Editorial

Zinc: A Miracle Element. Its Discovery and Impact on Human Health

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ABBREVIATIONS

AMP: Deaminase Adenosine Monophosphate Deaminase; ATP 7B: Membrane-Bound Copper-Binding Adenosine Triphosphatase; cGMP: Guanosine 3', 5' Cyclic Monophosphate; DC: Dendritic Cells; DNA: Deoxyribonucleic Acid; dTMP: Deoxythymidine 5' Mono-Phosphate; HL-60: Human promyelocytic Leukemia cell line; HUT-78: Human malignant lymphoblastoid cell line of Th0 phenotype; ICAM-1: Soluble Intercellular Adhesion Molecule-1; IFN-γ: Interferon-γ; IL: Interleukin; IGF-1: Insulin-like Growth Factor 1; IL-1β: Interleukin-1β; IL-2: Interleukin 2; IL-12 Rβ2: IL-12 receptor β2; MAPK: Mitogen-Activated Protein Kinase; MEK: MAP/ERK Kinase; mRNA: Messenger RNA; MT: Metallothionein; Myd 88: Toll-4 binding adapter-like (MAL) protein; NF-κB: Nuclear Factor kappa B (a zinc-dependent transcription factor); PDE: Phosphodiesterase; Raf-1: a serin/threonine (S/T) kinase; RDA: Recommended Dietary Allowances; RNA: Ribonucleic Acid; ROS: Reactive Oxygen Species; SCD: Sickle Cell Disease; SDC: Soluble Cell Disease; SOD: Superoxide Dismutase; STAT-4: Transcription Factor; sICAM-1: Soluble Intercellular Adhesion Molecule-1; T-bet: Transcription Factor Involved In T Cell Differentiation; T-cell: Thymic Dependent Cell; TCR: T Cell Receptor; Th1: T Helper One; TK: deoxymyidine Kinase; TLR 4: Toll Like Receptor 4; TNF-α: Tumor Necrosis Factor-α; TTP: Thymidine Triphosphate; US NAS/NRC: United States National Academy of Sciences National Research Council; WHO: World Health Organization; ZIP-4: SLC 39 a Solute Carrier; ZIP: SLC 39 a Solute Carrier

EDITORIAL

Although the hematologists and oncologists are very familiar with the role of iron in hemoglobin metabolism, they do not have the same familiarity with another transitional trace element, zinc and its great impact on human health. Nutritional deficiency of iron in the developing world never existed alone and it has been observed that zinc deficiency always co-exists with iron deficiency. This is because majority of the villagers in the developing world subsist on high cereal protein diet which is rich in phytate, an organic phosphate compound which renders both iron and zinc unavailable for absorption. Iron has been known to be important for hemoglobin synthesis for over a century but the essential role of zinc in human health has been only appreciated within the past fifty years.

In this short editorial review, I will present the historical aspect of discovery of zinc as an essential element for humans and its great impact on health and disease.

HISTORY OF THE DISCOVERY OF HUMAN ZINC DEFICIENCY

The essentiality of zinc for the growth of Aspergillus niger was first reported in 1869 [1]. Later its essentiality for the growth of plants and animals was recognized. However, until 1960 it was considered improbable that zinc was essential for human health and that its deficiency in humans would ever occur [2].

Strange set of circumstances took me to Shiraz, Iran in 1958. I was born in India, and came to the University of Minnesota Medical School for training as a clinical scientist under Professor Cecil James Watson, an outstanding Professor of Medicine in USA. I received my clinical training in Internal Medicine and became a specialist in Hematology. Additionally, I received training in basic sciences in the department of Physiology and received a PhD. After finishing my training, I was invited by Professor Hobart Reimann to join him at Nemazee Hospital and Shiraz University Medical School at Shiraz, Iran.

Within 2 weeks of my arrival, an Iranian Resident Physician, Dr. M. Nadimi presented to me a case of 21 y old male patient at the Medical Center Grand Round. This patient was extremely growth retarded. He looked like a 10 y old boy. He had no development of secondary sexual characteristics. His face showed roughened skin and he appeared mentally lethargic. The abdomen was protuberant and he had hepatosplenogaly.

