Impact of the Discovery of Human Zinc Deficiency on Health

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Abstract

The essentiality of zinc was recognized 46 years ago. Zinc deficiency resulting in growth retardation, hypogonadism, immune dysfunction and cognitive impairment affects nearly 2 billion subjects in the developing world. High phytate content of the cereal proteins consumed in the developing world, results in decreased availability of zinc for absorption. Zinc therapy has been very successful and life saving measure in patients with acrodermatitis enteropathica and Wilson's disease. Beneficial therapeutic responses of zinc supplementation have ovserved in acute diarrhea in children, chronic hepatitis C, shigellosis, leprosy, leishmaniasis, and common cold. Zinc supplementation was effective in decreasing incidences of infection in elderly and patients with sickle cell disease. Zinc supplementation was effective in preventing blindness in 25% of the elderly with dry type of age related macular degeneration. Zinc supplementation in the elderly decreased oxidative stress and decreased generation of inflammatory cytokines.

Zinc is an intracellular signaling molecule in monocytes, dendritic cells and macrophages and it plays an important role in cell-mediated immune functions and oxidative stress. Zinc is also an anti-inflammatory agent. These unique properties of zinc may have significant therapeutic benefits in several diseases in humans. In many diseases concurrent zinc deficiency may complicate the clinical features, affect adversely immunological status, increase oxidative stress and increase generation of inflammatory cytokines. Oxidative stress and chronic inflammation may play important causative roles in many chronic diseases, including atherosclerosis, several malignancies, neurological disorders, and auto-immune diseases. It is therefore, important that status of zinc is assessed and zinc deficiency corrected in these chronic diseases. A controlled clinical trial of zinc supplementation in these disorders in order to document the preventive and therapeutic effects of zinc is warranted.

zinc   immunity   growth   infection

• **Abbreviations**

TNF-α
  tumor necrosis factor alpha
IL-1β
  interleukin-1 beta
PHA
  phytohemagglutinim
IL-2
  interleukin-2
LPS
  lipopolysaccharide
NF-κB
  nuclear factor kappa B
SOD
  superoxide dismutase
NK cell
  natural killer cells

Key teaching points:

- This paper describes the discovery of zinc deficiency in humans.

- The clinical manifestations of zinc deficiency are summarized in this paper.

- The role of zinc therapy in growth retardation, acute infantile diarrhea in developing countries, zinc as an effective therapy for two genetic disorders, acrodermatitis enteropathica and Wilson's disease, and zinc as a preventive agent for blindness in patients with age related macular degeneration, have been described in detail in this manuscript.

- Zinc supplementation has been useful in many infections and this has been discussed in this manuscript.

- Mechanism of zinc action on immune cells has been briefly presented in this paper.

Introduction

It is truly a great honor for me to participate in the Festschrift honoring Dr. Stanley Wallach. In 1976, I was invited by Dr. Mildred Seelig to give a talk and receive the American College of Nutrition award in Montreal. This was my first introduction to the college. Dr. Seelig who was the life of the college, asked me to join the board. Later Stanley Wallach joined the board in 1982 and I worked with Stan very closely. We were completely relaxed and confident that as long as Mildred was the Executive Director, the college will continue to thrive. To my great surprise and disappointment, Mildred decided to step down, the year I was elected to be the President of the College. With great deal of effort and persuasion, we were able to recruit Stanley Wallach to be the Executive Director. Stan is truly a distinguished Physician Scientist. He is a member of the American Society of Clinical Investigation and Association of American Physicians and for many years I have enjoyed his company at the Association dinners. As you all know, his contributions to the college is truly immense and outstanding. I have truly enjoyed my friendship with Stan and I wish him many more years of good health and productivity. I am very pleased to contribute this article "Impact of the discovery of human zinc deficiency on health", honoring Dr. Wallach.

In this contribution I will present the historical aspects of the discovery of zinc deficiency in humans and its subsequent impact on human health.

