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ROLE OF ZINC IN BIOLOGICAL SYSTEM

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ABSTRACT

Zinc is a common element in human and natural environments and plays an important part in many biological processes. Zinc, which is defined as an essential trace element, or a micronutrient, is essential for the normal growth and the reproduction of all higher plants and animals and of humans. In addition, it plays a key role during physiological growth and fulfills an immune function. It is vital for the functionality of more than 300 enzymes, for the stabilization of DNA, and for gene expression. This review summarizes the role and manifestations of zinc in the environment and its importance for human health and metabolism, as well as its physiological role. Toxicity, teratogenicity, carcinogenicity and immunological functions of zinc are outlined with particular reference to the properties of zinc as an antioxidant, and its role in cancer prevention. Compared to adults, infants, children, adolescents, pregnant, and lactating women have increased requirements for zinc and thus, are at increased risk of zinc depletion. Zinc deficiency during growth periods results in growth failure. Epidermal, gastrointestinal, central nervous, immune, skeletal, and reproductive systems are the organs most affected clinically by zinc deficiency. Review on zinc biochemical and physiological functions, metabolism including, absorption, excretion, and homeostasis, zinc bio-availability (inhibitors and enhancers), human requirement, groups at high-risk, consequences and causes of zinc deficiency, evaluation of zinc status, and prevention strategies of zinc deficiency.

KEYWORDS: Zinc absorption, zinc bio-availability, zinc deficiency, zinc intervention, zinc nutrition, zinc requirement.

INTRODUCTION

A syndrome of anemia, hypogonadism and dwarfism was reported in a 21-year-old Iranian farmer in 1961 who was subsisting on a diet of unrefined flat bread, potatoes, and milk[2] Shortly after, a similar syndrome was observed in Egyptian adolescents who had similar dietary history to that of the Iranians, mainly subsisting on bread and beans.[3] Administration of supplemental zinc or diets containing adequate animal-protein foods improved growth and corrected the hypogonadism, while anemia responded to oral iron treatment. Subsequent studies showed that the syndrome was primarily the result of low dietary zinc intake in the diet. Since the discovery of zinc deficiency as a human health problem in 1961,[1] interest in the biochemical and clinical aspects of zinc nutrition has increased markedly. In this paper, we review zinc biochemical and physiological functions, metabolism including, absorption, excretion and homeostasis, zinc bioavailability (inhibitors and enhancers), human requirement, groups at high-risk, consequences and causes of zinc deficiency, evaluation of zinc status and prevention strategies of zinc deficiency. Administration of supplemental zinc or diets containing adequate animal-protein foods improved growth and corrected the hypogonadism, while anemia responded to oral iron treatment. Subsequent studies showed that the syndrome was primarily the result of low dietary zinc intake in the diet. Zinc is absorbed in the small intestine by a carrier-mediated mechanism.[5] Under normal physiologic conditions, transport processes of uptake are not saturated. The fraction of zinc absorbed is difficult to determine because zinc is also secreted into the gut. More recent studies have suggested different absorption rates for different population groups based on their type of diet and phytate: Zinc-deprived humans absorb this element with increased efficiency, whereas humans on a high-zinc diet show a reduced efficiency of absorption. Zinc is released from food as free ions during digestion. These liberated ions may then bind to endogenously secreted ligands before their transport into the enterocytes in the duodenum and jejunum. The portal system carries absorbed zinc directly to the liver, and then released into systemic circulation for delivery to other tissues. About 70% of the zinc in circulation is bound to albumin and any condition that alters serum albumin concentration can have a secondary effect on serum zinc levels. There are at least 10 ZnTs and 15 zip transporters in human cells.[12] They appear to have opposite roles in cellular zinc homeostasis. The recently characterized ZnTs have significantly increased understanding of the interrelationships of cellular zinc uptake and efflux but do not yet account for observations

