems has been further facilitated by the lack of redox properties of the zinc atom, which, in contrast to iron and copper, allows its utilization without the risk of oxidant damage.

Zinc is ubiquitous in subcellular metabolism. It is, for example, an essential component of the catalytic site or sites of at least one enzyme in every enzyme classification (Fierke 2000). Altogether, several hundred zinc metalloenzymes have been identified in the plant and animal kingdoms. A combination of chemical properties accounts for its use in this biological role. In addition to those highlighted earlier, the activity of the catalytic site is, in some zinc metalloenzymes, enhanced by the “entatic” (strained) condition of the metal geometry imposed by close proximity of the zinc atom to the extensive protein β -sheets adjacent to the catalytic sites.

Other zinc atoms have specific structural roles in enzyme molecules as well as in many other proteins and in biomembranes. These structural roles of zinc are, again, ubiquitous and of outstanding importance in cellular and subcellular metabolism. One outstanding example that has generated a great deal of recent interest is the zinc finger motif (Berg and Shi 1996, Rhodes and Klug 1993), the most common recurring motif in transcription proteins. The configuration of these “fingers,” which determines their binding to DNA, is determined by the single zinc atom at their base. The linking of

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these zinc fingers to corresponding sites on DNA initiates the transcription process and gene expression. Similar motifs have been identified in nuclear hormonal receptors, including those for estrogen, testosterone and vitamin D.

Although much remains to be learned about the extent of the role of zinc as an intracellular regulatory ion, the potential importance of zinc in this role is attracting increasing attention (Cousins 1998). The readily reversible capacity of zinc for cross-linking facilitates these regulatory roles. Notable examples that have been suggested but that require further research include involvement in the regulation of cellular growth and differentiation, including gene expression, and in the regulation of apoptosis (Zalewski et al. 1994).

This brief incursion into the biology of zinc is necessary if we are to fully appreciate the significance of zinc in human nutrition. Two aspects of this complex biology stand out. One is the ubiquity and versatility of this metal. The other is the central but still incompletely understood role, or complex combination of roles, that zinc has in gene expression and in cellular growth and differentiation. Some knowledge of these ramifications of the biology of zinc is important to any understanding and discussion of human zinc nutrition and deficiency. The ubiquity and versatility of zinc in subcellular metabolism suggest that zinc deficiency may well result in a generalized impairment of many metabolic functions (Williams 1989).

Even a partial understanding of the fundamental importance of zinc in cellular growth and differentiation alerts us to the special vulnerability to an inadequate supply of zinc of the rapidly growing embryo, fetus, infant and young child or of the patient mounting an immune response or requiring tissue repair. An appreciation of the extraordinary rapidity with which the effects of dietary zinc restriction of growth and differentiation are manifest in the animal (mammalian) model (Chesters 1982) correctly alerts us to the special vulnerability to zinc deficiency of cells that are rapidly turning over, notably those of the immune system. However, other organs and systems that are not noted for rapid cell turnover, e.g., the central nervous system (Frederickson 2000), are also vulnerable to zinc restriction.

The pattern of disturbance of zinc-dependent metabolism may well depend on a variety of host and environmental (including other dietary) factors as well as on the severity and acuteness of the zinc deficiency. Hence the human nutrition scientist and clinician are faced with a potentially bewildering range of manifestations of zinc deficiency that are typically difficult to detect and confirm.

The history of our understanding of human zinc deficiency

The history of our recognition of the significance of zinc in nutrition and, even more so, in clinical medicine and public health is remarkably brief (Hambidge et al. 1986), especially given the pervasiveness of this mineral in biology. Centuries after the recognition of the biological role of iron and of its importance to human health, the first role for zinc in biology, specifically in a microorganism, was not reported until late in the nineteenth century. Another half century passed before zinc deficiency was described in mammals, but this was followed quickly by recognition of the practical importance of zinc deficiency in animal husbandry, especially as the cause of parakeratosis in pigs. Although by the late 1950s it was well accepted that zinc was a necessary micronutrient for humans and abnormalities of human zinc metabolism had been observed, nutrition scientific opinion at that time tended to

dismiss the likelihood of human zinc deficiency, especially of nutritional environmental origin.