Discovery of Human Zinc Deficiency

I went to Shiraz, Iran, in June 1958 after finishing my formal training in medicine at the University of Minnesota Medical School, Minneapolis, Minnesota, USA. Dr. Hobart A. Reimann, formerly from University of Minnesota, department of Medicine, invited me to join him to set up a curriculum for teaching medicine to students and house staff in Shiraz, Iran. In Shiraz, I met Dr. James, A. Halsted, who was a Fulbright Professor at Pahlevi University and was primarily involved with Saadi hospital an equivalent to city hospital in USA. I was on the staff at Nemaee Hospital, a private hospital where rich Iranian patients were treated. In the fall of 1958, Dr. Halsted asked me to discuss a patient with anemia at the medical center grand rounds at the Saadi Hospital.

The patient was a 21-y-old male, who looked like a 10-y-old boy. He had severe growth retardation, anemia, hypogonadism, hepatosplenomegaly, rough and dry skin, mental lethargy, and geophagia. The patient ate only bread made from unleavened wheat flour and his intake of animal protein was negligible. He consumed nearly 0.5 kg of clay daily. The habit of geophagia (clay eating) was common in the villages around Shiraz. We documented that the anemia was due to iron deficiency 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 discarded.

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

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 [1]. Zinc deficiency was known to cause growth retardation and testicular atrophy in animals. However, essentiality of zinc and its deficiency in humans was unknown. Because heavy metals may form insoluble complexes was phosphate, we considered that some factors responsible for decreased availability of iron in the patients with geophagia may also have decreased availability of zinc. Later it was observed that phytate (inositol hexaphosphate), which is present in cereal grains, markedly impaired the absorption of zinc.

We published a clinical description of the Iranian cases as syndrome in 1961 and speculated that zinc deficiency may account for growth retardation and male hypogonadism in these subjects [1]. I left Iran in January 1961 and subsequently joined the department of Biochemistry and Medicine at Vanderbilt University Nashville, Tenn. 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 may be prevalent and was responsible for widespread growth retardation. He was intrigued by this suggestion. I subsequently moved to Egypt and started my studies on zinc at the US Naval Medical Research Unit No. 3 (NAMRU-3), Cairo. In Egypt patients similar to the growth- retarded Iranian subjects were encountered. The clinical features were remarkably similar except that the Iranian patients had more pronounced hepatosplenomegaly, history of geophagia, and no hookworm infection and the Egyptian subjects had both schistosomiasis and hookworm infestations but no history of geophagia [2].

Based on decreased zinc concentrations in plasma, red cells, and hair and the studies with zinc- 65 that revealed, greater plasma zinc turnover, smaller 24-h exchangeable pool, and decreased excretion of zinc-65 in stool and urine in the dwarfs in comparison to the controls, we concluded that the dwarfs were zinc deficient [2]. Further studies in Egypt showed that the growth was nearly 5 to 6 inches per year in patients who received supplemental zinc and was much greater in comparison to those who received iron instead or those who ate only an adequate animal-protein diet. Pubic hair appeared in all subjects within 7–12 wk. after zinc supplementation. Genitalia increased to normal size and secondary sexual characteristics developed within 12–24 wk. in all patients receiving zinc. In contrast, no such changes were observed in the iron-supplemented group or in the group on an animal- protein diet. Thus, we concluded that the growth retardation and gonadal hypofunction in these subjects were due to zinc deficiency. The anemia responded to oral iron treatment. Our studies showed that anemia and iron deficiency were not causative factors for growth retardation

and hypogonadism in human subjects. Thus our studies showed for the first time that zinc was essential for humans and that its deficiency occurred in developing countries.

Zinc deficiency is common throughout the developing world. Clinical pictures similar to those reported in zinc-deficient dwarfs from Iran and Egypt have been observed in many other countries. Cognitive impairment has also been observed. Zinc deficiency is likely to be present in countries where primarily cereal proteins are consumed by the population. A detailed studies of zinc deficiency in geophagia cases and beneficial results of zinc supplementation on growth were reported from Turkey by Cavdar et al in 1983 [3].

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.

During the past four decades, a spectrum of clinical deficiency of zinc in human subjects has emerged. 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 [4]. A severe deficiency of zinc has been reported to occur in patients with acrodermatitis enteropathica (a genetic disorder), following TPN (total parenteral nutrition) without zinc, following excessive use of alcohol, and following penicillamine therapy. 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.

