Zinc nutrition in health and diseases

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Zinc is the 27th most abundant element in the earth's crust and also the most widely used metals in biology. Zinc (3 g) is the second most abundant trace element in the human body after iron (4 g) and considerably more abundant than copper (0.1 g). Unlike other metals, zinc is virtually non-toxic owing to tight cellular homeostatic control of entry into, distribution in and excretion from cells; physico-chemical properties of zinc permit stable association with macromolecules through coordination flexibility. It always prefers tetrahedral complex formation and readily complexes with amino acids, peptides, proteins and nucleotides. Zinc also has an affinity for thiols, hydroxy groups and ligands with electron-rich nitrogen donors. Thus zinc participates extensively in the metabolism of protein, nucleic acid, carbohydrate and lipid. Other unique properties such as its inability to undergo reduction and oxidation, amphoteric nature at neutral pH and ability to assume multiple coordination geometries due to a variable oxidation sphere make it biochemically very versatile (IZiNCG 2004, Sensi et al. 2009, King 2011).

Biochemical functions

The chemical versatility of zinc has resulted in its participation in a diverse array of biochemical pathways. Extensive studies have focused on zinc-dependent biochemical mechanisms that determine physiologic functions. A brief description that accounts for the essentiality of zinc is given and the functions are illustrated in Figure 1.

Catalytic role. Zinc serves a catalytic role in enzymes from all six classes of enzymes with more than 300 enzymes. Alkaline phosphatase, carbonic anhydrase, carboxy peptidase, calcium-ATPase, thymidine kinase and creatine kinase are of special interest through which zinc takes part in metabolic processes of energy, carbohydrate, protein, lipid and nucleic acid. Zinc offers its potential antioxidant property by increasing the activity of superoxide dismutase and exerts free radical (O_2^-) scavenging activity. Concentration of zinc in

membrane fraction maintains membrane stability and cell integrity. Cell differentiation, proliferation and gene expression are also regulated by zinc.

Structural role. Zinc facilitates the folding of proteins into three-dimensional configurations, for their biologic activity. This involves chelation of zinc with cysteine and histidine amino acids to form zinc fingers. Zinc performs its structural function also by taking part in formation of insulin hexamer complex which is the storage form of insulin in pancreas. Deficiency of zinc has been causally associated with impaired immune function. Zinc structurally and functionally alters responses of both innate and adaptive immunity (Haase and Rink 2009). It influences cellular and humoral immunity by regulating various immune mechanisms like functions of immune cells (neutrophils, monocytes, natural killer cells, macrophages) balancing between TH1 and TH2 cytokines.

Regulatory role. Zinc performs its regulatory functions through zinc finger motif which is a protein and is known to bind DNA, RNA or protein. In zinc finger motif, a zinc ion coordinates to cysteine and histidine side chains to stabilize a short alpha helix that can recognize DNA in a sequence specific manner to offer diversified functions
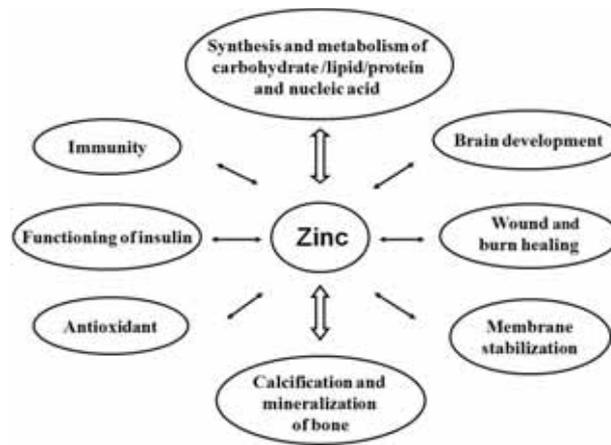

Figure 1. Diagrammatic representation of functions of zinc.

like DNA recognition, RNA packaging, transcriptional activation, regulation of apoptosis, protein folding and assembly, and lipid binding. Other than these zinc is involved in growth, brain development, bone mineralization, wound healing, etc. Zinc-dependent protein folding is essential for 11-cis-retinal to trans retinal through rodopsin cycle.

Dietary sources of zinc

Good sources of zinc are shellfish, beef and other red meat, eggs, milk, poultry and fish diets, nuts and legumes. The recommended dietary allowance (RDA) of zinc for Indians (ICMR 2010) is higher than that reported by Institute of Medicine (IOM 2001) for Americans (Table 1), which is mainly due to lower absorption of zinc from cereal pulse vegetarian diet consumed by Indians. Habitual Indian diet provides about 9–11 mg of zinc and a considerable proportion (52%) of which comes from cereals (Fig. 2).