at the whole body level. ZnTs-1 is a ubiquitously expressed protein that has been found to be present in the villi of the proximal small bowel. The role of metallothionein (MT), an intracellular metal binding protein, in the regulation of zinc absorption, particularly in conjunction with the ZnTs, also remains unclear. Hepatic and intestinal MT synthesis is stimulated by dietary zinc supplementation, by intraperitoneal zinc injection and by inflammation and the acute phase response. Dietary restriction also results in diminished MT synthesis. Recently, an ATPase, which transports Zn^{2+} and Cd^{2+} and to a lesser extent other heavy metals, has been discovered in Arabidopsis.[20] Surprisingly, there is still no evidence for a Zn^{2+} pump in either yeast or mammalian cells, though a Cu pump has been identified that is linked to heavy metal ion transport.[2] A Na^{+}-dependent secondary active mechanism has, however, been suggested to facilitate formation of the transmembrane Zn^{2+} gradient in neurons. Shifts in the endogenous excretion appear to occur quickly with changes in intake just above or below optimal intake while the absorption of zinc responds more slowly, but it has the capacity to cope with large fluctuations in intake.[5] With extremely low zinc intakes or with prolonged marginal intakes, secondary homeostatic adjustments may augment the gastrointestinal changes.

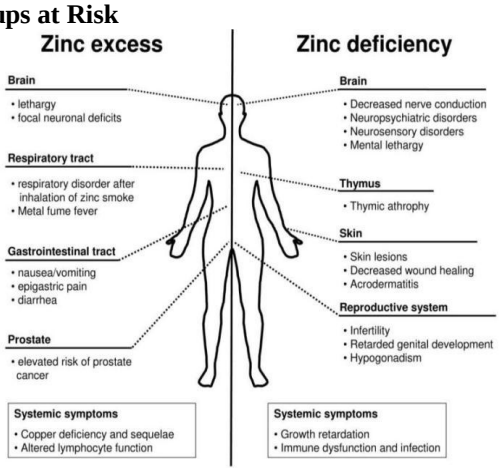
Excretion

Loss of zinc through gastrointestinal tract accounts for approximately half of all zinc eliminated from the body. Considerable amount of zinc is secreted through the biliary and intestinal secretions, but most of it is reabsorbed. This is an important process in the regulation of zinc balance. Other routes of zinc excretion include urine and surface losses (desquamated skin, hair, sweat). Measurements in humans of endogenous intestinal zinc have primarily been made as fecal excretion; these indicate that amounts excreted are responsive to zinc intake, absorbed zinc and physiologic need. The extreme reductions or increases in zinc intake, zinc losses either fell or increased during the first 6-12 d after the dietary change so that balance was achieved.[6] Thus, humans appear to have the capacity to regulate whole body zinc content over a 10-fold change in intake, as has been observed in experimental animals.

Inhibitors and enhancers

Various dietary factors can influence zinc absorption. Phytic acid (inositol hexa- and penta-phosphate) is the principal dietary factor known to limit zinc bio-availability by strongly binding zinc in the gastrointestinal tract.[3] It is the major phosphorus (P) storage compound in plant seeds, especially, cereals and legumes, and can account for up to 80% of seed total P.[1] Because of its high-density of negatively charged phosphate groups, phytate forms mixed salts with mineral cations, which are assumed to play an important role in mineral storage.[6,10,11] The inhibitory effects of Phytic acid (PA) on zinc can be predicted by the molar ratios of phytate: Zinc in the diet. Molar ratios in excess of 15: 1 according to World Health Organization. As calcium has the propensity to form complexes with Phytic acid and zinc that are insoluble, it has been proposed that the phytate: Zinc molar ratio should be multiplied by the dietary calcium concentration to improve the prediction of zinc bio-availability.,[3,5] However, the interactions between zinc and calcium are complex and not all studies have shown that calcium further increases the impact of Phytic acid on zinc absorption.[10] The potential interaction between iron and zinc has been a cause of concern. Solomons and Jacob[4] found that high doses of inorganic iron decreased zinc uptake as measured by changes in plasma zinc over the next 4 h after an oral dose. Human adults were administered 25 mg of zinc (as Zinc sulfate [ZnSO4]) in water solution, and iron was added at 25, 50 or 75 mg.[12] Plasma zinc was reduced significantly with increasing dose of iron. This suggests that iron fortification will not affect zinc absorption.[4] Some inhibitory effects would be seen only if very high iron to zinc ratio is administered apart from a meal. Proteins generally have positive influence on zinc absorption, because zinc absorption tends to increase with protein intake.[9,4,14] Consumption of animal proteins (e.g., beef, eggs and cheese) improve the bioavailability of zinc from plant food sources possibly because amino acids released from the animal protein keep zinc in solution[2,9] or the protein binds the phytate. Generally, binding of zinc to soluble ligands or chelators has a positive effect on zinc absorption as they increase the zinc solubility.[13]