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.

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, deceased NK cell activity, decreased IL-2 generation from T helper cells, decreased thymulin activity, hyperammonemia, hypogeusia, decreased dark adaptation, and decreased lean body mass were observed [4,5,6]. It is therefore clear that a mild deficiency of zinc in humans affects clinical, biochemical, and immunological functions adversely.

Several studies have nowconfirmed that zinc deficiency in the developing countries is fairly prevalent, affecting nearly two billion subjects and that growth retardation commonly observed in these countries may indeed be due to zinc deficiency [7]. During my stay in the Middle East, I never saw a zinc deficient dwarf who was older than 25 y. On further enquiry it appeared that most of the deaths were due to bacterial, viral or parasitic infections suggesting that zinc deficiency may have affected the immune functions adversely. We could not carry out immunological studies because of lack of facilities in the Middle East.

During the past two decades, we have investigated the role of zinc on immune cells extensively and I will briefly present our current knowledge in this area.

Zinc and Immunity

Zinc affects may aspects of the immune system [8,9]. Zinc is essential for cell-mediated innate immunity, phagocytosis and for function of neutrophils, natural killer cells and macrophages. Zinc deficiency affects adversely the growth of T and B cells and apoptosis is potentiated by zinc deficiency.

In young adult zinc deficient mice, thymic atrophy, decrease in absolute number of splenocytes, and decreased responses to both T-cell dependent (TD) and T cell independent (T1) antigens have been observed [10,11]. Animals maintained on a zinc deficient diet for as little as 2 weeks developed a severe impairment in their ability to generate a cytotoxic T killer response to the tumor challenge [12].

Immune Functions In Experimental Model Of Human Zinc Deficiency

We induced in humans a mild deficiency of zinc by restricting daily dietary zinc intake to 3–5 mg daily. The serum thymulin activity (a zinc dependent thymic hormone) was decreased within twelve weeks of zinc restricted diet. As a result of mild deficiency of zinc, decreased T4+ to T8+ ratio, decreased IL-2 generation and decreased NK cell lytic activity were observed in mildly zinc deficient subjects [5]. These changes were corrected after zinc supplementation. In the experimental human model of zinc deficiency, the generation of INF-γ was decreased but the production of Th$_2$ cytokines IL-4, IL-6 and IL-10 were not affected due to zinc deficiency [6]. IFN-γ is known to down-regulate Th$_2$ clone and IL-10 may down regulate Th$_1$ clone. IFN-γ is also a major component of Th$_1$ response panel, and it upregulates major histo-compatibility complex class 1 antigen expression. Thus, our data in human experimental model showed that the cell-mediated immune dysfunctions in human zinc deficiency may be due to an imbalance between Th$_1$ and Th$_2$ cell functions. Table 1 summarizes our data in the experimental model of human zinc deficiency.

View this table: In this window In a new window	**Table 1** Effect of Zinc Deficiency on Immune Functions in Experimental Human Models

Therapeutic Effects Of Zinc Supplementation In Humans

Several studies have now shown the benefits of zinc supplementation in humans.

Viral Infections

Our placebo-controlled trial of zinc lozenges for the treatment of common cold has been recently published [13]. Compared with the placebo group, the zinc group had a shorter mean overall duration of cold (4.0 vs 7.1 d, p<.0001). Blinding of subjects was adequate. Symptoms severity scores were decreased significantly in the zinc group. Plasma sIL-1ra and ICAM-1 levels decreased significantly in the zinc group.

sIL-1ra is an anti-inflammatory cytokine which functions as a specific inhibitor of IL-1α and IL-1β inflammatory cytokines. In zinc supplemented group sIL-1ra decreased, suggesting that overall inflammation was decreased in this group. Plasma ICAM-1 was also decreased in zinc treated subjects. Human rhinovirus type 14 "docks" with ICAM-1 on the surface of somatic cells. Thus, zinc may in effect act as an antiviral agent by reducing ICAM-1 levels. Another possibility is that zinc ions may form a complex with ICAM-1, preventing the binding of rhinovirus to cells.