The first major conceptual breakthrough came in 1961 (Prasad et al. 1961) with the hypothesis that zinc deficiency was a major etiological factor in the syndrome of "adolescent nutritional dwarfism" that had been identified principally and extensively in mid-Eastern countries. The impact of this hypothesis and the results of subsequent research to test it were diminished by several factors, including the complexities of the multiple nutrient deficiencies that contributed to this syndrome and the paucity of data derived from randomized controlled intervention studies. The latter, as are discussed further, are of special importance in the identification of human zinc deficiency. Moreover, the practical relevance of these findings, which were associated with a number of possible special environmental/nutritional etiological factors, to nutrition in North America was not readily apparent at that time. Nevertheless, this work made an outstanding contribution to the history of our recognition of zinc as a micronutrient of practical importance in human nutrition.

Approximately one decade later, severe zinc deficiency had been identified in industrialized countries, notably with the recognition that the phenotypic expression of the rare autosomal recessively inherited disorder acrodermatitis enteropathica was attributable to a defect in zinc metabolism (Moynahan 1974). Numerically more important at that time, and persisting through the 1970s and even beyond, was iatrogenic severe zinc deficiency, which was attributable to the failure to add zinc to intravenous infusates for patients who were totally dependent on intravenous feeding. Our understanding of the clinical sequelae of zinc deficiency still owes a great deal to descriptions of the presentation of patients with inherited and acquired severe zinc deficiency states. These are considered further in a subsequent section.

Since the early 1960s there has been recurring interest in the possible occurrence of zinc deficiency, or disturbed zinc metabolism, as a factor in a wide range of disease states, from the common cold to wound healing in surgical patients. There have also been numerous individual case reports of secondary zinc deficiency. In general, however, these studies were too limited in design or number to allow any definitive conclusions to be made about the prevalence and role of zinc deficiency in disease states in the United States.

Nutritional zinc deficiency, on the other hand, has been more thoroughly documented, including the results of a series of randomized controlled studies of dietary zinc supplementation in young children in Denver during the 1970s and 1980s. These indicated the occurrence of growth-limiting zinc deficiency in otherwise apparently normal infants and young children (Hambidge et al. 1985, Walravens et al. 1983, 1989, Walravens and Hambidge 1976).

These studies have provided one cornerstone for the large number of randomized, double-blinded controlled studies of dietary zinc supplementation that were conducted, primarily in developing countries, in the 1990s (Bhutta et al. 1999, Brown et al. 1998). The cumulative results of these studies have had a very positive impact in the advancement of our appreciation of the public health importance of human zinc deficiency on a global basis (Black 1998). This work provided clear documentation of the etiological role of zinc in several diseases and clinical circumstances and in disturbances of normal physiology, growth and development (see later).

The history of our understanding of the role of zinc in human nutrition and disease provides an excellent example of the mutual benefits of closely linking nutrition research in industrialized nations with that in the developing world.

The clinical spectrum and public health significance of human zinc deficiency

Severe zinc deficiency. Organ systems known to be affected clinically by severe zinc deficiency states include the epidermal, gastrointestinal, central nervous, immune, skeletal and reproductive systems (Hambidge and Walravens 1982). In view of what is now known about the biology of zinc, it is likely that zinc-dependent metabolic functions are impaired in all tissues. As a sobering reminder of our reliance on zinc not only for optimal health but also for life itself, patients with classic acrodermatitis enteropathica typically died in later infancy before the therapeutic benefits of oral zinc supplementation were recognized and routinely applied.