Recent studies on zinc absorption using stable isotopes in Indian adolescent children have shown that the fractional absorption is in the range of 27–30% (Nair et al. 2013). The major dietary ligand that inhibits zinc absorption is phytate. Various absorption studies have shown that a phytate : zinc molar ratio of 10 or more is inhibitory in nature. Presence of divalent cations such as iron and calcium in high amounts also inhibits absorption of zinc. High meat diets enhance absorption of zinc from cereal-based diets as these form stable chelate complexes with amino acids such as cysteine, histidine and methionine.

Zinc balance – whole body fluxes

Zinc is absorbed at the jejunum and ileum by specific transporters. All absorbed zinc is transported to other
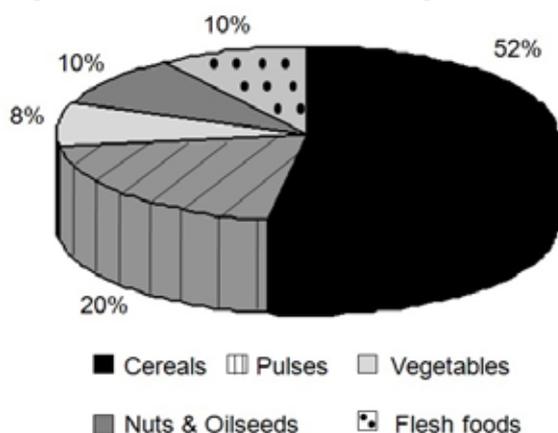
tissues through the plasma bound mainly to albumin. About 99% of total body zinc is intracellular and there are no known storage sites or organs for zinc. The highest concentration of zinc is found in the choroid of the eye and optic nerve, followed by the other organs like prostate, bone, liver and kidneys. Nearly one-third of total body zinc exchanges between blood circulations with other tissues. The total plasma zinc content is about 2.5 mg, which represents 0.1% of total body zinc and varies as a function of age, sex and pregnancy (IZiNCG 2004). Most of the zinc in plasma is taken up by the liver and eventually appears in the pancreas (insulin granules) and kidney. Unlike iron, zinc is excreted from the gastrointestinal tract (1.5 mg day^{-1}). Zinc is found in the pancreatic and biliary secretions (3–5 mg day^{-1}). Urinary excretion of zinc amounts to about 0.63 mg day^{-1} and other endogenous losses (sweat, semen, menstruation and desquamation of the skin and absorptive epithelium) add to this loss (~3 mg day^{-1}). Reabsorption of secreted zinc in gut lumen serves as important measure to maintain zinc balance (FAO/WHO 2001). The amount of dietary zinc absorbed is therefore to replenish these losses and maintain a positive zinc balance. Changes in fractional absorption, endogenous fecal zinc excretion and urinary resorption along with avid retention of zinc released from select tissues such as bone are required to maintain plasma zinc concentrations within a tight range (Fig. 3).

Epidemiology of zinc deficiency

Zinc deficiency is a consequence of consumption of habitual diet high in phytate or low in flesh foods. The

Figure 2. Habitual zinc intake in India (computed from NNMB, 2006).

Table 1. Recommended dietary allowances of zinc as per recommendation by Indian Council of Medical Research (ICMR), India and Institute of Medicine (IOM), USA.