Groups at Risk



Infants and children

Young children are at greater risk of zinc deficiency because of increased zinc requirements during growth. Exclusively breast-fed infants of mothers with adequate zinc nutriture obtain sufficient zinc for the 1st 5-6 months of their life.[11] After this age, complementary foods containing absorbable zinc are required to satisfy their requirements. In many low-income countries, complementary feeding is delayed and cereal foods are then used for feeding. These foods have low content of total and absorbable zinc and thus, fail to meet the needs for zinc. Conversely, early introduction of such foods

may interfere with the absorption of zinc from breast milk due to their high phytate content.[4,7]

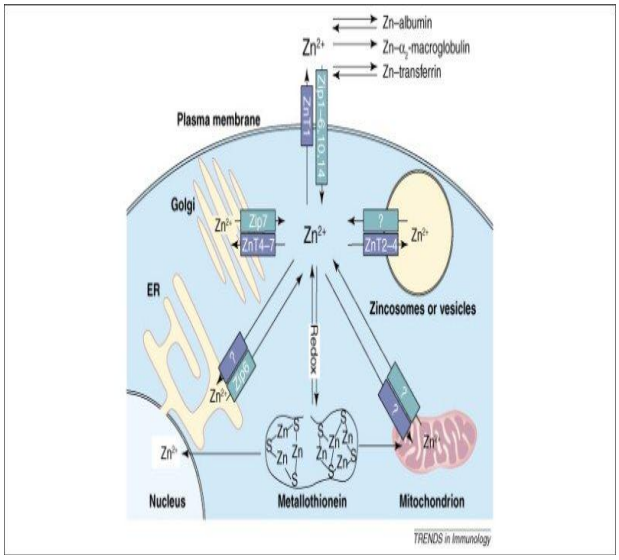
Zinc requirements of malnourished children are estimated to be between 2 mg/kg and 4 mg/kg body weight.[4,8] These requirements are much higher than those for healthy children (0.17 mg/kg at 1-3 years), presumably because of prior zinc depletion and reduced zinc absorption due to changes in the intestinal tract.[14]

Adolescents

The physiological requirements for zinc peak during adolescence at the time of the pubertal growth spurt, which generally occurs in girls between 10 years and 15 years and in boys between 12 years and 15 years. Even after the growth spurt has ceased, adolescents may require additional zinc to replenish depleted tissue zinc pools.[4,9]

Pregnant and lactating women

Increased nutritional demands during pregnancy and lactation predispose women to zinc deficiency.[2,6] These demands are greater during lactation, although, physiological adjustments in zinc absorption help to meet the needs for lactation. A number of studies have demonstrated a negative impact of therapeutic supplemental iron on zinc absorption during pregnancy[5] and lactation.[5,1] In pregnant women where dietary intakes of zinc were low, supplemental iron, in dosages as low as 60 mg/day prevented them from meeting their needs for zinc.[5] Situations that seem most likely to encounter problematic interactions are those in which the iron is administered in solute on or as a separate supplement rather than incorporated into a meal.[5,2]