The effect of zinc lozenges on the duration or severity of common cold symptoms has been examined in at least 14 other studies since 1984. No effect of zinc was demonstrated in a few trials. They were criticized for having inadequate sample sizes or for using inadequate doses of zinc or formulations that reduced the release of zinc ions from the lozenges. Zinc acetate and gluconate are suitable salts, inasmuch as zinc ions are released at physiological pH. Several zinc lozenges use glycine or citrate as ligands which prevent release of zinc ions and therefore, are not effective in curing common cold. Two other factors are also important in these trials. One is that zinc lozenges must be started within 24 h of the onset of common cold and the other is that daily total dose of elemental zinc should be at least 75 mg.

Infection with the human immunodeficiency virus (HIV) results in the acquired immune deficiency syndrome (AIDS), a disease where zinc supplementation was used as a supporting therapeutic intervention [14,15]. The initial study found an increase in HLA.DR positive cells, a stimulation of lymphocytic transformation by PHA and concavalin A, and augmented phagocytosis by polymorphonuclear neutrophils [15]. Mocchegiani et al [16] showed an increase in the number of Th cells and a reduced frequency of opportunistic infections with Pneumocystis firoveci and candida.

The results of zinc supplementation in AIDS are very variable [17,18]. The explanation for the contradictory reports may be that only zinc deficient patients would respond to zinc supplementation and zinc sufficient patients may not exhibit any beneficial effects. Inasmuch as zinc is essential for immune functions, those patients of AIDS who are zinc deficient should receive zinc in order to correct their zinc status. Obviously many more studies are needed in this important area.

Several studies have investigated the effect of zinc supplementation on hepatitis C. After zinc treatment, decreases in the incidence of gastro-intestinal disturbances, body weight loss, and mild anemia were found in patients with chronic hepatitis C [19,20]. Zinc in combination with IFN-α was more effective against chronic hepatitis C than IFN-α alone [20]. It's also possible that since zinc is also an antioxidant this may have benefited a few cases of hepatitis. Zinc may also be able to inhibit herpes simplex virus [21] and rhinoviruses [22]. The in vitro relevance of an inhibition of viral replication as a mechanism for antiviral actions of zinc in humans remains to be determined.

Bacterial Infections

Zinc can reduce the duration, severity and incidence of diarrhea in children in the developing countries [23,24,25]. The combined results of seven trials of continuous zinc supplementation confirmed that zinc significantly reduced the incidence of prevalence of diarrhea. A recent report, however, shows that this may not be the case for infants younger than six months of age [26]. Correction of zinc deficiency improves the absorption of water and electrolytes by the intestine, leads to a faster regeneration of the gut epithelium and increases the levels of enterocyte brush-border enzymes [24,27]. Finally loss of zinc contributes to immune dysfunction which is corrected by zinc supplementation. Several reports have shown beneficial effects of zinc in treatment of shigellosis [28,29]. Most of these effects are mediated by a modulation of immune function.

Zinc supplementation to leprosy patients has shown beneficial effects [30,31]. One study found a reduction in the required dose of clofazimine, a withdrawal of primarily essential steroids, and an improved toleration of dapsone after zinc treatment. They also observed a reduced incidence and severity of erythema nodosum leprosum, a gradual decrease in the size of granuloma and a gradual increase in the number of lymphocytes [30–32]. Zinc supplementation to patients with Mycobacterium tuberculosis, showed an increase in plasma retinol concentration, earlier sputum conversion, and resolution of x-ray lesions [33]. Effective clearance of Mycobacterial infections requires a Th$_1$ mediated activation of infected macrophages by IFN-γ. Zinc acts by inducing T cell activation or alteration of lymphokine production, which in turn may activate macrophages to promote bacterial clearance [34]. In humans, zinc deficiency is characterized by a reduction of IL-2 and IFN-γ and zinc induces the generation of both IL-2 and IFN-γ [5,6].

Zinc may be an effective adjunct therapy for the treatment and eradication of H-pylori infection. Treatment with polaprezinc (zinc-L-carnosine), which is used as an anti-ulcer drug in Japan, leads to an improved cure rate when administered together with antimicrobial triple therapy [35].