The specific biochemical correlates underlying the clinical features have not been easy to identify. This applies, for example, to the epidermal lesions, of which the prominent skin lesions, with their characteristic distribution primarily around the body orifices and at the extremities (acral), are the most apparent. A better understanding of the disturbed biology underlying each of the clinical features of acrodermatitis enteropathica is, first and foremost, of importance for the optimal medical management of patients with this autosomal recessively inherited disease and other severe zinc deficiency disorders. The identification of humans with a phenotypic presentation very reminiscent of the lethal milk mutation in mice alerts us to the likelihood that other inherited defects in zinc transport may occur in additional organs (Atkinson et al. 1989, Piletz and Ganschow, 1978, Zimmerman et al. 1982). Beyond the value to the individuals affected with this inborn error or errors, elucidation of the clinical features of severe zinc deficiency states and their biochemical correlates is of value in advancing our understanding of milder zinc deficiency states. Although less impressive in their clinical presentation, the latter are of numerically much greater importance. Moreover, most of the clinical features of acrodermatitis enteropathica were documented in milder zinc deficiency states.

Three examples of how clinical and laboratory observations in acrodermatitis enteropathica have assisted in the identification of parallel consequences of milder acquired zinc deficiency syndromes are as follows: (1) Diarrhea is prominent as a clinical feature of most cases of acrodermatitis enteropathica (Hambidge 1992). (2) A wide variety and severity of immune defects (especially compromised T-cell function) have long been recognized in acrodermatitis enteropathica, with corresponding vulnerability to a wide range of viral, bacterial and fungal infections. Although in advanced cases it is difficult to separate the effects of zinc deficiency from those of secondary protein energy malnutrition, the rapidity of immune function improvement with the initiation of zinc therapy speaks to a specific and direct role for zinc deficiency. (3) Similar considerations apply to central nervous system function. The initiation of zinc therapy in acrodermatitis enteropathica is followed with remarkable rapidity by an increase in hedonic tone, motivation, alertness and responsivity (Walravens et al. 1978). There is a correspondingly rapid decrease in irritability, nervousness and restlessness.

Milder zinc deficiency states

Recent rapid progress in documentation of the public health significance of milder, but clinically important, zinc deficiency states, especially in the developing world, coupled with exciting progress in our understanding of the biology of zinc, has propelled zinc into the limelight as a micronutrient of special importance in human nutrition. This section provides

a brief overview of the challenges of detecting and determining the prevalence of milder zinc deficiency states and of their clinical effects and public health relevance. These issues will be addressed more extensively in subsequent papers in this supplement.

Detection. Once alerted to the reality of human zinc deficiency and its consequences, the most obvious factors that have hampered progress in our understanding of the prevalence of this micronutrient deficiency have been, and continue to be, the lack of adequate laboratory biomarkers (Hambidge and Krebs 1995, Wood 1999) and the lack of pathognomonic clinical features of zinc deficiency states.

Measurements of zinc concentrations in plasma have been shown to be useful in identifying children who are more likely to have a growth response to zinc supplements (Brown 1999) or diarrhea (Bahl et al. 1998). The potentially confounding factor of hypozincemia as part of the acute phase response to infection may not be a major detriment (Brown 1998). Unfortunately, however, this assay lacks the sensitivity necessary to give it a strong endorsement as a biomarker of zinc status. The application of other indices, e.g., hair zinc concentrations, although capable of yielding interesting and useful data (Ferguson et al. 1993, Hambidge et al. 1972), has been even less well defined. This also applies to what theoretically may be even more appealing putative biomarkers, notably indices related to a zinc-dependent function, e.g., the activity of a zinc-dependent enzyme. In general, initial enthusiasm has not been followed by convincing application, and typically there has been a lack of independent confirmation of the usefulness of these proposed indices.

Consequently, elucidation of the prevalence and the clinical effects of milder zinc deficiency states has depended to a very large extent on the results of well-designed and executed, controlled, randomized intervention studies with dietary zinc supplements. Such studies have made a vital contribution to recent progress. Most notably they have confirmed the contribution of zinc deficiency to impaired physical and neuropsychological development and to the prevalence of gastrointestinal and respiratory infections in multiple communities.