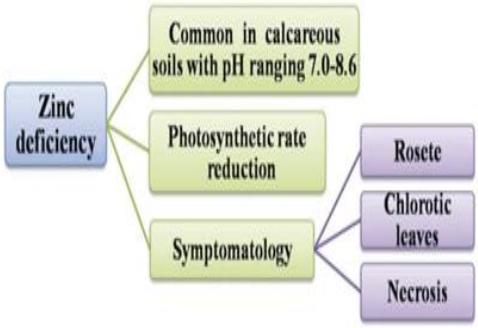


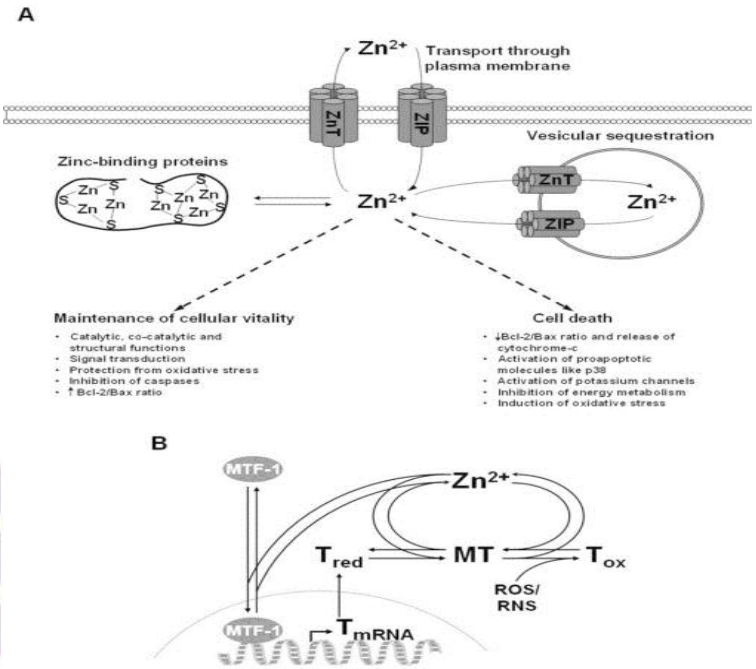
Elderly

Diet surveys indicate that zinc intakes by elderly persons are often inadequate, even in rich countries.[3] Several factors may contribute to poor zinc nutrition among the elderly, in particular, reduced consumption of zinc-rich foods such as red meat. In addition, there is some evidence that the efficiency of zinc absorption may decrease with age.[3]

Deficiency of Zinc

Organ systems known to be affected clinically by zinc deficiency states include the epidermal, gastrointestinal, central nervous, immune, skeletal and reproductive systems. Clinical signs of severe zinc deficiency were identified in industrialized countries notably in persons suffering from acrodermatitis enteropathica, a rare genetic disorder that specifically affects zinc absorption.[11]





Growth and development

This effect is of most significance during the periods of rapid growth such as pregnancy, infancy and puberty during which zinc requirements are highest.[1] The mechanisms involved, however, are not well understood.

Risk of infections

Plausible explanations for a link between zinc deficiency and diarrhea include impairment of the immune system and of intestinal mucosal cell transport.[3] A causal relationship between zinc deficiency and diarrhea is indicated by the beneficial effects of zinc supplements and concurrent increase in growth velocity. It is uncertain to what extent oral supplementation with zinc can reduce episodes of malaria in endemic areas. According to some studies, malaria also appears to be reduced by zinc supplementation.[6,3] However, there are studies showing no effect of zinc supplementation against malaria.[4] Further studies are required to establish this effect.

Relationship between zinc deficiency and age

Decline in immunocompetence, delayed wound healing and certain neurological and psychological changes. In general, clinical manifestations of zinc deficiency vary with age. In early infancy, diarrhea is a prominent symptom. Zinc deficiency also leads to impaired cognitive function, behavioral problems, impaired memory, learning disability and neuronal atrophy.[10] Skin problems become more frequent as the child grows older. Alopecia, growth retardation and recurrent infections are common in school-age children. Chronic non-healing skin ulcers and also recurrent infections are common among the elderly. These effects have been observed in controlled clinical trials showing positive response to supplemental zinc.[11] Infectious diseases and malnutrition are the principal causes of childhood morbidity and mortality globally. Providing adequate zinc nutriture is perhaps one of the effective preventive measures to decrease the rates of morbidity and mortality in children of the developing world when vitamin A or iron is not deficient.[8,5] Childhood obesity and its co-morbidities as insulin resistance and metabolic syndrome are becoming a major health problem. Zinc supplementation might be useful in controlling some of these metabolic aspects.[8] Moreover, serum zinc level is found to be lower in children of parents with premature atherosclerosis and this might be an evidence for the protective role of zinc in the process of inflammation and atherosclerosis.