His genitalia were infantile. He was severely anemic. The anemia was due to iron deficiency but there was no evidence of blood loss. He ate only bread made of unleavened bread and there was no intake of animal protein. Additionally he consumed 0.5 kg of clay daily. I discovered later that this unusual syndrome was fairly common in the villages around Shiraz, Iran [2].

This case presented two major dilemmas. One was that how did he become severely iron deficient without any blood loss? The second problem was that I could not account for severe growth

retardation and hypogonadism on the basis of iron deficiency. 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 [2]. I hypothesized that a high phosphate content in the diet and geophagia (day eating), may have decreased the availability of both iron and zinc, which resulted in deficiency of both elements [2].

I subsequently joined the Department of Biochemistry and Medicine at Vanderbilt University, Nashville, Tennessee and moved to US Naval Medical Research Unit 3, Cairo, Egypt, to study zinc deficiency in villages near Cairo. Our studies showed that zinc concentration in plasma, erythrocytes, and hair were decreased significantly in the dwarfs in comparison to the controls [3]. Zn studies showed that 24 h exchangeable zinc pool was decreased and plasma zinc turnover rate was increased in the dwarfs in comparison to the controls [3]. Twenty-four hour urinary excretion of zinc was decreased in the dwarfs. Most importantly zinc supplementation resulted in 12.5 – 15.2 in growth in one year and the genitalia became normal within 3-6 mo of zinc supplementation [4]. These results documented for the first time that zinc was essential for humans and that its deficiency occurred in the Middle East [3-5].

For nearly one decade the idea that zinc deficiency occurred in humans remained very controversial. However, 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) [6] and in 1978 the FDA made it mandatory to include zinc in the total parenteral nutrition fluids [7]. The details of the circumstances leading to the discovery of human zinc deficiency in the Middle East have been recently published [8].

It is now apparent that a nutritional deficiency of zinc in humans is prevalent throughout the world, particularly in areas where cereal proteins are primary in local diets. The cereal proteins contain high amount of an organic phosphate compound, phytate which complexes zinc and makes it unavailable for absorption. The current WHO estimate is that zinc deficiency may affect nearly two billion subjects.

**MANIFESTATION OF ZINC DEFICIENCY**

Both sexes are affected by zinc deficiency in the developing countries. Major manifestations of zinc deficiency include growth retardation, testicular and ovarian dysfunction, immune dysfunctions and cognitive impairment [9]. Increased susceptibility to infections and increased mortality were observed in the developing world [10]. Zinc deficiency also caused oxidative stress and up-regulated generation of inflammatory cytokines form monocytes-macrophages of zinc deficient subjects [10].

Severe deficiency of zinc is seen in patients with acrodermatitis enteropathica, a lethal autosomal, recessive trait disorder which affects infants of Italian, American or Iranian lineage [11]. The disease manifests soon after weaning from breast feeding. The dermatologic manifestations include bullous pustular dermatitis in the extremities and oral, anal and genital areas around the orifices, paronychia and alopecia. Ophthalmic signs include blepharitis, conjunctivitis, photophobia and corneal opacities. Neuropsychiatric signs include irritability, emotional instability, tremors and cerebellar ataxia, weight loss, growth retardation, and male hypogonadism, are prominent clinical features. Congenital malformation of fetuses and infants born of pregnant AE women has been well documented [12]. AE patients are very susceptible to infections and usually die as a result of serious infections. The immune dysfunction is mainly due to T-cell mediated functional abnormalities. Zinc supplementation corrects all these manifestations including immunological dysfunctions [13].

The AE gene has been localized to a ~3.5 cm region on the 8 q 24 chromosome [14]. The gene encodes a histidine-rich protein, now referred to as ZIP-4, which is a member of a large family of transmembrane proteins known as zinc transporters. Mutations of AE gene have been documented in these patients [15].

Kay and Tasman-Jones [16] and later Okada [17] and Aiikawa [18] reported the occurrence of severe zinc deficiency in subjects receiving total parenteral nutrition for over three months without zinc. In USA inclusion of zinc in total parenteral fluid was made mandatory by FDA in 1978 [7].