Parasitic Infections

Patients with cutaneous, mucosal and visceral leischmaniasis have lower plasma zinc levels [8]. Zinc supplementation results in a decrease in erythemas and size of induration and an increase in cure rate.

Effect of Zinc on Vaccination

In a study which investigated whether micronutrients supplementation had any effect on the vibriocidal antibody response in children to a killed oral cholera vaccine, only zinc supplementation improved sero conversion to vibriocidal antibody, and hence, has the potential to improve the efficacy of oral cholera vaccine in children [8].

Preventive Effects Of Zinc Supplementation

Elderly Subjects

A randomized double-blind, placebo-controlled trial of zinc supplementation (45 mg elemental zinc/d) was conducted in elderly subjects ages 55–87 y for 12 mo.[36]. The incidence of infections and ex vivo generation of TNF-α and plasma oxidative stress markers were significantly lower in the zinc supplemented than in the placebo group. Plasma zinc and PHA induced IL-2 mRNA in isolated mononuclear cells (MNC) were significantly higher in the zinc-supplemented than in the placebo group. This study demonstrated the beneficial effect of zinc supplementation on cell mediated immunity, oxidative stress markers and inflammatory cytokines in the elderly.

Sickle Cell Disease (SCD) Patients

A randomized double-blind, placebo-controlled trial of zinc supplementation was carried out in patients with SCD [37]. The zinc group received 25 mg elemental zinc (as acetate) three times a day for three months. The other group received placebo.

A decreased incidence of infection in the zinc supplemented group was observed in comparison to the placebo group. After zinc supplementation, plasma zinc and antioxidant power increased; plasma nitrite and nitrate (NOx), lipid peroxidation products, DNA oxidation products, and soluble vascular cell adhesion molecule-1 (VCAM-1) decreased compared to the placebo group. Significant decreases in LPS induced TNF-α and IL-1β mRNAs, and TNF-α induced NF-κB-DNA binding in MNC were observed in zinc group compared with the placebo group. Ex vivo addition of zinc to MNC isolated from the placebo subjects decreased TNF-α and IL-1β mRNAs. Zinc supplementation also increased relative levels of IL-2 and IL-2Rα mRNAs in PHA stimulated MNC. The beneficial effects of zinc supplementation included prevention of infections in SCD subjects, improvement in generation of Th$_1$ cytokines, and decrease in oxidative stress and generation of inflammatory cytokines.

