

Essentiality and toxicity of zinc¹

by Ananda S Prasad, MD²

Zinc is virtually nontoxic if ingested orally in amounts up to 45 mg · d⁻¹ (elemental zinc) by an adult. There is no evidence that zinc is genotoxic, and exposure of humans to it is not known to be carcinogenic. No disorders are known to be associated with an excessive accumulation of zinc, in contrast to iron, copper, mercury, cadmium, and other metals which accumulate in tissues and produce toxic effects.

Of the transition and group IIB elements necessary for the biological functions of numerous enzymes and proteins, zinc is the one most frequently present. In microorganisms, plants, and animals over 300 enzymes have been identified that are known to require zinc for their function. Many nucleoproteins directly involved in the replication and transcription of deoxyribonucleic acid (DNA) are now known to contain functionally important zinc atoms.

Nutritional and conditioned deficiency of zinc is a widespread problem throughout the world. Industrial exposure to excessive concentrations of zinc produces toxic symptoms, but such exposure is uncommon.

Biochemical functions

Zinc is required not only for many enzymatic functions, but also for DNA synthesis and cell proliferation (1). It coordinates with cysteine and histidine residues in certain peptides and produces a tertiary structure which has an affinity for unique segments of DNA in promoter gene regions (zinc-finger proteins, zinc thiolate clusters, etc). The binding of zinc-finger proteins to promoter areas enhances DNA transcription and increases the synthesis of the protein product for the messenger RNA (ribonucleic acid) sequence concerned (2).

Zinc may regulate the activity of protein kinase C, a critical enzyme elicited by membrane receptor ac-

tivation in the signal transduction pathway, followed by enhanced phosphoinositol turnover. It enhances the affinity of human growth hormone for the extracellular binding domain of the human prolactin receptor. It also stabilizes membranes essential for the maintenance of normal structures by binding to ligands in them.

Zinc is an antioxidant, interacting with the SH groups of macromolecules and thus inhibiting oxidation. It competes for binding sites on membranes with metals such as copper and iron, which are known to enhance membrane lipid peroxidation. Zinc induces the production of metallothionein, which has a molecular weight of 6000–7000 Da and contains 20 cysteine molecules. The excess SH groups in metallothionein can function as excellent scavengers of hydroxyl radicals.

Zinc deficiency in humans

Nutritional zinc deficiency has been reported from many countries throughout the world (3). The prevalence of zinc deficiency is high in populations consuming large quantities of cereal proteins containing organic phosphate compounds, since these compounds render zinc unavailable from the diet. Consumption of alcohol leads to hyperzincuria and zinc deficiency. Our recent unpublished data indicate that mild zinc deficiency may be widespread in the elderly population of developed countries. Nutritional deficiency of zinc may also be widespread in women of child-bearing age throughout the world (4). Several causes of conditioned zinc deficiency have now been recognized, including malabsorption disorders, sickle-cell anemia, chronic liver and renal diseases, and other chronic debilitating disorders (3).

Zinc deficiency during growth leads to dwarfism and failure to develop secondary sexual characteristics (5). Neurosensory disorders such as hypogeusia, abnormal smell, and decreased dark adaptation, as well as problems with the healing of ulcers and wounds, have been observed in zinc-deficient humans. Hormonal effects of zinc deficiency include decreased serum testosterone levels in men, increased serum prolactin levels in patients with chronic renal disease, and decreased activity of serum thymulin, a thymic hormone. Cell-mediated immune functions, particularly as related to lymphocytes, are adversely affected by zinc deficiency in humans (6); the effects include anergy, changes in lymphocyte sub-

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populations, decreased production of cytokines such as interleukin-1 (IL-1) and interleukin-2 (IL-2), and decreased activity of natural killer cells. Abnormality of cognitive functions due to zinc deficiency has also been reported (4).

Effects of zinc excess

My co-workers and I have regularly supplemented zinc-deficient human subjects (patients with sickle-cell anemia and chronic renal disease and healthy elderly people) with 30–45 mg of elemental zinc per day for several months and have not observed either copper deficiency or any other toxic effects. However, we observed the induction of copper deficiency in some patients with sickle-cell anemia when we administered 150 mg of elemental zinc in six divided doses in order to decrease the irreversible sickling *in vivo* (7). This was the first demonstration that excessive oral zinc intake in humans may induce copper deficiency, and it led to the development of successful zinc therapy for patients with Wilson's disease (8). Such therapy reduces copper absorption by inducing metallothionein in intestinal cells. Since metallothionein has a greater affinity for copper than for zinc, copper is trapped in the intestinal mucosal cells and is ultimately excreted by the desquamation of cells. Major manifestations of copper deficiency induced by excessive oral zinc intake include neutropenia and sideroblastic anemia. Both are reversed by copper supplementation.