A severe deficiency of zinc has been reported in patients with Wilson’s disease who received Penicillamine therapy as a decoppering agent [19]. Penicillamine induces excessive zinc loss leading to zinc deficiency.

A moderate deficiency of zinc is characterized by growth retardation, male hypogonadism in adolescents, rough skin, poor appetite, mental lethargy, delayed wound-healing, cell-mediated immune dysfunctions and abnormal neurosensory changes [2,3,10]. These manifestations have been documented in subjects with nutritional deficiency of zinc in adolescents of the Middle East and many other subjects with conditioned deficiency of zinc [10].

A moderate level of zinc deficiency has been observed in many gastro intestinal disorders. These include malabsorption syndrome, Crohn’s disease, regional ileitis and steatorrhea.

Low serum and hepatic zinc and paradoxically hyperzincuria were reported in patients with cirrhosis of the liver [20]. Some patients with liver cirrhosis who have night blindness but do not respond to vit A supplementation do respond to zinc [13].

Elevated blood ammonia levels are known to be a factor in the development of hepatic coma. We reported previously that dietary zinc restriction leads to hyperammonemia [21,22]. Rabbani and Prasad [22] reported a decrease in hepatic ornithine transcarbamoylase activity and an increase in plasma ammonia levels in zinc-deficient rats. Additionally increased activity of the purine nucleotide enzyme adenosine monophosphate deaminase as a result of zinc deficiency has also been observed, which may also contribute to increased ammonia levels [23]. Zinc therapy has been reported to be beneficial in subjects with hepatic encephalopathy [24]. 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 immunity and night blindness may be due to secondary zinc-deficient state induced by hyperzincuria.
Mahajan [25,26] documented for the first time that patients with chronic renal failure showed decreased concentration of zinc in plasma, leukocytes and hair; increased plasma ammonia levels and increased activity of plasma ribonuclease. Zinc supplementation corrected the above parameters, improved uremic hypogeusia and sexual dysfunction [25,26].

Our studies have documented the occurrence of zinc deficiency in adult sickle cell disease (SCD) patients [27,28]. Growth retardation, hypogonadism in males, hyperammonemia, abnormal dark adaptation, and cell mediated immune dysfunction in SCD patients has been related to zinc deficiency. The biochemical evidence of zinc deficiency in SCD patients include decreased concentrations of zinc in plasma, erythrocytes, lymphocytes and hair; hyperzincuria, decreased carbonic anhydrase activity in erythrocytes, decreased alkaline phosphatase activity in neutrophils, decreased deoxythindine kinase activity in newly synthesizing skin connective tissue and collagen, and hyperammonemia[27,28]. Zinc supplementation in SCD patients corrected all the above parameters, resulted in significant improvements in growth and secondary sexual characteristics, normalization of plasma ammonia levels and correction of dark adaptation abnormality. Zinc supplementation also improved cell-mediated immune dysfunction, decreased incidences of intercurrent infections and also decreased occurrences of pain crises [27,28]. A recent Cochrane Review has concluded that zinc supplementation is the only currently available therapeutic manipulation which results in beneficial effects on decreasing the incidences of infections and pain crises, the two most serious clinical problems of SCD [29].

Our studies in patients with head and neck cancer have documented that these patients are commonly zinc deficient [30]. Zinc supplementation to these patients resulted in a decrease in the incidence of clinical infections [30].

