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Discovery of Human Zinc Deficiency: Impact on Human Health

The essentiality of zinc for the growth of *Aspergillus niger* was recognized for the first time in 1869.¹ Several decades later it was reported to be essential for the growth of the plant²; and in 1934 zinc was shown to be essential for the growth of the rats.³ Until 1961, however, it was generally believed that zinc deficiency in humans could never occur, inasmuch as the presence of zinc was ubiquitous, and food analysis showed adequate amounts of zinc in human diets.

In 1958, I moved from Minnesota to Shiraz, Iran to help Dr. Hobart Reimann set up a residency training program in medicine at the Nemazee Hospital. Within a short period of my arrival in Shiraz, a 21-y-old male patient with dwarfism, hypogonadism, hepatosplenomegaly, rough and dry skin, mental lethargy geophagia, and iron deficiency anemia was presented to me at the Medical Center grand round. This patient looked like a 10-y-old

boy. I was completely unaware of the existence of this syndrome in the medical literature. The diet of this patient was also unusual, inasmuch as his intake of animal protein was negligible, and he subsisted only on unleavened bread. In addition, he consumed 0.5 kg of clay daily.

The local physicians explained the growth retardation and hypogonadism on the basis of hypopituitarism for which there was no real evidence. Ten additional, similar cases were admitted under my service at the Nemazee Hospital within 3 mo, which led me to reject the explanation that hypopituitarism was responsible for growth retardation and hypogonadism.

I could not explain growth retardation and testicular hypofunction on the basis of iron deficiency inasmuch as these manifestations are not seen in iron-deficient experimental animals. It was known, however, that zinc deficiency in animals produced growth retardation and testicular atrophy. Therefore, I speculated that some dietary factors responsible for decreased iron availability in geophagic patients also might have decreased the availability of zinc. O'Dell and Savage⁴ in 1960 reported that phytate, an organic phosphate compound present in cereals, markedly impaired the absorption of zinc and also iron.

In Iran, the laboratory facilities were limited and it was not possible to investigate zinc metabolism in our patients. The technique for assay of zinc in biological samples also was very difficult during those days and no more than two or three laboratories in the world had the capability to assay zinc in biological samples.

After treatment with pharmaceutical iron and administration of a good diet containing adequate animal protein, the Iranian dwarfs improved clinically. The growth increased, secondary sexual characteristics developed, and the anemia was corrected.⁵ One surprising finding was that serum alkaline phosphatase increased after treatment, although there was no change in other liver-function tests. Retrospectively, I explained this on two bases: 1) ordinary pharmaceutical iron contained unknown amounts of zinc as a contaminant, and 2) a well-balanced hospital diet containing animal protein provided adequate amounts of zinc, thus inducing the activity of alkaline phosphatase, a known zinc metalloenzyme.⁵

In 1961, I moved to US Naval Medical Research Unit No. 3, Cairo, Egypt. There my colleagues and I studied Egyptian dwarfs in depth. We reported that zinc in plasma, red blood cells, hair, and 24-h urine was significantly decreased in the dwarfs in comparison with the normally developed Egyptian subjects between the ages of 16 and 18 y. With the use of ⁶⁵Zn, we showed that the plasma-disappearance curve was more rapid and the 24-h exchangeable pool of zinc was decreased in the dwarfs in comparison with the control subjects. This was the first documentation that zinc deficiency occurred in humans.⁶ Further studies in Egypt showed that the rate of growth in dwarfs (average of 5 inches) was greater in subjects who received supplemental zinc than in those who received iron instead or who received only an adequate animal-protein diet.⁷ Gonadal changes also were reversible by zinc supplementation.

The next decade was very controversial and some investigators questioned the existence of zinc deficiency in humans. Two important events in early 1970s ended this controversy. The first one was a publication by Barnes and Moynahan⁸ who reported that acrodermatitis enteropathica, a fatal genetic disorder, was caused by zinc deficiency and that the patients were incapable of absorbing dietary zinc. Zinc supplementation completely cured this condition. The second event occurred in 1974 when a landmark decision was made by the Food and Nutrition Board of the National Academy of Sciences to establish recommended dietary allowances for zinc for humans. The impact of this decision was overwhelming, inasmuch as it affected the agricultural and pharmaceutical industries, in that they were now required by law to label the zinc contents of their products.

Although zinc deficiency in humans initially was believed to be rare, it became apparent that clinical pictures similar to those reported for zinc-deficient dwarfs from the Middle East were

common in many developing countries, where primarily cereal proteins were consumed by the population. Several reports also documented that zinc deficiency affected males and females. Indeed, it has been estimated that a nutritional deficiency of zinc affects more than 2 billion individuals in the present-day developing world.