In a study by the National Eye Institute, NIH, it was reported that zinc and antioxidants (vitamin C, Vitamin E and beta carotene) significantly reduced the odds of developing advanced age related macular degeneration (AMD) of dry type and prevented blindness in the high-risk group of elderly subject [38,39]. Zinc alone had similar effect and prevented blindness in 25% of the elderly. These subjects received 80 mg zinc daily as oxide and in order to prevent copper deficiency due to high dosage of zinc, also 2 mg of copper a day was administered. One may hypothesize that zinc reduced the oxidative stress and was thus beneficial in AMD. Also interestingly the zinc supplemented group showed increased longevity [39]. The risk of mortality was reduced by 27% in participants of the Age-Related Eye disease Study (AREDS) (aged 55–81 y) who received high dose zinc (80 mg/d as oxide) during median follow-up of 6.5 years [39].
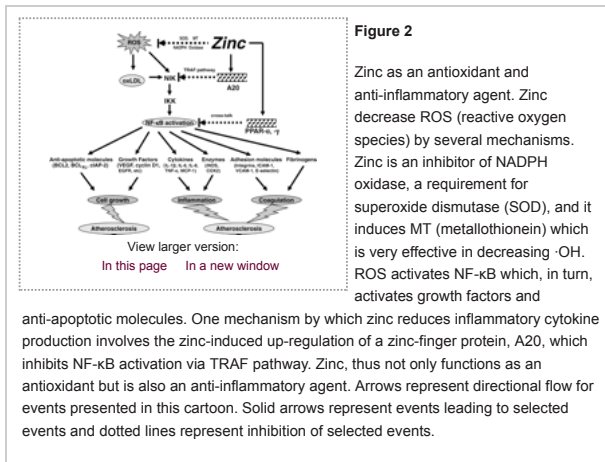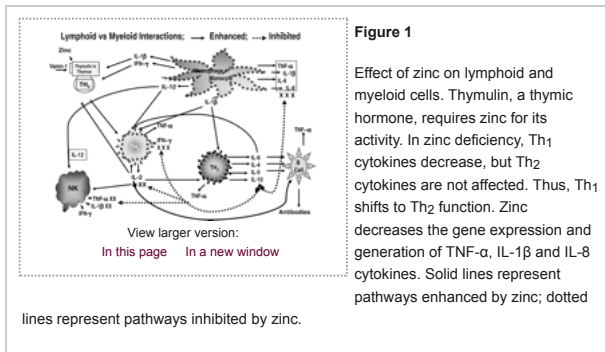
A seven month randomized double blind, placebo-controlled trial was conducted in 40 military cadets to evaluate the effectiveness of zinc (15 mg zinc as gluconate orally daily) in reducing the risk of upper respiratory tract infections [40]. Self reported symptoms as were recorded by a weekly website survey. The zinc supplemented group experienced significantly more symptom free intervals than those in the placebo group (p=0.01). No significant differences were found between the two groups who consulted physician for their cold symptoms. Although the study was suggestive that zinc may have decreased the incidence of upper respiratory tract infections in the cadets, it was not conclusive. A trial with higher levels of zinc supplementation is warranted. We have used 45 mg zinc (as acetate) supplementation in the elderly for one year with excellent outcome [36] and no copper deficiency was observed. We recommend daily intake of 2 mg copper, which is RDA for copper for prevention of copper deficiency in subjects who are taking zinc supplementation above 50 mg daily.

A recent observational study showed, that 29% of nursing home residents have low serum zinc levels (<70 µg/dl) despite supplementation with 7 mg/d of zinc (as sulfate) over a period of one year [41]. All-cause mortality was 39% lower in those with normal (≥ 70 µg/dl) versus low (≤ 70 µg/dl) pre-intervention or baseline serum zinc concentrations (p=0.049). These findings suggest that zinc may play a crucial role in influencing all-cause mortality in the elderly. In the observational study, subjects with normal post-intervention or final serum zinc concentrations had lower incidence of pneumonia, reduced total antiobiotic use (by almost 50%), and shorter duration of pneumonia and antibiotic use (all p values ≤ 0.004) relative to those with low serum zinc concentrations.

Mechanism Of Zinc Effects On Immune Cells

Figs. 1 and 2 summarize the effects of zinc on cell mediated immunity, and define its role as an antioxidant and anti-inflammatory agent [6]. Fig. 1 shows the landscape of zinc action on immune cells. Zinc is an essential component of thymulin, a thymic hormone involved in maturation and differentiation of T-cells. The gene expressions of IL-2 and IFN-γ, (Th$_1$ cytokines) are zinc dependent. IL-2 is involved in the activation of NK and T cytolytic cells. IL-12 is generated by

stimulated macrophages-monocytes and is zinc dependent and IFN-γ and IL-12 together play a major role in the killing of parasites, viruses, and bacteria by macrophages-monocytes. Th2 cytokines are not affected by zinc deficiency except for IL-10 production which is increased in the zinc deficient elderly subjects. This was corrected by zinc supplementation. Increased IL-10 affects adversely Th1 and macrophage functions.

Figure 1

Effect of zinc on lymphoid and myeloid cells. Thymulin, a thymic hormone, requires zinc for its activity. In zinc deficiency, Th1 cytokines decrease, but Th2 cytokines are not affected. Thus, Th1 shifts to Th2 function. Zinc decreases the gene expression and generation of TNF-α, IL-1β and IL-8 cytokines. Solid lines represent pathways enhanced by zinc; dotted lines represent pathways inhibited by zinc.