These well-documented sequelae of zinc deficiency are summarized briefly in this section and considered in more detail elsewhere in this supplement. They have also been the focus of recent extensive review elsewhere (Zinc for Child Health, 1997).

Growth. The one clinical feature that is most studied is the impairment of physical growth. As with other features of zinc deficiency, the most definitive investigations have been those based on randomized, controlled studies of dietary zinc supplementation. In the Colorado studies in the 1970s and 1980s, the principal focus was on physical growth. The principal reason for this focus was the earlier clear demonstration in animal models that zinc had no pharmacological effect on growth (Williams and Mills 1970). Hence, the demonstration of an increase in growth velocity associated with modest dietary zinc supplements under double-blind, controlled, randomized study conditions provided convincing evidence for a preexisting growth-limiting zinc deficiency state. In all, four such studies were undertaken in Colorado. Subjects ranged from healthy cow's milk formula-fed infants (Walravens and Hambidge 1976), at a time before zinc fortification of cow's milk formulas became the norm, to older infants, toddlers or young children with nonorganic failure to thrive. Subsequently, many other studies of zinc supplementation have included growth measurements. These results have been subjected to rigorous and repeated meta-analysis with confirmation of the effect of zinc supplements in increasing height and

weight velocity when administered to children in many countries (Brown et al. 1998).

In some instances, effects have been observed on body composition rather than on weight or on linear growth velocity (Bates et al. 1993, Cavan et al. 1993, Kikafunda et al. 1998). These different responses serve as a reminder of how much there remains to be learned about variations in the presentation of zinc deficiency and the factors responsible. They also are a reminder that the biochemical and hormonal factors underlying these effects on growth remain unclear. It is possible that the relative magnitude of the contributions of different factors can vary under different environmental and host circumstances. One of the environmental issues of note is the total diet, including concurrent deficiencies or imbalances of other micronutrients (Solomons et al. 1999).

Diarrhea. That zinc added to conventional therapy is effective in reducing the duration of acute and persistent diarrhea has been confirmed through pooled analysis of data derived from multiple studies (Bhutta et al. 1999). The severity of the illness may also be reduced. Pooled analyses have also confirmed that zinc supplementation of children at a community level in the developing world results in significant reductions in the incidence and prevalence of diarrhea. Losses of zinc via the intestine are likely to be increased in diarrheal states and may contribute to zinc deficiency and to a vicious cycle. Supplementation studies have not always included rigorous or perhaps any data on habitual diet, although it appears very likely that dietary intake of bioavailable zinc is typically low in the populations studied. More attention to these factors in future studies will be helpful in determining etiology as well as optimal prevention strategies.

The long-term recognition that diarrhea is characteristically, although not inevitably, a prominent feature of acrodermatitis enteropathica; the plausible mechanistic explanations for the links between zinc deficiency and diarrhea, e.g., functional impairment of the immune system and of intestinal mucosal cell transport mechanisms (Ghishan 1984); the modest supplements required to achieve a beneficial effect; and, perhaps above all, the concurrent increase in growth velocity are all compatible with the conclusion that the favorable effects on diarrhea are attributable to correction of a zinc deficiency state that is the cause of, or contributing to, the diarrhea.

Pneumonia. Pooled analyses of the results of community zinc supplementation studies in children in developing countries have demonstrated a very substantial and statistically significant reduction in the prevalence of pneumonia (Bhutta et al. 1999).

Other infections. Malaria is among other infections that appear to be reduced by zinc supplementation (Bates et al. 1993, Black 1998) and that must be considered as a priority for further research.

Neuropsychological performance. Evidence of improved brain development attributable to improved zinc status has been derived from studies of activity levels in young children in India (Sazawal et al. 1996) and Guatemala (Bentley et al. 1997). Neuropsychological performance has been reported to improve with zinc supplementation in young Chinese children (Penland et al. 1998, Sandstead et al. 1998) but only when other micronutrient nutrition is adequate.