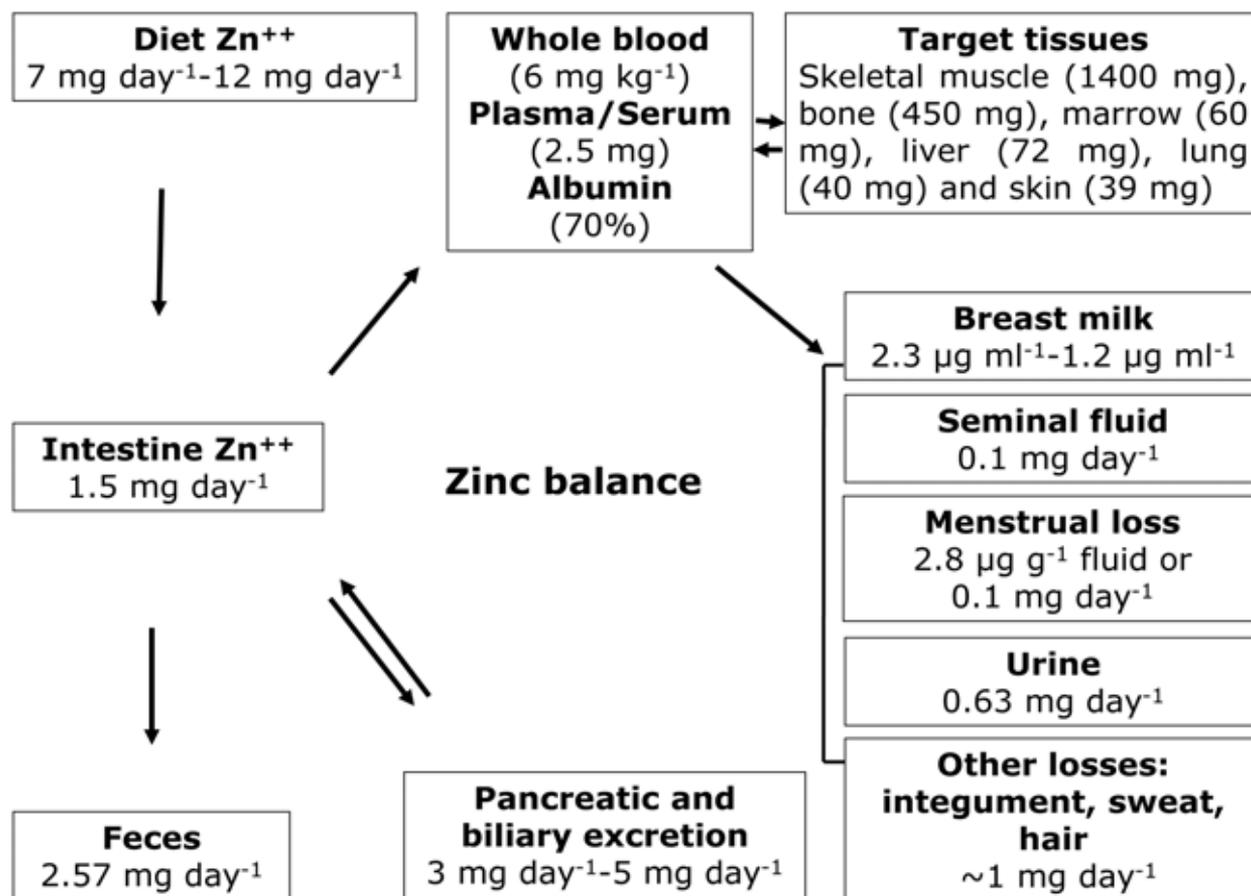| Group	ICMR, India	IOM, USA
Adult man	12	11
Adult woman[1]	10	8
Pregnant/lactating woman	12	8
Children		
1–3 years	5	3
4–6 years	7	5
7–9 years	8	5
Boys – 10–12 years	9	8
Girls – 10–12 years	9	8
Boys – 13–15 years	11	11
Girls – 13–15 years	11	9
Boys – 16–17 years	12	11
Girls – 16–17 years	12	9

1. Non-pregnant and non-lactating.

Figure 3. Zinc balance: whole body fluxes (based on IZiNCG 2004 and ICMR 2010).

sequence of events leading to clinical deficit is impairment of biochemical function, metabolic effects of oxidative damage to membranes and DNA functional defects. Zinc deficiency has been suggested as a risk factor with adverse long-term effects on growth, immunity and diarrhea. Zinc is required for normal brain development and physiology; both deficiency and excess lead to alterations in behavior, abnormal central nervous system (CNS) development and neurological disease. It is abundant in the CNS and trafficking of zinc in neuronal tissues is governed in part through the unique tissue-specific expression of zinc transporters. Deficiency of zinc during pregnancy leads to malformations such as cleft lip, palate and brain (hydrocephalus, anencephalus or exencephalus), abnormal position of heart, missing lobes of lungs, and abnormal urogenital organs, limbs and eyes (Sensi et al. 2009). Due to zinc deficiency, experimental animals failed to conceive. Also abnormalities of blastocyst development were observed, which resulted in low birth weight, and prolonged and difficult parturition. Zinc is also a potential neurotoxin, as neuronal injury is observed in Alzheimer's disease.

Moderate to severe zinc deficiency is associated with growth retardation, respiratory infection and diarrhea especially in children. Marginal zinc deficiency is also present in developing countries like India especially among children but lack of sensitive and specific biomarkers restricted exploration of particular data (King 2011). Thus, as with iron, the adverse-effect profile of even marginal zinc deficiency results in decreased productivity and loss in disability-adjusted life years (DALYs) and much of the evidence comes from improvements in outcome measures upon supplementation.

Zinc supplementation has been suggested when (1) more than 25% of population receive below mean requirement of zinc; (2) more than 20% of children under 5 years have (stunting) HAZ scores >-2SD; and (3) more than 20% of population have below cut-off values of serum zinc (IZiNCG 2004). Zinc deficiency among <5-year-old children is a major cause of death due to morbidity. Various studies have shown that preventive zinc supplementation in populations at risk of zinc deficiency reduces the risk of morbidity (Yakoob et al. 2011).

Prevalence of zinc deficiency in India. Worldwide and in India, the problem of iron deficiency and subsequent anemia is the foremost of public health concerns and sub-clinical zinc deficiency is now recognized to be widespread. Zinc deficiency accounts about 17% of the world's population at risk (Wessells and Brown 2012) and 4.4% under 5 years child death globally (Black et al. 2008).

