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ПРОБЛЕМНАЯ СТАТЬЯ

# HISTORY OF THE DISCOVERY OF ZINC ESSENTIALITY FOR HUMANS

# ИСТОРИЯ ОТКРЫТИЯ ЭССЕНЦИАЛЬНОСТИ ЦИНКА ДЛЯ ЧЕЛОВЕКА

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ABSTRACT: Essentiality of zinc for humans and its deficiency was recognized in 1963. During the past 50 years, it has become apparent that deficiency of zinc in humans is prevalent. Nutritional deficiency of zinc may affect nearly 2 billion subjects in the developing world. Consumption of cereal proteins high in phytate decreases the availability of zinc for absorption. Conditioned deficiency of zinc is also very common. Growth retardation, hypogonadism in males, rough skin, impaired immunity, neuro-sensory disorder and cognitive impairment are some of the clinical manifestations of zinc deficiency. Zinc is involved in many biochemical functions and nearly 2000 transcription factors require zinc for gene expression. In therapeutic dosages, zinc has been used for the treatment of acute diarrhea in infants and children, common cold, Wilson's disease, sickle cell disease and for prevention of blindness in patients with age related macular degeneration.

РЕЗЮМЕ: Впервые эссенциальность цинка для человека была показана в 1963 г. Тогда же был описан дефицит цинка. В течение последних 50 лет стало очевидно, что дефицит цинка в организме человека широко распространен. Недостатку поступления цинка с пищей подвергаются около 2 млрд. человек в развивающихся странах. Потребление белков злаков, богатых фитатом, снижает доступность цинка при всасывании. Условный дефицит цинка также очень распространен. Задержка роста, гипогонадизм у мужчин, грубая кожа, нарушения иммунитета, нейросенсорные расстройства и когнитивные нарушения являются клиническими проявлениями дефицита цинка. Цинк участвует во многих биохимических функциях и требуется почти 2000 факторам транскрипции для экспрессии генов. В терапевтических дозах цинк был использован для лечения острой диареи у младенцев и детей, простуды, болезни Вильсона—Коновалова, серповидно-клеточной анемии и при профилактике слепоты, связанной с возрастной макулярной дегенерацией.

## BRIEF HISTORY OF THE DISCOVERY OF ZINC AS AN ESSENTIAL ELEMENT FOR HUMAN HEALTH

Raulin in 1869 showed for the first time that zinc was essential for the growth of Aspergillus niger (Raulin, 1869). In 1934 Todd et al. reported that zinc was essential for the growth of the rats. In animals the manifestations of zinc deficiency included growth failure, loss of hair, thickening and hyperkeratinization of the epidermis, and testicular atrophy (Todd et al., 1934). Although the essentiality of zinc for animals was established, its ubiquity made it seem improbable that zinc deficiency in humans could lead to significant problems in clinical medicine.

*Discovery of human zinc deficiency*

I arrived in Shiraz, Iran, in June 1958 after finishing my formal training in medicine. Dr. Hobart A. Reimann, Chief of Medicine at the Nemazee Hospital of

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Pahlevi University in Shiraz, Iran, invited me to join him to set up a curriculum for teaching medicine to students and house staff. In Shiraz, I met Dr. James, A. Halsted, who was a Fulbright Professor at Pahlevi University and was primarily involved with Saadi hospital. In the fall of 1958, I was invited by Dr. Halsted to discuss a patient with anemia at the medical center grand rounds at the Saadi Hospital. The case was presented to me by the chief resident, Dr. M. Nadimi, a graduate of the Shiraz Medical School.