An adverse lymphocyte proliferative response in 11 human volunteers after oral ingestion of 300 mg of elemental zinc per day for six weeks was reported in one study (9). Unfortunately, copper status was not monitored, and the study was not controlled. *In vitro*, the proliferation of lymphocytes following phytohemagglutinin (PHA) stimulation was determined in normal zinc-containing media. *In vivo*, the plasma zinc levels in the subjects studied were twice the normal levels. Only one mitogen (phytohemagglutinin) at a single dose was used as a test of lymphocyte immune function, and no dose-response curve was derived. The data were expressed in terms of the stimulation index (SI) rather than as absolute counts (SI = absolute counts of stimulated cells divided by background counts of unstimulated cells). Thus a high background count of unstimulated cells from zinc-treated subjects, resulting in a lower SI, would have been interpreted as a reduced mitogen-induced proliferative response when that was not really the case. In view of the fact that zinc itself is a well known mitogen, the background response of the zinc-supplemented subjects might well have been high as a result of exposure to high zinc levels. The absolute numbers of lymphocytes and proportions of T and B cells were not affected. There were no placebo controls in this study.

Klevay (10) reported an increase in serum total cholesterol following excess zinc intake. Subsequent

studies with animals and humans have led to the conclusion that the effects on serum lipids following such excess intake were due to the induction of copper deficiency. Hooper et al (11) reported a decrease in serum high-density lipoprotein (HDL) portion of cholesterol from 40.5 mg · dl⁻¹ to 33.5 mg · dl⁻¹ in 12 men who received 160 mg of elemental zinc a day for 35 d. No change in serum total cholesterol was observed. A much smaller effect on HDL cholesterol was observed in another study after oral administration of 50 mg zinc daily for 6–12 weeks. No other effects on lipid parameters were observed (12).

Freeland-Graves et al (13) observed only a transient effect on serum HDL cholesterol in women who received 100 mg of elemental zinc a day. In a study reported by Samman & Roberts (12), plasma total cholesterol and HDL cholesterol showed no changes in 21 men and 26 women who received 150 mg of elemental zinc a day for six weeks. In the women, the low-density lipoprotein portion of cholesterol decreased by 9%.

In a recent study by Brewer et al (14), the effects of 150 mg of elemental zinc supplementation per day for two years on patients with Wilson's disease (13 men and 11 women) were examined. Both serum total cholesterol and HDL cholesterol declined; however, the ratio between total cholesterol and HDL cholesterol remained lower than 5.0, which is regarded as the risk level for cardiovascular disease. For the women, the ratio decreased significantly from 4.36 to 3.83, indicating an improvement in the cardiovascular disease risk factor for women after zinc supplementation.

Kok et al (15) reported data on mortality from cancer and cardiovascular disease and correlated them with zinc and copper status in a population from The Netherlands. A protective effect of high zinc status on the risk of cancer and cardiovascular disease was compatible with the interpretation of their data. In the United States, data from the Second National Health and Nutritional Examination Survey (NHANES II) showed that the diastolic and systolic blood pressure of both men and women were inversely correlated with serum zinc (16).

The incidence of esophageal tumors induced by methylbenzyl nitrosamine was significantly higher in rats maintained on diets low in zinc (3 ppm) than in rats with normal diets (60 ppm zinc). The esophageal epithelium is sensitive to zinc deficiency, and parakeratosis of the esophageal mucosa has been known to occur in zinc-deficient animals. Diets low in zinc, magnesium, and nicotinic acid have been associated with a higher incidence of esophageal cancer in human populations (17).

Accidental ingestion of three ounces of liquid zinc chloride resulted in caustic erosive pharyngitis and esophagitis, hypocalcemia, hyperamylasemia, lethargy, and confusion. Gastrointestinal manifestations of the accidental ingestion of large amounts of zinc included nausea, diarrhea, and abdominal cramps.

The effects of excessive zinc inhalation (metal fume fever) include metallic taste, flu-like symptoms, cough, and shortness of breath. In a carefully controlled human model study of metal fume fever, polymorphonuclear leukocytosis was noted in the pulmonary lavage fluid (18). Respiratory functions were not affected.

Concluding remarks

Zinc deficiency poses a major public health problem throughout the world. Zinc is, relatively speaking, a nontoxic element if ingested in an oral dose of up to 45 mg · d⁻¹. In higher amounts, copper deficiency is induced. There is no evidence to suggest that the oral intake of zinc up to 45 mg per day adversely affects cell-mediated immune functions or serum lipids.

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