

Editorial

Zinc in Health and Disease

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Although the essentiality of zinc for animals has been recognized since 1934^[1], it was not until the early 1960's that zinc was recognized as essential for humans^[2,3]. Zinc deficiency was first documented in Middle Eastern dwarfs in 1963^[3] and has since been documented worldwide. It is now estimated that in populations in the developing world, nearly two billion persons may have deficiency of zinc of varying severity. Growth retardation, susceptibility to infection and cognitive impairment have been related to zinc deficiency in the developing world. It is clear that zinc deficiency is a major public health problem worldwide with substantial consequences^[4,5].

A meta-analysis of 25 prospective intervention trials of zinc supplementation on children's growth showed that zinc supplementation had a highly statistically significant effect on linear growth and body weight gain^[6]. It has also been shown that zinc supplementation improves neuropsychologic functions in zinc deficient Chinese children^[7].

During our studies in the Middle East, we observed that most of the zinc deficient dwarfs did not live beyond the age of 25 years. The cause of death was presumed to be infection, but the exact nature of the infection was not documented. It is known that parasitic diseases, bacterial and viral infections are very prevalent in developing countries. Due to the limited facilities in Iran and Egypt, we could not study the effects of zinc deficiency on immune functions.

On my return to USA, we have now studied the effects of zinc deficiency on immunity in an experimental human model. We have shown that the activity of serum thymulin (a thymus specific hormone involved in T cell functions) was decreased in mildly zinc deficient subjects^[8]. A mild deficiency of zinc caused an imbalance between Th1 and Th2 functions^[9]. Production of interferon and interleukin (IL)-2 (products of Th1) were decreased, whereas production of IL-4, IL-6,

and IL-10 (products of Th2) were not affected due to zinc deficiency. Zinc deficiency decreased the lytic activity of natural killer (NK) cells and the percentage of precursors of cytolytic T cells. IL-1 β production, a product of monocytes and macrophages, was increased as a result of zinc deficiency in humans^[9]. Thus, zinc deficiency in humans affected thymic functions adversely, caused a shift from Th1 to Th2 function, and activated monocytes and macrophages^[10].

A conditioned deficiency of zinc has been recognized in many diseased states. These include malabsorption syndrome, cirrhosis of the liver, chronic renal disease, subjects receiving total parenteral nutrition without zinc, sickle cell disease, following penicillamine therapy, diabetes, other chronic disorders, and malignancy^[4,5]. In our experience, one third of well-to-do elderly subjects in Detroit area may have a mild deficiency of zinc. Poor appetite, and decreased caloric and animal protein intake are possible factors responsible for zinc deficiency. In some cases, malabsorption and hyperzincuria are additional factors causing zinc deficiency.

The benefits of zinc supplementation on infections in human populations have been demonstrated now. In well-controlled clinical trials, zinc supplementation was shown to reduce the incidence and duration of acute and chronic diarrhea and acute lower respiratory tract infections in infants and children^[11].

Zinc supplementation also reduces the incidence of clinical disease caused by *Plasmodium falciparum*^[11]. Zinc supplementation given to patients with sickle cell disease in a placebo-controlled trial showed decreased incidences of staphylococcus aureus pneumonia, *S. pneumoniae* tonsillitis, and *Escherichia Coli* urinary tract infection in comparison to non-supplemented subjects^[12].

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Zinc is an In Vivo Antioxidant

There is now increasing evidence that oxidative stress is an important contributing factor in several chronic human diseases, such as atherosclerosis and related vascular diseases, mutagenesis and cancer, neurodegeneration, immunologic disorders, and the aging process^[13]. Greater than 95% of the oxygen consumption in aerobic organisms is the result of enzymatic reduction to H₂O in mitochondria, by the terminal oxidase of the respiratory chain. The NADPH oxidases are a group of plasma membrane associated enzymes, which catalyze the production of O₂⁻ from oxygen by using NADPH as the electron donor. Zinc is an inhibitor of this enzyme. Cytotoxic cytokines such as TNF- α , IL-1 β , and IL-8 generate increased amounts of free radicals. In HL-60, a malignant human monocyte macrophage cell line, our studies have shown that zinc decreased the production of cytotoxic cytokines. The dismutation of O₂⁻ to H₂O₂ is catalyzed by an enzyme superoxide dismutase (SOD) which contains both copper and zinc. Zinc is known to induce production of metallothionein, which is very rich in cysteines and this protein is an excellent scavenger of \cdot OH. Thus, it is clear that zinc has multiple roles as an antioxidant.