**THERAPEUTIC IMPACT OF THE DISCOVERY OF ZINC AS AN ESSENTIAL ELEMENT FOR HUMAN**

Zinc supplementation has been shown to prevent and treat diarrhea effectively in infants and young children throughout the developing world [31,32]. Mortality and morbidity is significantly decreased, saving millions of lives throughout the world. A reporter of Time magazine in 2009 visited many countries in Africa and heard stories as to how zinc treatment had saved lives of young children, whereas prior to the availability of zinc, children with acute diarrhea lost their lives. She wrote an article in Time Magazine and called ZINC a miracle element (Vivienne Walt, Wellness, The Miracle Mineral, TIME, Dec 7, 2009). WHO reporter of Time magazine in 2009 visited many countries in Africa and heard stories as to how zinc treatment had saved lives of young children, whereas prior to the availability of zinc, children with acute diarrhea lost their lives. She wrote an article in Time Magazine and called ZINC a miracle element (Vivienne Walt, Wellness, The Miracle Mineral, TIME, Dec 7, 2009). WHO reporter of Time magazine in 2009 visited many countries in Africa and heard stories as to how zinc treatment had saved lives of young children, whereas prior to the availability of zinc, children with acute diarrhea lost their lives. She wrote an article in Time Magazine and called ZINC a miracle element (Vivienne Walt, Wellness, The Miracle Mineral, TIME, Dec 7, 2009). WHO reporter of Time magazine in 2009 visited many countries in Africa and heard stories as to how zinc treatment had saved lives of young children, whereas prior to the availability of zinc, children with acute diarrhea lost their lives. She wrote an article in Time Magazine and called ZINC a miracle element (Vivienne Walt, Wellness, The Miracle Mineral, TIME, Dec 7, 2009). WHO reporter of Time magazine in 2009 visited many countries in Africa and heard stories as to how zinc treatment had saved lives of young children, whereas prior to the availability of zinc, children with acute diarrhea lost their lives. She wrote an article in Time Magazine and called ZINC a miracle element (Vivienne Walt, Wellness, The Miracle Mineral, TIME, Dec 7, 2009). WHO reporter of Time magazine in 2009 visited many countries in Africa and heard stories as to how zinc treatment had saved lives of young children, whereas prior to the availability of zinc, children with acute diarrhea lost their lives. She wrote an article in Time Magazine and called ZINC a miracle element (Vivienne Walt, Wellness, The Miracle Mineral, TIME, Dec 7, 2009). WHO reporter of Time magazine in 2009 visited many countries in Africa and heard stories as to how zinc treatment had saved lives of young children, whereas prior to the availability of zinc, children with acute diarrhea lost their lives. She wrote an article in Time Magazine and called ZINC a miracle element (Vivienne Walt, Wellness, The Miracle Mineral, TIME, Dec 7, 2009). WHO reporter of Time magazine in 2009 visited many countries in Africa and heard stories as to how zinc treatment had saved lives of young children, whereas prior to the availability of zinc, children with acute diarrhea lost their lives. She wrote an article in Time Magazine and called ZINC a miracle element (Vivienne Walt, Wellness, The Miracle Mineral, TIME, Dec 7, 2009). WHO reporter of Time magazine in 2009 visited many countries in Africa and heard stories as to how zinc treatment had saved lives of young children, whereas prior to the availability of zinc, children with acute diarrhea lost their lives. She wrote an article in Time Magazine and called ZINC a miracle element (Vivienne Walt, Wellness, The Miracle Mineral, TIME, Dec 7, 2009). WHO reporter of Time magazine in 2009 visited many countries in Africa and heard stories as to how zinc treatment had saved lives of young children, whereas prior to the availability of zinc, children with acute diarrhea lost their lives. She wrote an article in Time Magazine and called ZINC a miracle element (Vivienne Walt, Wellness, The Miracle Mineral, TIME, Dec 7, 2009). WHO reporter of Time magazine in 2009 visited many countries in Africa and heard stories as to how zinc treatment had saved lives of young children, whereas prior to the availability of zinc, children with acute diarrhea lost their lives. She wrote an article in Time Magazine and called ZINC a miracle element (Vivienne Walt, Wellness, The Miracle Mineral, TIME, Dec 7, 2009). WHO reporter of Time magazine in 2009 visited many countries in Africa and heard stories as to how zinc treatment had saved lives of young children, whereas prior to the availability of zinc, children with acute dia...

We tested the efficacy of zinc acetate lozenges in the common cold in two trials in human volunteers who were recruited within 24 h of the onset of symptoms of common cold. We conducted a randomized, double blind, placebo controlled trial of zinc [33,34]. Participants took lozenges containing 12.8 -13.3 mg of zinc (as acetate), every 2 – 3 h while awake. The overall duration of common cold symptoms were reduced to 4 – 4.5 d in the zinc treated group in comparison to the placebo group who suffered from the symptoms for 7 to 8 days. We concluded that zinc acetate lozenges given within 24 h of the onset of common cold in proper doses were very effective in decreasing the duration and severity of the common cold. The chemical formulation of the zinc lozenges and doses of zinc are also critical for optimal response. We also proposed that the beneficial effects seen in the zinc group were due to the antioxidant and anti-inflammatory effects of zinc.