The patient was a 21-y-old male, who looked like a 10-y-old boy. In addition to severe growth retardation and anemia he had hypogonadism, hepatosplenomegaly, rough and dry skin, mental lethargy, and geophagia. The patient ate only bread from wheat flour and intake of animal protein was negligible. He consumed nearly 0.5 kg of clay daily. Later we discovered that the habit of geophagia (clay eating) was fairly common in the villages around Shiraz. Further studies documented the existence of iron-deficiency anemia in our patient but, there was no evidence of blood loss. Inasmuch as 10 additional similar cases were brought to the hospital for my care within a short period of time, hypopituitarism as an explanation for growth retardation and hypogonadism was ruled out.

The anemia of the subjects promptly responded to oral administration of iron. The probable factors responsible for anemia in these patients were insufficient availability of iron in the diet, excessive sweating probably causing greater iron loss from the skin than would occur in a temperate climate and geophagia further decreasing iron absorption.

It was difficult to explain all of the clinical features solely by tissue iron deficiency inasmuch as growth retardation and testicular atrophy are not seen in iron-deficient experimental animals. The possibility that zinc deficiency may have been present was considered. As noted earlier, zinc deficiency was known to produce retardation of growth and testicular atrophy in animals. Because heavy metals may form insoluble complexes with phosphate, we speculated that some factors responsible for decreased availability of iron in these patients with geophagia may also have decreased the availability of zinc. O'Dell and Savage (1960) had observed that phytate (inositol hexaphosphate), which is present in cereal grains, markedly impaired the absorption of zinc.

We published aclinical description of the Iranian cases as a syndrome and speculated that zinc deficiency may account for growth retardation and male hypogonadism in these subjects (Prasad et al., 1961). I left Iran in January 1961 and joined the department of Biochemistry and Medicine of Vanderbilt University under Dr. William J. Darby. Although Dr. Darby wanted me to study porphyrin metabolism in Pellagra in Egypt, I shared with him my speculation that zinc deficiency in the Middle East was prevalent and was responsible for widespread growth retardation. He approved my plans to investigate zinc metabolism in growth-retarded subjects. I then moved to Egypt. My team consisted of Harold Sandstead, MD, and A. Schulert, PhD, both from Vanderbilt University, A. Miale Jr. MD from US Naval Medical Research Unit No.3 (NAMRU-3) and Z. Farid, MD, a local physician, also from NAMRU-3.

In Egypt subjects similar to the growth-retarded Iranian subjects were encountered. The clinical features were remarkably similar except that the Iranian subjects had more pronounced hepatosplenomegaly, a history of geophagia, and no hookworm infection and the Egyptian subjects had both schistosomiasis and hookworm infestations but no history of geophagia.

We carried out a detailed investigation of the Egyptian cases at NAMRU-3 in Cairo. The dietary history of the Egyptian subjects was similar to that of the Iranians. The consumption of animal protein was negligible. Their diet consisted mainly of bread and beans (Vicia fava). These subjects were shown to have zinc deficiency. The evidences were decreased zinc concentrations in plasma, red cells, and hair and by studies with zinc-65 that revealed, the plasma zinc turnover was greater, the 24-h exchangeable poo1 was smaller, and the excretion of zinc-65 in stool and urine was less in the subjects than in the control Subjects (Prasad et al., 1963).

Hypozincemia in humans in the absence of advanced cirrhosis of the liver had not been described before. Liver-function tests and biopsy revealed no evidence of cirrhosis in these subjects. Furthermore, in contrast to cirrhosis patients who excrete abnormally high quantities of zinc in urine, our patients excreted less zinc in urine than did control subjects. Other chronic debilitating diseases that might affect the serum zinc concentrations were ruled out.

It was a common belief among clinicians in Iran that severe growth retardation and sexual hypofunction, as noted above, were the results of visceral leishmaniasis and geophagia. In our studies no evidence of visceral leishmaniasis was found. The role of geophagia was not entirely clear; however, it was suspected that the excess amount of phosphate in the clay may have prevented absorption of both dietary iron and zinc. The predominantly wheat diet in the Middle East, now known to contain high quantities of phytate and fiber, most probably reduced the availability of zinc. In Egypt, the cause of dwarfism was commonly considered to be schistosomiasis. Chinese investigators had also implicated schistosomiasis as a causative factor for growth retardation.