Relevance to childhood morbidity and mortality rates. Probably for reasons discussed in the section on the biology of zinc, the effects of zinc deficiency are remarkably diverse and notable for being nonspecific. The latter does not detract from their importance. It has been estimated (Zinc for Child Health, 1997) that the beneficial effects of zinc supplements

for diarrhea prevention are of the same magnitude as those achieved by cleaning the water supply and providing quality sanitation. In the case of children under 5 y, the public health benefits of zinc supplementation in the prevention of acute lower respiratory disease and malaria have also been calculated to be superior to any other preventive modalities (R. Black, personal communication, 1998). These infectious/nutritional diseases are the principal causes of childhood morbidity and mortality globally. The impairment of physical growth and the impairment of neuropsychological development are well-recognized associated features. The sum of recent evidence indicates that the maintenance of optimal zinc nutrition is perhaps the most effective, even if only partial, preventive measure that can be undertaken to decrease morbidity rates in young children in the developing world.

Pregnancy and prenatal development. Studies in the developing world are just starting to give much needed attention to pregnancy and the effects of maternal zinc status on both prenatal and postnatal development (Caulfield 1999a). Early results of these endeavors indicate that poor maternal zinc status in pregnancy can have adverse effects on fetal brain function (Meriardi et al. 1998). In contrast to recent observations in the United States (Goldenberg et al. 1995), the lack of effect of maternal supplementation on fetal growth has been unexplained (Caulfield et al. 1999b).

Zinc deficiency in North America. The results of the Colorado supplementation studies in the 1970s and 1980s indicated that growth-limiting nutritional zinc deficiency existed in otherwise healthy infants, toddlers and preschool children even after the routine fortification of infant formulas with zinc in the 1970s. This is not to imply that the already generous quantities of zinc in these formulas should be increased further but rather that there are other etiological factors—some partially understood, others still unidentified—that require rigorous research. That this remains so today is suggested by preliminary reports of the results of a large recent zinc supplementation study of preadolescent school children in Texas (Sandstead, personal communication, 1998). In addition to differences in weight gain (Eggar et al. 1999), significant effects were observed for immunity, cognition and psychoeducational performance (Penland et al. 1999). The growth data for this age group are reminiscent of slightly earlier studies in Ontario, Canada (Gibson et al. 1989).

Notable among recent reports of favorable responses to zinc supplementation in other age groups, which are indicative of zinc deficiency in the populations studied, has been that of Goldenberg et al. (1995), who reported a significantly and substantially greater birth weight in infants whose mothers had received a zinc supplement during pregnancy. Length and head circumference were also greater. Elderly persons, another nutritionally vulnerable group of our population, have received relatively limited attention with respect to zinc nutrition. In such a heterogeneous population, it is not surprising that study results have been mixed. The inclusion of zinc in a major micronutrient intervention study for macular degeneration is an excellent example of the research needed at this time. Psychoneurological status, decline in immune status, and decline in lean body mass all merit consideration with respect to zinc status.

The enhanced or potentially enhanced risk of zinc deficiency in relation to a wide range of disease states is discussed elsewhere in this supplement. Of growing interest, in large part the result of advances in our understanding and appreciation of the role of zinc in neurophysiology, is the role of zinc deficiency in selected neuropsychiatric diseases. One important reminder provided by non-U.S. recent studies is that our

study designs demand excellence and that multiple independent as well as multicenter studies are essential if the putative role of zinc deficiency in a wide range of clinical conditions is to be confirmed or refuted.