The prevalence of zinc deficiency has not been adequately quantitated due to lack of sensitive markers of zinc status and the current estimates are calculated based on inadequate dietary intake and improvements upon supplementation. Mild to moderate zinc deficiency prevails among infants and young children because of low bioavailable cereal-based complementary feeding practice (Bhaskaram and Hemalatha 1995, Hotz 2001). A recent study conducted in southern India among 479 adolescent girls (aged 10–16 years) in social welfare hostels revealed that 37.6% girls had normal serum zinc level and 62.4% were marginally zinc deficient along with a decreasing trend of serum zinc level with increase in age (Sucharitha 2013). A study carried out in western India (Pune and Maharashtra) among 632 girls of 10–16 years from secondary schools found average zinc intake of 3.6 ± 1.2 mg day^{-1} which accounts only 40% of RDA, 72.5% were found below 0.7 mg L^{-1} plasma zinc and 23.6% with low erythrocyte zinc levels (Kawade 2012). Thus, there is a need for nationwide mapping of zinc nutrition to identify the vulnerable segments of the population for targeting programs. Depletion of soil zinc across the country may add to variation in zinc content in diet leading to variation in status.

Strategies to control zinc deficiency

There are four strategies to combat zinc malnutrition – supplementation, dietary modification to increase zinc intake and absorption, chemical fortification of foods/ biofortification and dietary diversification/processing methods to reduce phytate to improve zinc absorption.

Supplementation. Recent meta analysis have provided global evidence for supplementation with zinc in pregnancy to reduce preterm births (14%) without any effect on low birth weight. Zinc supplementation in populations at risk of zinc deficiency was also found to reduce the risk of morbidity (Brown et al. 2009, Imdad and Bhutta 2011). In children younger than 5 years, preventive zinc supplementation for 24 weeks was observed to improve mean height by 0.37 cm, reduce diarrhea by 13% and pneumonia by 19% (Mori et al. 2012). Frequency of diarrheal episodes has been documented to reduce by 18–59% with zinc

supplementation. Responses with respect to lack of impact among infants with normal zinc status on growth and morbidity have also been reported (Osendarp et al. 2002). In India, diarrheal morbidity in children, 6–11 months of age, was not found to improve with zinc supplementation (Sazawal et al. 1997) and linear growth was found unaltered between zinc supplemented and control group in a 190 days randomized controlled clinical trial among 4-month-old infants (Radhakrishna et al. 2013).

Food fortification. There are limited studies on the impact of chemical fortification of staples with zinc. In a double blind randomized controlled trial (RCT) among zinc-deficient 19–49-year-old women (serum zinc ≤70 µg dl^{-1}), 50 and 100 ppm fortified bread was found to improve zinc status compared to non-fortified bread. The dose of 100 ppm was found to improve phytic acid-zinc molar ratio leading to enhancing zinc bioavailability from moderate to high without bringing unacceptable organoleptic changes (Badii et al. 2012).

Conventional plant breeding technique to improve zinc content of staple crops or biofortification is an emerging strategy. Zinc biofortified rice (*Oryza sativa*), wheat (*Triticum aestivum*) and millets have been at various stages of development and cultivation of such crops may ensure the reduction of burden of zinc deficiency. In Bangladesh, zinc biofortified rice failed to impact fractional zinc absorption compared to the conventional rice among children using dual stable isotope technique (Islam et al. 2013). Absorption of iron and zinc from pearl millet (*Pennisetum glaucum*) biofortified with these minerals was tested recently among 2-year-old children. The results suggest that the use of the biofortified crops significantly increased dietary iron and zinc content but zinc absorption was comparable to non-fortified crops (Kodkany et al. 2013). Thus efforts are needed not only to increase the zinc content in the staple foods but also to enhance its absorption to satisfy the requirements in vulnerable segments of the population.

Dietary diversification/processing methods to reduce phytate to improve zinc absorption. In order to address this issue, emphasis on dietary diversification and food processing is key component to improve zinc bioavailability. Isotope dilution study conducted among 20–42-year-old women revealed that zinc absorption is significantly higher from the non-vegetarian diet (33%) over vegetarian diet (26%) (Hunt et al. 1998). However, inclusion of fruits rich in ascorbic acid did not improve zinc absorption in adolescents (Nair et al. 2013). Food processing methods such as soaking, germination and fermentation have shown to reduce phytate content and

thereby improve absorption of zinc. These methods are simple and can be practiced at household level to improve zinc nutrition (Chavan and Kadam 1989, Turk and Sandberg 1992).

In summary, zinc deficiency stunts growth and causes serious metabolic disturbance. Country-wide prevalence estimates of zinc deficiency and designing strategies to increase zinc intake and absorption are the main research priorities to improve zinc nutrition in the population.

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