Our studies in the Middle East only included males. Female subjects refused to participate in our studies. Later studies from Iran by Halsted et al. (1972) demonstrated that zinc deficiency in females manifesting growth retardation was prevalent.

Studies in Egypt showed that the rate of growth was greater in patients who received supplemental zinc as compared with those receiving iron instead or those receiving only an adequate animal-protein diet (Sandstead et al., 1972). Pubic hair appeared in all

subjects within 7–12 weeks after zinc supplementation. Genitalia increased to normal size and secondary sexual characteristics developed within 12–24 weeks in patients who received zinc (Sandstead et al., 1972). In contrast, no such changes were observed in a comparable length of time in the iron-supplemented group or in the group on an animal-protein diet. Thus, the growth retardation and gonadal hypofunction in these subjects were related to zinc deficiency. The anemia was due to iron deficiency and responded to oral iron treatment.

It is now evident that nutritional as well as conditioned deficiency of zinc may complicate many disease states in human subjects. In 1968 MacMahon et al. (1968) observed, for the first time, zinc deficiency in a patient with steatorrhea. Several other examples of zinc deficiency in patients with malabsorption have now been recorded. In 1972 a number of Denver children from middle-class families, were reported to show symptomatic nutritional zinc deficiency (Hambidge et al., 1972). Growth retardation, poor appetite, and impaired taste acuity were related to zinc deficiency in those children and all the symptoms were corrected with zinc supplementation.

Zinc deficiency in human populations throughout the world is prevalent, although its incidence is not known. Clinical pictures similar to those reported in zinc-deficient dwarfs have been observed in many countries. It is believed that zinc deficiency should be present in countries where primarily cereal proteins are consumed by the population. One would also expect to see a spectrum of zinc deficiency, ranging from severe cases to marginally deficient examples, in any given population.

In 1973, Barnes and Moynahan (1973) studied a 2-y-old girl with severe acrodermatitis enteropathica who was being treated with diiodohydroxyquinoline and a lactose-deficient synthetic diet. The clinical response to this therapy was not satisfactory and the physicians sought to identify contributing factors. The concentration of zinc in the patient's serum was profoundly decreased; therefore, they administered oral zinc sulfate. The skin lesions and gastrointestinal symptoms cleared completely and the patient was discharged from the hospital. When zinc was inadvertently omitted from the child's regimen, she suffered a relapse; however, she promptly responded to oral zinc. In their initial reports the authors attributed zinc deficiency in this patient to the synthetic diet. It soon became clear that zinc might be fundamental to the pathogenesis of this rare inherited disorder and that the clinical improvement reflected improvement in zinc status. This original observation was quickly confirmed in other patients throughout the world. The underlying pathogenesis of the zinc deficiency in these patients is due to malabsorption of zinc due to a mutation in ZIP4, a zinc transporter (Wang et al., 2002).

In 1974 a landmark decision to establish recommended dietary allowances (RDAs) for humans for zinc was made by the Food and Nutrition Board of the National Research Council of the USA National Academy of Sciences.

## CLINICAL EFFECTS OF ZINC DEFICIENCY

*Clinical spectrum of human zinc deficiency*

During the past five decades, a spectrum of clinical deficiency of zinc in human subjects has been recognized. On the one hand, the manifestations of zinc deficiency may be severe; and, on the other end of the spectrum, zinc deficiency may be mild or marginal. A severe deficiency of zinc has been reported to occur in patients with acrodermatitis enteropathica, following TPN without zinc, following excessive use of alcohol, and following penicillamine therapy.