Causes of zinc deficiency

The general causes of zinc deficiency include inadequate intake, increased requirements, malabsorption, increased losses and impaired utilization[1] Inadequate dietary intake of absorbable zinc is the primary cause of zinc deficiency in most situations.[7] Malabsorption of zinc may occur in a number of situations for example, acrodermatitis enteropathica.[5] Malabsorption syndromes and inflammatory diseases of the bowel, resulting in poor absorption and loss of zinc, may lead to secondary zinc deficiency particularly in the presence of marginal dietary intakes.[1] Conditions of impaired intestinal integrity not only reduce absorption, but also result in increased endogenous losses of zinc. Diarrheal diseases are common in many low-income countries. The fact that zinc deficiency increases the susceptibility to childhood diarrhea while increased losses of endogenous zinc associated with diarrhea further deplete body zinc, results in a vicious cycle that merits further study.[6,8]

Stunting prevalence

Height-for-age, a measure of nutritional stunting, is the best known and easiest to measure of the adverse outcomes associated with zinc deficiency in populations. Stunting prevalence is expressed as the percentage of children under 5 years of age with height-for-age below the expected range of a reference population (i.e., <2.0 standard deviations with respect to the reference median).[3,8,9] Growth stunting could be the consequence of deficiency of one or several nutrients.[11] In communities in which stunting is prevalent, it is highly likely that several nutrient deficiencies occur simultaneously in the stunted children.

MT

Growth stunting could be the consequence of deficiency of one or several nutrients. In communities in which stunting is prevalent, it is highly likely that several nutrient deficiencies occur simultaneously in the stunted children. However, similar to several of the enzymes and to serum zinc, MT may be affected by other factors, such as infection and stress, although this has not been confirmed by direct studies.

Exchangeable zinc pools (EZPS)

The zinc that is available for maintaining zinc-dependent functions is thought to be mobilized from small, rapidly exchanging zinc pools found primarily in the plasma and liver.[8,3] The size of this pool can be estimated from the tracer-trace disappearance curves using kinetic modeling software. When dietary zinc was reduced to a marginal level (4.6 mg/day) in a group of healthy men, EZP mass did not change.[8,6] Thus total EZP mass does not appear to be a good indicator of modest short-term changes in zinc intake. However, longer-term low intakes or acute zinc depletion causing a reduction in whole-body zinc content appears to cause a concomitant reduction in EZP.[12]

PREVENTION OF ZINC DEFICIENCY (INTERVENTION STRATEGIES)

Numerous zinc supplementation trials have shown that a wide range of health benefits can be realized by increasing the intake of zinc where diets are inadequate in this micronutrient.[4,9] The results of these trials strongly argue for the development of programs to improve zinc status in high-risk populations.

Dietary diversification/modification

Dietary diversification or modification is a sustainable long-term approach to improving the intake of several nutrients simultaneously.[12] Dietary diversification or modification strategies at the community or household level have the potential to increase the intake of bio-available zinc. Such strategies include (1) Agricultural interventions (2) Production and promotion of animal-source foods through animal husbandry or aquaculture (3) Processing strategies at the commercial or household level to enhance zinc absorption from plant-based diets.[8]

Supplementatione

Supplementation programs are useful for targeting vulnerable population subgroups, which are at a particular high-risk of micronutrient deficiencies. The easiest way to supplement zinc could be to include it in programs already delivering daily or weekly nutrient supplements for the prevention of iron deficiency anemia and other micronutrient deficiencies. The recommended zinc dosages are 5 mg/day for children.