In order to study the role of zinc as an in vivo antioxidant, we recruited 20 healthy human volunteers, ten received 45 mg elemental zinc as zinc gluconate per day and ten received identical looking placebo pills. The presence of reactive oxygen species (ROS) is known to activate NF- κ B, thus we assayed NF- κ B binding to DNA as a marker for ROS production. We observed that in zinc supplemented subjects the NF- κ B activation was decreased by almost fifty percent in comparison to placebo treated subjects, providing evidence that zinc functions as an in vivo antioxidant (unpublished observation).

The Age-related Eye disease study, an eleven-center double-masked clinical trial supported by National Eye Institute, NIH, enrolled participants in an AMD (age related macular degeneration) trial if they had extensive small drusen, intermediate drusen, large drusen, non-central geographic atrophy, or pigment abnormalities in one or both eyes, or advanced AMD or vision loss due to AMD in one eye^[14]. Participants were randomly assigned to receive daily oral tablets containing^[1] antioxidants (vitamin C, 500 mg; vitamin E 400 IU; and beta carotene 15 mg);^[2] zinc 80 mg as zinc oxide and copper 2 mg as cupric oxide;^[3] antioxidants plus zinc; or^[4] placebo. A total of 3640 participants, ages ranging from 55 to 80 years were enrolled and their average follow up period was 6.3 years. Both, zinc and antioxidants-plus zinc

significantly reduced the odds of developing advanced AMD in this higher-risk group. The group taking the antioxidant-plus zinc supplements reduced the risk of developing advanced AMD by about 25 per cent and reduced the risk of vision loss by about 19 percent. The group taking the zinc alone reduced the risk of developing advanced AMD by about 21 percent and vision loss by about 11 per cent, whereas the group taking the vitamins alone reduced the risk for developing advanced AMD by about 17 percent and vision loss by about 11 percent. This study demonstrates that in therapeutic dosage, zinc is an effective in vivo antioxidant. We conclude that in therapeutic amounts zinc is a powerful in vivo antioxidant.

Therapeutic Role of Zinc

Other roles of zinc as a therapeutic agent have also emerged during the last decade. Zinc has been approved by FDA as an effective agent for the treatment and long-term management of Wilson's disease^[15]. Use of zinc in individuals, who may be genetically susceptible, may be an excellent agent to prevent damage to vital organs, due to excess copper accumulation. Zinc prevents copper accumulation and may decrease copper burden in patients with Wilson's Disease^[15].

Zinc in therapeutic dosage (75 mg of elemental zinc daily in three separate doses) was observed to be effective in decreasing incidences of infections, painful vaso-occlusive crisis, and hospital admissions in patients with sickle cell disease^[12]. Beneficial effects of zinc in patients with hepatic encephalopathy have been reported by several investigators^[16]. Our recent studies have shown that zinc acetate lozenges as a therapeutic agent reduces the duration and severity of common cold by 50%^[17].

Biochemical Role of Zinc

The progress in the role of zinc in biochemical and molecular biological fields has also been phenomenal. Although the first enzyme recognized as a zinc metalloenzyme was carbonic anhydrase as reported by Keilin and Mann in 1940^[4,5], when I started my studies in the early 1960's, only three other enzymes, alcohol dehydrogenase, carboxypeptidase and alkaline phosphatase were known to be zinc metalloenzymes. At present, zinc metalloenzymes have been recognized in all classes of enzymes, and more than 300 catalytically active zinc metalloproteins have been recognized^[4,5]. Since 1985, more than 2000 zinc dependent transcription factors involved in gene expression of various proteins have been recognized^[4,5]. Our recent

studies show that in zinc deficient cells, the binding of some of the zinc dependent transcription factors to DNA is decreased and it is likely that this may result in decreased gene expression of some proteins^[18].

SUMMARY

In summary, during the past forty years since the discovery of the importance of zinc in human health, many examples of nutritional zinc deficiency and conditioned deficiency of zinc in diseased states have been recognized. Nutritional deficiency of zinc is widespread in developing countries. Unfortunately, however, very little has been done to correct this deficiency. Growth retardation, gonadal dysfunction in males, cognitive impairment, and immune disorders in zinc deficient population are severe morbidities and I sincerely hope that various world organizations will take steps to solve these problems in the near future. The field of zinc metabolism is truly an exciting area of research for clinicians, immunologists, biochemists, molecular biologists and nutritional epidemiologists.

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