*Acrodermatitis enteropathica*

Acrodermatitis enteropathica (AE) is a lethal, autosomal, recessive trait that usually occurs in infants of Italian, Armenian, or Iranian lineage (Barnes, Moynahan, 1973). This disease is not present at birth but usually develops in the early months of life soon after weaning from breast feeding. The dermatologic manifestations of severe zinc deficiency in patients with AE include bullous pustular dermatitis of the extremities and the oral, anal, and genital areas (around the orifices) combined with paronychia and generalized alopecia. Ophthalmic signs may include blepharitis, conjunctivitis, photophobia, and corneal opacities. Neuropsychiatric signs include irritability, emotional disorders, tremors, and occasional cerebellar ataxia. The patients with AE generally have weight loss, growth-retardation; and males exhibit hypogonadism. A high incidence of congenital malformation of fetuses and infants born of pregnant women with AE has been reported (Hurley, 1976).

Patients with AE have an increased susceptibility to infections. In AE, thymic hypoplasia, absence of germinal centers in lymph nodes and plasmacytosis in the spleen are found consistently. All T cell mediated functional abnormalities are completely corrected with zinc supplementation. Abnormal chemotaxis correctable with zinc therapy has also been reported in AE patients. In general, the clinical course is downhill with failure to thrive and complicated by intercurrent bacterial, fungal, and other opportunistic infections. Gastrointestinal disturbances are usually severe, including chronic diarrhea, malabsorption, steatorrhea, and lactose intolerance. The disease, if unrecognized and untreated, is fatal. Zinc supplementation results in complete recovery.

AE gene has been localized to a ~3.5-cM region on 8q24. The gene encodes a histidine-rich protein, which is now referred to as hZIP-4, which is a member of a large family of transmembrane proteins, some of which are known to serve as zinc-uptake proteins. In patients with AE, mutations in this gene have been documented (Wang et al., 2002).

*Total parenteral nutrition (TPN)*

Zinc deficiency following TPN (without zinc) was first recognized by Kay and Tasman-Jones (1975)

and by Arawaka et al. (1976) in adults and children respectively. Patients on TPN with diarrhea may lose 6 to 12 mg of zinc/d. This excessive loss of zinc may result in a severe deficiency of zinc. In such cases not only dermatologic manifestations are seen but also alopecia, neuro psychiatric manifestations, weight loss, and intercurrent infections, particularly involving opportunistic infections, are also observed. Carbohydrate utilization is impaired, and there is a negative nitrogen balance. If zinc deficiency in such cases is not recognized and treated, the condition may become fatal.

In summary, the manifestations of severe zinc deficiency in humans include bullous pustular dermatitis, alopecia, diarrhea, emotional disorder, weight loss, intercurrent infections due to cell mediated immune dysfunctions, hypogonadism in males, neuro-sensory disorders, and problems with healing of ulcers. If this condition is unrecognized and untreated, it becomes fatal.

*Moderate deficiency of zinc*

A moderate level of zinc deficiency has been reported in a variety of conditions. These include nutritional due to dietary factors, malabsorption syndrome, alcoholic liver disease, chronic renal disease, sickle cell disease, and chronically debilitated conditions.

*Nutritional*

Growth retardation, hypogonadism in the males, poor appetite, mental lethargy, rough skin, and intercurrent infections were the classical clinical features of chronically zinc deficient subjects from the Middle East as reported by Prasad et al. in the early 1960s (Prasad et al., 1961, 1963). The basis for zinc deficiency was nutritional inasmuch as zinc was poorly available from their diet due to high content of phytate and phosphate. All the above mentioned features were corrected by zinc supplementation.

As mentioned before, it is now apparent that a nutritional deficiency of zinc in humans is fairly prevalent throughout the world, particularly in areas where cereal proteins are primary in local diet. Just as in Iran, in Turkey also geophagia is a common problem and the majority of the adolescents with geophagia exhibit both iron and zinc deficiencies.