Fortification

Food fortification is a more cost-effective and sustainable strategy to overcome micronutrient malnutrition than supplementation. Where micronutrient deficiency is widely distributed in a population and dietary modification or diversification is difficult to achieve, fortification of centrally processed foods is an appropriate alternative.[14]

CONCLUSIONS

Although only recently recognized, the importance of zinc as essential trace metal in the body and in particular as signaling molecule is substantiated greatly. Zinc is a trace element with various roles in physiological processes (Kaur et al., 2014).[13] It has been used as a drug in the prevention and treatment of some diseases and new strategies for more targeted delivery or modification of zinc signaling are promising future therapeutic approaches, especially in brain disorders (Ayton et al., 2015; Lee et al., 2015).[15] In addition, the present knowledge about zinc signaling in the various processes and involved pathways seems to be disconnected by specific types of zinc signal used, with different kinetics and sources of zinc. However, most likely, interplay between the different systems described above may exist by common underlying principles of zinc signaling. The high rate of the world's population that is at risk for inadequate zinc supply underlines the need for further research on zinc signaling and the need for public health programs to control zinc deficiency.

REFERENCES

1. King JC, Cousins RJ. Zinc. In: Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ, editors. Modern Nutrition in Health and Disease. 10th ed. Baltimore: Lippincott Williams and Wilkins, 2006; 271–85.
2. Prasad AS, Miale A, Jr, Farid Z, Sandstead HH, Schulert AR. Zinc metabolism in patients with the syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism and hypognadism. J Lab Clin Med., 1963; 61: 537–49.
3. Sandstead HH, Prasad AS, Schulert AR, Farid Z, Miale A, Jr, Bassilly S, et al. Human zinc deficiency, endocrine manifestations and response to treatment. Am J Clin Nutr., 1967; 20: 422–42.
4. Cousins RJ. Zinc. In: Filer LJ, Ziegler EE, editors. Present Knowledge in Nutrition. 7th ed. Washington DC: International Life Science Institute Nutrition Foundation, 1996; 293–306.
5. Cousins RJ. Absorption, transport and hepatic metabolism of copper and zinc: Special reference to metallothionein and ceruloplasmin. Physiol Rev., 1985; 65: 238–309.
6. 2nd ed. Bangkok, Thailand: 2004. FAO/WHO. Expert Consultation on Human Vitamin and Mineral Requirements, Vitamin and mineral requirements in human nutrition: Report of joint FAO/WHO expert consolation; p. 341.
7. Turnlund JR, King JC, Keyes WR, Gong B, Michel MC. A stable isotope study of zinc absorption in young men: Effects of phytate and alpha-cellulose. Am J Clin Nutr. 1984; 40: 1071–7.
8. Steel L, Cousins RJ. Kinetics of zinc absorption by luminally and vascularly perfused rat intestine. Am J Physiol., 1985; 248: G46–53.
9. Krebs NF. Overview of zinc absorption and excretion in the human gastrointestinal tract. J Nutr., 2000; 130: 1374S–7S.
10. Tubek S. Selected zinc metabolism parameters in premenopausal and postmenopausal women with moderate and severe primary arterial hypertension. Biol Trace Elem Res., 2007; 116: 249–56.
11. International Zinc Nutrition Consultative Group (IZiNCG) Brown KH, Rivera JA, Bhutta Z, Gibson RS, King JC, et al. International Zinc Nutrition Consultative Group (IZiNCG) technical document #1. Assessment of the risk of zinc deficiency in populations and options for its control. Food Nutr Bull., 2004; 25: S99–203.
12. Cousins RJ, Liuzzi JP, Lichten LA. Mammalian zinc transport, trafficking and signals. J Biol Chem., 2006; 281: 24085–9.
13. Devergnas S, Chimienti F, Naud N, Pennequin A, Coquerel Y, Chantegrel J, et al. Differential regulation of zinc efflux transporters ZnT-1, ZnT-5 and ZnT-7 gene expression by zinc levels: A real-time RT-PCR study. Biochem Pharmacol., 2004; 68: 699–709.
14. Sekler I, Sensi SL, Hershfinkel M, Silverman WF. Mechanism and regulation of cellular zinc transport. Mol Med., 2007; 13: 337–43.
15. Liuzzi JP, Cousins RJ. Mammalian zinc transporters. Annu Rev Nutr., 2004; 24: 151–72.