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Impact of the discovery of human zinc deficiency on health

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ABSTRACT

The essentiality of zinc in humans was established in 1963. During the past 50 y, tremendous advances in both clinical and basic sciences of zinc metabolism in humans have been observed. Growth retardation; cell-mediated immune dysfunction, and cognitive impairment are major clinical effects in human. At present we know of >300 enzymes and >1000 transcription factors that require zinc for their activities. Zinc is a second messenger of immune cells, and intracellular free zinc in these cells participate in signaling events. Zinc has been very successfully used as a therapeutic modality for the management of acute diarrhea in children, Wilson's disease, the common cold and for the prevention of blindness in patients with age-related dry type of macular degeneration. Zinc not only modulates cell-mediated immunity but is also an antioxidant and anti-inflammatory agent. Zinc supplementation in the elderly results in decreased incidence of infections, decreased oxidative stress and decreased generation of inflammatory cytokines.

Contents

Introduction

The essentiality of zinc for the growth of *Aspergillus niger* was reported in 1869 [1] and for the growth of plants in 1926. In rats, its role in growth was reported in 1933 [2]. It was, however, considered improbable that zinc deficiency in humans could lead to significant adverse health effects.

Discovery and clinical manifestations of zinc deficiency in humans

Strange set of circumstances took me to Shiraz, Iran. There I was on the staff at Nemazee Hospital, Shiraz and also on the faculty at University of Shiraz, Medical School. Soon after my arrival there, an Iranian physician presented to me at the Medical Center grand round, a 21-y old man who looked like a 10 y-old boy and who was severely anemic. His genitalia were infantile. He had rough and dry skin, mental lethargy, hepatosplenomegaly, and geophagia. He ate only bread (whole wheat flour) and had no intake of animal protein. He consumed 0.5 kg of clay daily. He was severely iron deficient but there was no blood loss. Later I observed that this syndrome was fairly common in the villages around Shiraz, Iran [3]. Fig. 1 shows the photograph of four dwarfs. On the left is a friend of mine who was on the staff in the department of Radiology at Nemazee Hospital.

Iron deficiency alone could not account for extreme growth retardation and testicular atrophy, inasmuch as these are not seen

Abbreviations: IFN-γ, interferon-γ; IL-1β, interleukin-1β; IL-2, Interleukin 2; IL-6, interleukin 6; IL-8, interleukin 8; IL-12 Rβ2, IL-12 receptor β2; LPS, lipopolysaccharide; MyD88, myeloid differentiation primary response 88 (human); RDA, recommended dietary allowances; T-bet, transcription factor involved in T cell differentiation; Th1, T helper one; TNF-α, tumor necrosis factor-α; TRIF, Toll-like receptor domain containing adapter – inducing interferon-β; ZnT, SLC 30 a solute carrier.

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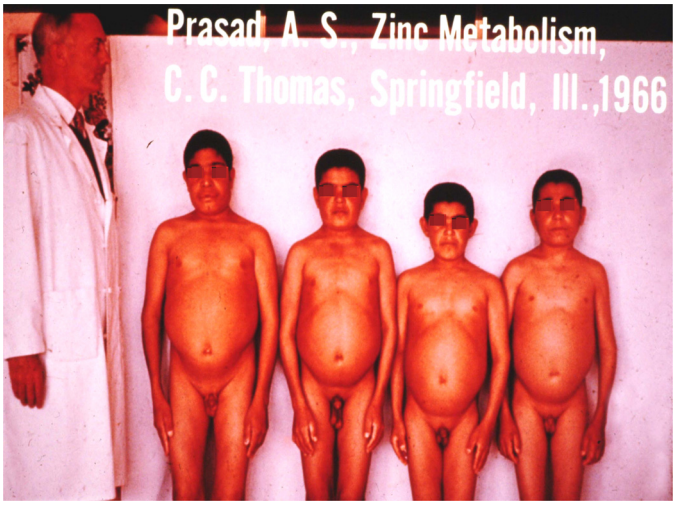

Fig. 1. This is a photograph of four extremely growth retarded Iranian subjects from the villages near Shiraz, Iran. They were also extremely anemic due to iron deficiency. Their genitalia were infantile and they had hepato-splenomegaly. They ate only bread and also consumed one pound of clay every day. Later studies from Egypt documented that this syndrome was due to both iron and zinc deficiency. Growth Retarded Iranian Subjects.
Ref. Prasad A.S., Zinc Metabolism, C.C. Thomas, Springfield, IL, 1966.