Cavdar et al. (1980) observed a decreased zinc level in almost 30 percent of pregnant women in Turkey, all of whom were of low socioeconomic status. Their diet consisted mainly of cereals. In view of the serious teratogenic effects of maternal zinc deficiency in experimental animals as well as epidemiological evidence that maternal zinc deficiency could be a factor responsible for severe congenital malformation of the central nervous system in humans, correction of this nutritional problem in pregnant women are urgently needed.

*Gastrointestinal disorders and liver disease*

A moderate level of zinc deficiency has been observed in many gastrointestinal disorders. These include malabsorption syndrome, Crohn's disease, regional ileitis, and steatorrhea. A low serum and hepatic zinc and, paradoxically, hyperzincuria was demonstrated in patients with cirrhosis of the liver many years ago.

Some patients with cirrhosis of the liver who had night blindness, did not respond to Vitamin A therapy, however, an improvement following zinc supplementation was reported. Hepatic coma may be precipitated by administration of methionine to cirrhosis patients with an Eck fistula. Similarly, elevated blood ammonia seems to be intimately related to the development of hepatic coma. It is known that zinc-deficient rats have a defect in the metabolism of sulphur-containing amino acids. Zinc deficiency also affects urea synthesis and, thus abnormalities related to metabolism of amino acids and ammonia may act in concert to produce hepatic coma. We have reported an elevated level of plasma ammonia in human subjects as a result of dietary zinc restriction (Prasad et al., 1978). Rabbani and Prasad (1978) observed a decrease in hepatic ornithine transcarbamoylase (OCT) activity and an increase in plasma ammonia levels in zinc-deficient rats. An increased activity of the purine nucleotide enzyme adenosine monophosphate deaminase (AMP-deaminase) as a result of zinc deficiency has also been observed; and it is possible that several factors may account for increased plasma ammonia levels in zinc deficiency associated with cirrhosis of the liver. Zinc therapy has been reported to be beneficial in subjects with hepatic encephelopathy. More studies are needed in this important area.

It is likely that some of the clinical features of cirrhosis of the liver, such as loss of body hair, testicular hypofunction, poor appetite, mental lethargy, difficulty in healing, abnormal cell mediated immune functions, and night blindness, may indeed by related to the secondary zinc-deficient state in this disease.

*Renal disease*

Mahajan et al. (1979) documented that patients with chronic renal failure had low concentrations of zinc in plasma, leukocytes, and hair as well as increased plasma ammonia levels and increased activity of plasma ribonuclease. Uremic hypogeusia improved following zinc supplementation. Impotence is common in uremic males and is not improved by hemodialysis (HD). A double-blind clinical trial of zinc supplementation was carried out using zinc acetate to determine the effect of zinc on uremic gonadal dysfunction (Mahajan et al., 1982). The results of this study suggested that zinc deficiency was a reversible cause of sexual dysfunction in uremia.

*Zinc deficiency in sickle cell disease*

Our studies have documented the occurrence of zinc deficiency in adult sickle cell anemia (SCA) patients (Prasad, 1993; Prasad et al., 1999). Growth retardation, hypogonadism in males, hyperammonemia, abnormal dark adaptation, and cell mediated immune disorder in SCA have been related to a deficiency of zinc. The biochemical evidences of zinc deficiency in SCA included a decreased level of zinc in the plasma, erythrocytes, and hair, hyperzincuria and decreased activities of certain zinc dependent enzymes such as

carbonic anhydrase in the erythrocytes, alkaline phosphatase in the neutrophils, deoxythymidine kinase activity in newly synthesizing skin connective tissue and collagen, and hyperammonemia. Inasmuch as zinc is known to be an inhibitor of ribonuclease (RNase), an increased activity of this enzyme in the plasma of SCA subjects was regarded as an evidence of zinc deficiency. Zinc supplementation to SCA subjects resulted in significant improvement in secondary sexual characteristics, normalization of plasma ammonia level, and reversal of dark adaptation abnormality. As a result of zinc supplementation, the zinc level in plasma, erythrocytes, and neutrophils increased, and an expected response to supplementation was observed in the activities of the zinc-dependent enzymes. We have also reported a beneficial effect of zinc on longitudinal growth and body weight in 14 to 18 year old patients with sickle cell anemia. Zinc deficiency in patients with sickle cell anemia was associated with impaired DTH (delayed type hypersensitivity reactions) and decreased NK (natural killer cells) cell lytic activity, which were corrected by zinc supplementation.