The clinical morbidities associated with zinc deficiency are considerable. These include growth retardation, hypogonadism in males, impaired cognitive functions, and cell-mediated immune disorders.

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.⁹ Zinc supplementation also has been shown to improve neuropsychologic functions in zinc-deficient Chinese children.¹⁰

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

On my return to the United States, my colleagues and I studied the effects of zinc deficiency on immunity in an experimental human model. We showed that the activity of serum thymulin (a thymus-specific hormone involved in T-cell functions) was decreased in mildly zinc-deficient subjects.¹¹ Zinc deficiency in an experimental human model caused an imbalance between T-helper cell (Th)1 and Th2 functions.¹² Production of interferon- γ and interleukin (IL)-2 (products of Th1) was decreased, whereas production of IL-4, IL-6, and IL-10 (products of Th2) was not affected by zinc deficiency. Zinc deficiency decreased the lytic activity of natural-killer cells and the percentage of precursors of cytolytic T cells. IL-1 β , a product of monocytes and macrophages, was increased as a result of zinc deficiency in humans.¹³ Thus, zinc deficiency in humans adversely affected thymic functions, caused a shift from Th1 to Th2 function, and activated monocytes and macrophages.

Our recent, unpublished studies have shown that zinc is involved in the gene expression of IL-2 in HUT-78, a Th0 human malignant lymphoblastoid cell line. In H1-60, a malignant human monocyte-macrophage cell line, zinc decreases the gene expression of IL-1 β and tumor necrosis factor- α . These effects are most likely due to the effect of zinc on zinc-dependent transcription factors involved in the gene expression of those cytokines. Further studies are required to precisely document the role of zinc on the relevant transcription factors responsible for those effects. Results of those studies are likely to have an important impact on human health and management of autoimmune disorders.

A conditioned deficiency of zinc has been recognized in many diseased states such as malabsorption syndrome, cirrhosis of the liver, chronic renal disease, subjects receiving total parenteral nutrition without zinc, sickle-cell disease, after penicillamine therapy, diabetes, other chronic disorders, and malignancy.¹⁴ In our experience, one-third of well-to-do elderly subjects in the Detroit area may have mild zinc deficiency. Poor appetite and decreased caloric and animal-protein intakes are possible factors responsible for zinc deficiency. In some cases malabsorption and hyperzincuria are additional factors causing zinc deficiency.¹⁴

The benefits of zinc supplementation on infections in human populations has been demonstrated. In well-controlled clinical trials, zinc supplementation reduced the incidence and duration of acute and chronic diarrhea and acute lower respiratory-tract infections in infants and children.^{15,16}

Zinc supplementation also reduced the incidence of clinical disease caused by *Plasmodium falciparum*.¹⁷ Zinc supplementation 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 with non-supplemented subjects.¹⁸

The role of zinc as a therapeutic agent has emerged during the past decade. Zinc has been approved by the Food and Drug Administration as an effective agent for the treatment and long-term management of Wilson's disease.¹⁹ Zinc might be an excellent agent to prevent damage to vital organs due to excess copper accumulation in genetically susceptible individuals. Zinc prevents copper accumulation and also may decrease copper burden in patients with Wilson's Disease.¹⁹

Zinc in therapeutic dosages (75 mg of elemental zinc daily in three separate doses) was effective in decreasing incidences of infections, painful vasocclusive crises, and hospital admissions in patients with sickle-cell disease.¹⁸ Beneficial effects of zinc in patients with hepatic encephalopathy have been reported by several investigators.²⁰ Our recent studies have shown that zinc-acetate lozenges as a therapeutic agent reduces the duration and severity of the common cold by 50%.²¹

The progress concerning the role of zinc in biochemical and molecular biological fields has been phenomenal. Although the first enzyme recognized as a zinc metalloenzyme was carbonic anhydrase, as reported by Keilin and Mann in 1940,²² when I started my studies in the early 1960s, 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.²³ Since 1985 more than 2000 zinc-dependent transcription factors involved in gene expression of various proteins have been recognized.^{24,25} Our recent studies (unpublished) showed that, in zinc-deficient cells, the binding of some of the zinc-dependent transcription factors to DNA is decreased, which likely results in decreased gene expression of some proteins.

In summary, during the 40 y 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 the developing countries. Unfortunately, very little has been done to correct this deficiency. Growth retardation, gonadal dysfunction in males, cognitive impairment, and immune disorders in zinc-deficient populations 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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