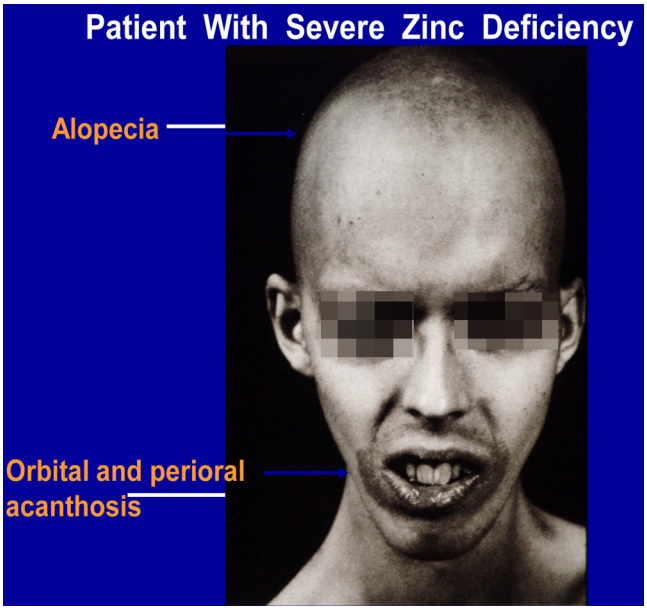

Fig. 2. This is a photograph of a young subject who had Wilson's disease and he received penicillamine therapy for his disease. This resulted in severe deficiency of zinc. Here the photograph shows loss of hair and some parakeratosis around mouth and eyes. Patient with Severe Zinc Deficiency due to Penicillamine Therapy.
Ref. [11].

in iron-deficient experimental animals. An examination of the Periodic table suggested to me that deficiency of another transitional element, perhaps zinc, may have also been present, which may account for growth retardation and hypogonadism. We hypothesized that a high phosphate content in the diet and geophagia may have decreased the availability of both iron and zinc, which resulted in deficiency of both elements [3].

Our later studies in Egypt documented conclusively that zinc deficiency occurred in humans [4]. This was based on extensive studies of zinc metabolism in these subjects. We assayed zinc in plasma, red cells, hair, and urine and used Zn^{65} to study zinc turnover rate and 24 h exchangeable zinc pool. All these studies confirmed that indeed these dwarfs were zinc deficient. This was the first demonstration that zinc deficiency occurred in humans [4]. Zinc supplementation resulted in 12.7–15.2 cm of growth in 1 y and the genitalia became normal within 3–6 mo of zinc supplementation [5].

The idea that zinc deficiency occurred in humans remained very controversial for over a decade, however, many investigators confirmed our observation and in 1974, the National Research Council of the National Academy of Sciences declared zinc as an essential element for humans and established a recommended dietary allowance (RDA) for zinc [6]. In 1978 the FDA (Food and Drug Administration, USA) made it mandatory to include zinc in the total parenteral nutrition fluids [7].

The clinical manifestations of zinc deficiency, as we reported from Middle East were as follows: growth retardation, hypogonadism, rough skin, poor appetite, mental lethargy and intercurrent infections.

It came to my attention in the Middle East that these extremely growth retarded subjects did not survive beyond the age of 25 y and they died because of bacterial, viral, and/or parasitic infections. This suggested to me that perhaps zinc was very important for immune functions.

It is the estimate of the World Health Organization (WHO), that nearly two billion subjects in the developing world may have nutritional deficiency of zinc. In the developing world the diet consists of mainly cereal proteins with high phytate content which complexes zinc and decreases its availability.

Conditioned deficiency of zinc is also widely prevalent throughout the world. Zinc deficiency has been reported in patients with liver disease; chronic alcoholism, malabsorption syndrome, chronic renal disease, and other chronic diseases including malignancy [8].

A severe deficiency of zinc is seen in patients with acrodermatitis enteropathica (AE). AE is a lethal, autosomal, recessive trait that usually occurs in infants of Italian, Armenian or Iranian lineage [9]. The disease develops in the early months of life soon after weaning from breast feeding. The manifestations include bullous pustular dermatitis, parakeratosis, growth retardation, neuropsychiatric manifestations and severe cell-mediated immune dysfunction resulting in intercurrent infections. The AE gene has been localized to a ~3.5-cm region on the 8q24 chromosome. The gene encodes a histidine-rich protein, now referred to as ZIP-4, which is a member of a large family of transmembrane protein known as zinc transporters. In patients with AE, mutations in this gene have been documented [10]. The disease if unrecognized and untreated is fatal. Therapeutic levels of zinc supplementation, however, result in complete recovery.

A severe deficiency of zinc has also been observed in patients with Wilson's disease who received penicillamine therapy as decoppering agent. This treatment may induce severe loss of zinc and cause severe deficiency of zinc. Fig. 2 shows a photograph of a patient who received penicillamine for treatment of Wilson's disease and later developed severe zinc deficiency. Fig. 3 shows that he made excellent recovery following therapy with zinc supplementation [11].

Although clinical and biochemical aspects of severe and moderate deficiency of zinc in humans were well defined, the recognition of mild level of zinc deficiency remained very difficult.

In order to define the mild deficiency of zinc in humans, we developed an experimental model of zinc deficiency. In a group of human volunteers we developed a mild level of zinc deficiency by using a semi-synthetic experimental diet [12–14]. The details have been published elsewhere.