A three month placebo controlled zinc supplementation trial (25 mg zinc as acetate three times a day) in 36 sickle cell disease patients showed that the zinc supplemented group had decreased incidence of infections, increased hemoglobin and hematocrit, plasma zinc and antioxidant power in comparison to the placebo group (Bao et al., 2008). Plasma nitrite and nitrate (NOx), lipid peroxidation products, DNA oxidation products, and soluble vacular cell adhesion molecule-1 decreased in the zinc supplemented group in comparison to the placebo group (Bao et al., 2008). Zinc-supplemented subjects showed significant decreases in lipopolysaccharide-induced tumor necrosis factor-alpha (TNF-$\alpha$) and IL-1$\beta$ mRNAs and TNF-induced nuclear factor of kB-DNA binding in mononuclear cells (MNCs) compared with the placebo group. Zinc supplementation also increased relative levels of IL-2 and IL-2R$\alpha$ mRNAs in PHA-p stimulated MNCs.

In summary, the manifestations of a moderate deficiency of zinc include growth retardation and male hypogonadism in the adolescents, rough skin, poor appetite, mental lethargy, delayed wound healing, cell-mediated immune dysfunctions, and abnormal neurosensory changes.

*Mild deficiency of zinc*

Although the clinical, biochemical, and diagnostic aspects of severe and moderate levels of zinc deficiency in humans are fairly well defined, the recognition of mild levels of zinc deficiency has been difficult. We therefore, developed an experimental model of zinc deficiency in order to define mild deficiency of zinc in humans. In a group of human volunteers we induced a mild state of zinc deficiency by dietary means. Adult male volunteers were hospitalized at the Clinical Research Center of the University of Michigan Medical School Hospital. A semi-purified diet, which supplied approximately 3.0 to 5.0 mg of zinc on a daily basis, was used to produce zinc deficiency. The details of methodology have been published elsewhere (Prasad, 1993).

The volunteers were ambulatory and were encouraged to do daily moderate exercise throughout the study period. Prior to the study, a thorough history, physical examination and routine laboratory tests such as CBC, liver function tests, SMA-12, and serum electrolytes were performed and found to be normal. Zinc in lymphocytes, granulocytes and platelets were determined and found to be in the normal range.

They were given a hospital diet containing animal protein daily for four weeks. This diet averaged 12 mg of zinc per day, consistent with the recommended dietary allowance of the National Research Council, National Academy of Sciences. Following this, they received 3.0 to 5.0 mg of zinc a day while consuming soy protein-based experimental diet. This regime was continued for 28 weeks, at the end of which two cookies containing 27 mg of zinc supplement was added to the experimental diet. The supplementation was continued for 12 weeks.

Throughout the study the level of all nutrients including protein, amino acids, vitamins, and minerals (both macro and micro elements) were kept constant meeting the standards set by RDA, except for zinc, which was varied as outlined above. By this technique we were able to induce a specific mild deficiency of zinc in human volunteers.

In our studies in the experimental human model in whom only a mild deficiency of zinc in males was induced by dietary means, decreased serum testosterone level, oligospermia, decreased NK cell activity, decreased IL-2 activity of T helper cells, decreased thymulin activity, hyperammonemia, hypogeusia, decreased dark adaptation, and decreased lean body mass were observed. It is, therefore, clear that even a mild deficiency of zinc in humans affects clinical, biochemical, and immunological functions adversely.

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