A meta-analysis of zinc therapy for common cold by Cochrane review has been published recently [35]. They concluded that zinc significantly reduced the overall duration and severity of common cold symptoms if the therapy was started within 24 h of the onset of the cold. Zinc supplementation for the prevention of the common cold also showed that the incidence of the common cold, school absenteeism and use of antibiotics were decreased significantly [35].

Wilson’s disease is an inherited autosomal disorder of copper accumulation [36]. The excretion of liver copper in the bile is decreased. This leads to failure of proper copper excretion in the stool and copper accumulates in the liver. Eventually copper accumulation takes place not only in the liver but also in the kidneys, pancreas and the brain. Patients typically present with liver disease, neurological disorders or psychiatric disturbances. The genetic mutation of Wilson’s disease gene leads to a defective production of a protein called ATP7B (membrane bound copper-binding ATP), which is responsible for key step in biliary excretion of copper [31-39].

We reported that zinc in therapeutic levels resulted in inducing copper deficiency in sickle cell disease patients [40]. This lead Brewer [36-39] to develop zinc as an effective anti-copper drug for Wilson’s disease. Zinc has been approved by FDA for use as a therapeutic modality for Wilson’s disease. Zinc is the drug of choice for maintenance therapy of Wilson’s disease. It has no toxicity, relatively speaking, is non teratogenic and it can be given to subjects of all ages and even the pregnant women.

Age-related macular degeneration (AMD) affects nearly 25% of individuals older than 65 y of age, and late-stage disease accounts for nearly 50% of legal blindness in Europe and North-America [41,42].

Age-Related Eye Disease Study group (AREDS), supported by National Eye Institute (NIH), conducted an 11-center double blind clinical trial in patients with dry-type AMD [43,44]. Atrial of 3640 participants was enrolled. Their ages ranged from 55 to 80 y, and the average following period was 6.3 y. Participants were randomly assigned to receive daily orally one of the following: 1) Antioxidant vitamins (vitamin C 500 mg, vitamin E 400 IU and β carotene 15 mg); 2) zinc 80 mg as zinc oxide and copper 2 mg as copper oxide to prevent copper deficiency induced by zinc; 3) antioxidant vitamins plus zinc or; 4) placebo.
In the group receiving antioxidant vitamins plus zinc, the risk of advanced AMD developing was reduced by ~25% and vision loss by ~19%. In the group taking zinc alone, the risk of advanced AMD was reduced by ~21% and vision loss by 11%. In the group taking vitamins alone advanced AMD was decreased by 17% and vision loss decreased by 10%. No significant side effects of therapeutic zinc were observed. Most interestingly only the zinc supplemented group showed increased longevity [43,44]. The risk of mortality was reduced by 27% in the AREDS studies in subjects aged 55-81 y who received only therapeutic zinc daily. A later follow up analysis of data has shown that the decreased mortality was due to a decrease in the adverse cardio-vascular events, [44] suggesting that zinc may have beneficially affected the atherosclerotic process in this group.

The daily intake of zinc in the elderly subjects in the Western world including the USA is only 8 -10 mg whereas the RDA is 15 mg. Our study in the Detroit area showed that 35% of the well-off ambulatory elderly subjects may have a deficiency of zinc based on their plasma zinc levels. Zinc deficiency and susceptibility to infections due to cell-mediated immune dysfunctions have been reported in the elderly [45,46].

Oxidative stress and inflammatory cytokines have been implicated as contributing factors for several chronic diseases attributed to aging, such as atherosclerosis and related cardiovascular disorders, mutagenesis and cancer, neurodegenerative disorders, type 2 diabetes mellitus, and Alzheimer’s disease (AD).