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Figure 2

Zinc as an antioxidant and anti-inflammatory agent. Zinc decrease ROS (reactive oxygen species) by several mechanisms. Zinc is an inhibitor of NADPH oxidase, a requirement for superoxide dismutase (SOD), and it induces MT (metallothionein) which is very effective in decreasing ·OH. ROS activates NF-κB which, in turn, activates growth factors and anti-apoptotic molecules. One mechanism by which zinc reduces inflammatory cytokine production involves the zinc-induced up-regulation of a zinc-finger protein, A20, which inhibits NF-κB activation via TRAF pathway. Zinc, thus not only functions as an antioxidant but is also an anti-inflammatory agent. Arrows represent directional flow for events presented in this cartoon. Solid arrows represent events leading to selected events and dotted lines represent inhibition of selected events.

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Zinc is an intracellular signaling molecule in monocytes, dendritic cells and macrophages [42,43]. Fig. 2 summarizes our concept regarding the role of zinc as an antioxidant and anti-inflammatory agent. ROS is known to activate NF-κB. Zinc decreases ROS generation. NADPH oxidase is inhibited by zinc and SOD is both zinc and copper containing enzyme. SOD is known to decrease oxidative stress. Metallo-thionein (MT) is induced by zinc and MT which contains 26 moles of cysteine per mole of protein decreases ·OH burden. Zinc via A20 inhibits NF-κB activation and this results in a decrease in generation of inflammatory cytokines and adhesion molecules. This Figure also shows that zinc may have a preventive role in some cancers such as colon and prostate and in atherosclerosis inasmuch as chronic inflammation has been implicated in the development of these disorders.

Treatment of Acrodermatitis Enteropathica with zinc

Acrodermatitis enteropathica is a relatively rare genetic disorder in which the absorption of dietary zinc is affected adversely such that the affected individuals become severely zinc deficient. If untreated, the disease becomes fatal. Mutation in the ZIP4 gene (a zinc transporter) is responsible for this disorder. Treatment with therapeutic levels of zinc is highly successful and now these patients survive and lead a normal life [4].

Treatment of Wilson's Disease with Zinc

Wilson's disease is a genetic disorder in which copper accumulates in liver, kidneys, intestines, brain, and other organs. Several years ago, we observed beneficial effect of zinc on sickling of deoxygenated sickle cell [4] and this led to zinc administration in therapeutic doses (50 to 150 mg zinc as acetate daily orally) to treat sickle cell disease patients in order to decrease the vasoocclusive pain crises. We observed that at this level of zinc administration, we induced copper deficiency in our patients [4]. This led us to evaluate zinc as a therapeutic modality for the treatment of Wilson's disease [4]. Zinc acts by induction of intestinal cell metallothionein which once induced, has a high affinity for copper and prevents the serosal transfer of copper into the blood. The intestinal cells turn over rapidly and take the complexed copper into the stool where it is excreted. Zinc blocks food copper and endogenously excreted copper via salivary, gastric and other gastrointestinal juices. As a result, zinc produces a chronic negative copper balance [4]. For maintenance therapy of Wilson's disease, zinc is the treatment of choice. Zinc has not toxic effects and it can be used successfully for treatment of pre-symptomatic patients and pregnant women.

Conclusion

Zinc deficiency as manifested by growth retardation, immune dysfunction and cognitive impairment, is widespread in the developing countries and may affect nearly 2 billion subject's world wide. A correction of this deficiency will truly have a great impact on human health in the world. Zinc has been used therapeutically with great success for two fatal genetic disorders, acrodermatitis enteropathica and Wilson's disease. Zinc is essential for cell-mediated immunity and it has been used successfully for treatment of acute infantile diarrhea, common cold, several bacterial infections and zinc is effective in decreasing the incidences of infection in the elderly and sickle cell disease patients. Zinc has been observed to prevent blindness in 25% of the patients with dry type of age related macular degeneration and decreased mortality in 27% of participants in age related eye disease study (AREDS) conducted by NIH during a median follow up of 6.5 years. Zinc is an antioxidant and also an anti-inflammatory agent. Inasmuch as oxidative stress and chronic inflammation have been implicated in many chronic diseases in human, a controlled trial of zinc supplementation in these disorders is required.

Acknowledgments

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