Zinc homeostasis

There is, at least superficially, a puzzling dichotomy between the evidence for effective homeostatic mechanisms that allow the human to adapt to low zinc intake (King 1986, Lei et al. 1996) and the growing evidence that zinc deficiency occurs even in circumstances where, at least superficially, intake of this micronutrient appears to be adequate. This dichotomy may be explained by two factors. One is variation in the bioavailability of dietary zinc. This will require more long-term studies that include measurements of intestinal conservation of endogenous zinc as well as of absorption of this metal under a wide range of different dietary and host circumstances. The second is that "adaptation" may occur only after a subtle but physiologically potentially important diminution in one or more metabolically important body pools of this micronutrient. Compatible with this possibility are the observed correlations between estimates of the quantity of zinc that exchanges with zinc in plasma within 2 days and both the dietary zinc intake and the quantity of zinc absorbed (Lei et al. 1996).

Recent progress in our knowledge of the molecular biology of zinc, especially the identification of several zinc transporters, provides cause for optimism that high quality focused research in the immediate future will lead to a relatively clear understanding of the regulation of zinc metabolism and the maintenance of zinc homeostasis at a molecular level. It is also reasonable to assume that parallel progress can be achieved at a whole body level, leading to a clearer and quantitative understanding of zinc homeostasis and metabolism at a whole body level. Of note is the progress that is beginning to be achieved with the application of zinc stable isotope techniques (Hambidge et al. 1998) supported in more complex studies by progressively more sophisticated and reliable techniques for model-based compartmental analysis (Miller et al. 1998, Wastney et al. 1986).

Prevention and management of zinc deficiency

As is the case for all nutrients, the challenge is to achieve intakes of bioavailable zinc and tissue levels within a physiological range. It has become progressively more apparent that there is a cost to pay for intakes and levels above this range. Currently this is commonly considered to be a total of 50 mg elemental zinc per day for adults, with levels of intake for children that are less clear. It is important to be appropriately sensitive to this upper limit, even if a decision is made to temporarily exceed this for anticipated (but often uncertain) pharmacological benefits. It is even more important to be aware that these upper limits are for total daily intake, which may be higher than anticipated due to the increasing trend to fortify foods with zinc. The use of zinc, as a single micronutrient supplement, for research purposes has proved invaluable, and such studies will continue to have an important role in advancing our understanding of the prevalence and effects of human zinc deficiency. There is already, however, also an important role for studies that include arms for multinutrient supplements and, even more important, for studies of dietary modifications that affect mineral bioavailability, whether these are at a local community level or involve more global strategies. Meanwhile, widespread zinc supplementation either

as a single micronutrient or as a component of a multimicronutrient mix is, at best, a stop-gap measure. There is a wide gulf between successful zinc intervention projects for research purposes and the long-term use of such supplements to prevent zinc deficiency. Practical issues that must be addressed include those of long-term acceptability, compliance and safety, as well as the more provocative but real issue of whether supplements are the best choice. Dietary zinc intake in the United States and elsewhere is seldom less than World Health Organization calculations for basal requirements. Although major issues of bioavailability are generally accepted in many developing countries (Gibson, 1994), the possible reasons for indifferent bioavailability of dietary zinc in the United States is much less clear. With well-designed studies, we can now address these issues quantitatively.

Enough is now known about the clinical and public health importance of zinc deficiency to establish beyond doubt the outstanding practical relevance of this trace element in human nutrition. Recent parallel progress with basic research has served to emphasize the ubiquity of zinc in biology and the dependence of a wide range of vital metabolic processes on an adequate supply of this metal. This progress should serve as a stimulus and cornerstone for expanded research to (1) accelerate elucidation of the biology of zinc; (2) achieve better understanding of the pathophysiology and clinical significance of zinc deficiency; (3) unravel the complexities of zinc metabolism; (4) clarify the subtleties of zinc homeostasis and nutritional requirements, including the impact of dietary and host factors that affect bioavailability; (5) identify adequate biomarkers of zinc status to assist in identifying populations and individuals at special risk and in determining the incidence and prevalence of zinc deficiency; and (6), finally, to develop optimal strategies for the management and prevention of zinc deficiency.

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