Our previous studies in humans have shown that zinc not only corrects cell-mediated immune dysfunctions but is also an antioxidant and anti-inflammatory agent [47,48]. We carried out a randomized, placebo controlled trial of zinc supplementation in the elderly subjects [47,48]. Our study showed that zinc supplementation (45 mg/d elemental zinc as gluconate) in the elderly subjects decreased the incidence of infection by nearly 66%. Also zinc supplementation resulted in decreased oxidative stress markers and decreased generation of inflammatory cytokines from mononuclear cells [47-49]. These are highly significant effects of zinc supplementation in the elderly, and may imply that zinc may also prove to be an excellent agent for prevention of some of the chronic diseases seen in elderly age group.

MILD DEFICIENCY OF ZINC

The best information regarding a mild deficiency of zinc emerged from our studies carried out in an experimental model of human zinc deficiency. 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 in Ann Arbor, MI. A semi-purified diet that supplied ~3.0-5.0 mg/d of zinc was used to induce a specific deficiency of zinc [21,50-52]. As a result of mild deficiency of zinc, we observed a decreased serum testosterone induction of a specific deficiency of zinc [21,50-52]. As a result of mild deficiency of zinc, we observed a decreased serum testosterone 

BIOCHEMICAL IMPACT OF THE DISCOVERY OF ZINC DEFICIENCY

Keilin and Mann [53] reported in 1939 that carbonic anhydrase was a zinc-metalloenzyme. However, until early sixties only three other enzymes, carboxypeptidase, alcohol dehydrogenase and alkaline phosphatase, were recognized to require zinc for their activities [54]. Today we know of over 300 enzymes that require zinc for their structural stability or activity.

In our studies, we have observed that measurement of deoxoymidine kinase (TK) in rapidly regenerating tissue, 5’ectonucleotidase activity assay in lymphocytes and assay of neutrophil alkaline activity are sensitive indicators of zinc deficiency in humans [13].

Growth is the first limiting effect of zinc deficiency in experimental animals [55]. Zinc deficiency decreases circulating insulin-like growth factor 1 (IGF-1) concentration independent of total energy intake [55-58]. In humans, zinc deficiency decreases circulating IGF-1 concentration [56]. IGF-1 receptor possesses tyrosine kinase activity. On activation of the receptor by IGF-1 a cascade of phosphorylation occurs within the cell leading to regulation of cell cycle and cell division. Tyrosine phosphorylation of the receptor is essential for its activation and it’s my hypothesis that inasmuch as zinc is known to inhibit protein tyrosine phosphatases, [57,58] zinc deficiency will decrease the phosphorylation of tyrosine kinase of the IGF-1 receptor.

IGF-1 activation leads to stimulation of thymidine uptake in cells [56-58]. We have reported earlier that in zinc deficient rats and also in human, the activity of TK, an enzyme required for conversion of deoxoymidine to deoxoymidine 5’phosphate, a precursor of thymidine triphosphate (TTP), is considerably decreased in the implanted sponge connective tissue, and this leads to a decrease in DNA synthesis and protein, and collagen synthesis in rats [59].

Thus zinc has multiple roles in growth. It is required for IGF-1 generation, phosphorylation of IGF-1 receptor and upregulation of TK, all of which are essential for DNA synthesis and growth. Zinc is required for the gene expression of TK and TK is not a zinc containing enzyme [59].

ZINC AND IMMUNE CELLS

Zinc deficiency affects T helper subset 1 cell function adversely in humans [61,62]. Serum thymulin activity and generation of Th1 cell cytokines IL-2 and IFN-γ were affected adversely within 8-12 wk of institution of a zinc deficient diet in human volunteers, whereas, plasma zinc decreased only after 20 to 24 wk on zinc deficient diet, suggesting that immune functions are most sensitive to zinc restriction [52].

Zinc is a second messenger for immune cell and intracellular zinc is directly altered by an extracellular stimulus and the intracellular free zinc then participates in signaling events [61,62]. Hirano [61] showed that a decrease in free intracellular zinc is critical for LPS mediated CD4+ T cell activation by
dendritic cells (DCs). LPS binds to Toll-like receptor 4 on DCs and initiates Myd88 and TRIF mediated signaling [61]. TRIF-mediated signaling increases the ZnT-5 mRNA and decreases ZIP-6 mRNA thus resulting in a decrease in the free intracellular zinc in DCs. Reduction in free intracellular zinc increases surface expression of major histocompatibility complex class II molecules, which is required for the activation for CD4+ T cells [61].

Zinc is essential for T cell differentiation. Factors involved in this process are IFN-γ, IL-12 receptor β1, T-bet and STAT-4. Zinc is known to upregulate the mRNAs of all these factors [63].

Zinc is involved in development of monocytes/macrophages and it regulates phagocytosis and production of proinflammatory cytokines by these cells. LPS stimulation of zinc sufficient monocytes results in down regulation of inflammatory cytokines such as TNF-α, IL-1β IL-6 and IL-8 [64,65]. Zinc inhibits the membrane phosphodiesterase, leading to elevated levels of guanosine 3’-5’ cyclic monophosphate which is followed by subsequent suppression of the nuclear factor κB (NF-κB) and NF-κB dependent expression of mRNAs of TNF-α, IL-1β and other inflammatory cytokines [64,65]. Zinc also induces another A20 transcription factor which inhibits NF-κB signaling via TNF receptor associated factor pathways, resulting in down regulation of the mRNAs of inflammatory cytokines [48]. Based on these observations we propose that zinc is an effective anti-inflammatory agent.

Together O₂⁻, H₂O₂ and OH radicals are reactive oxygen species (ROS) and excessive generation of ROS causes oxidative stress. NADPH oxidase activation in monocytes-macrophages generates O₂⁻ (free radical) and zinc is an inhibitor of this enzyme. Superoxidismutase (both zinc and copper containing enzyme) generates H₂O₂ from free radicals. Generation of OH from H₂O₂ is catalyzed by Fe²⁺ and cu²⁺ and zinc effectively competes with both copper and iron ions, thus decreasing the generation of OH. Metallothionein, a zinc dependent protein is very effective in neutralizing OH. Thus zinc is an important antioxidant. We have reported earlier that zinc supplementation to elderly subjects, results in decreased oxidative stress marker, decreased generation of anti-inflammatory cytokines and improved cell mediated immunity resulting in decreased incidences of intercurrent infections.

The homeostasis of intracellular zinc concentration is very tightly regulated. We now know of 14 ZIP (SLC39A) and 10 ZNT (SLC30A) transporters which are involved in the homeostasis of intracellular zinc. The present estimate is that nearly 10 percent of the entire genome proteins contain zinc and there are over two thousand zinc dependent transcription factor that are involved in gene expression of various proteins [13]. Twenty years ago, it was considered improbable that zinc deficiency would affect any of the transcription factors adversely. We have, however, now reported that a few of the transcription factors are affected adversely. Examples of the zinc dependent transcription factors that are affected adversely due to zinc deficiency are NF-κB, AP-1, SP-1, A20, T-bet and STAT-4 [10].

In this brief article, I have reviewed the historical aspects of the discovery of zinc as an essential element for human health. Nutritional deficiency and conditioned deficiency of zinc is fairly common throughout the world. It is estimated by WHO that a nutritional deficiency of zinc may be affecting nearly two billion subjects, resulting in growth retardation, immune dysfunction, increased incidences of infection and mortality and cognitive functions impairment. Zinc therapy has reduced the mortality of children who developed diarrhea and millions of lives are being saved worldwide. Zinc therapy has been highly beneficial for patients with genetic disorders, Wilson’s disease, acrodermatitis enteropathica, and sickle cell disease. Zinc lozenges, if properly used, are effective in decreasing the duration and severity of common cold. Zinc supplementation to zinc deficient elderly subjects, not only corrects cell-mediated immunity but also decreases oxidative stress and down regulates generation of inflammatory cytokines. Zinc supplementation to patients with AMD, decreases the incidence of blindness and prevents advanced AMD in a significant proportion of the elderly population. Also, in a large study, it was shown that the mortality was decreased in AMD patients who received zinc and this decrease was due to a decreased adverse cardiovascular event. Clearly all these observations demonstrate the great impact and importance of zinc for human health.

Inasmuch as zinc is also an antioxidant and anti-inflammatory agent, I hypothesize that future studies are likely to show that zinc may show therapeutic benefits in the management of diabetes type 2, atherosclerosis, neuro-degenerative disorders, some cancers which are preceded by chronic inflammation and Alzheimer’s disease.

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