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The Relevance of Zinc in Human Health

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ABSTRACT

Zinc is an essential micronutrient for human health. In spite of the proven benefits of adequate zinc nutrition, approximately 2 billion people still remain at risk of zinc deficiency. Zinc is found as component of more than 300 enzymes and hormones and plays a crucial part in the health of our skin, teeth, bones, hair, nails, muscles, nerves and brain function as well as it is essential for growth. Zinc controls the enzymes that operate and renew the cells in our bodies. The formation of DNA, the basis of all life on our planet, would not be possible without zinc. After the discovery of zinc deficiency in the 1960s, it soon became clear that zinc is essential for the function of the immune system. Zinc ions are involved in regulating intracellular signaling pathways in innate and adaptive immune cells. Zinc homeostasis is largely controlled via the expression and action of zinc "importers" (ZIP 1–14), zinc "exporters" (ZnT 1–10), and zinc-binding proteins. Anti-inflammatory and anti-oxidant properties of zinc have long been documented, however, underlying mechanisms are still not entirely clear. Zinc deficiency is an important public health problem, affecting large number of women and children in India and worldwide. Zinc deficiency is the fifth leading risk factor for disease in the developing world. In this review, we take a holistic look at iron, their metabolism and importance for human health.
Keywords: Zinc, Human health, Zinc deficiency, Immunity, Trace element.

INTRODUCTION

Zinc is a essential trace elements for all forms of life. The significance of zinc in human nutrition and public health was recognized relatively recently. Zinc insufficiently has been recognized by a number of experts as an important public health issue, especially in developing countries. The prevalence and clinical consequences of zinc deficiency on growth delay, diarrhoea, pneumonia, disturbed neuropsychological performance and abnormalities of fetal development. Zinc is such a critical element in human health that even a small deficiency is a disaster. Zinc supplementation is a powerful therapeutic tool in managing a long list of illnesses. Zinc, an essential trace mineral, is required for the metabolic activity of 300 of the body's enzymes, and is considered essential for cell division and the synthesis of DNA and protein. These enzymes are involved with the metabolism of protein, carbohydrate, fat and alcohol. Zinc is also critical to tissue growth, wound healing, taste acuity, connective tissue growth and maintenance, immune system function, prostaglandin production, bone mineralization, proper thyroid function, blood clotting, cognitive functions, fetal growth and sperm production.

The distribution of zinc in the human body and its physiological function is multi-faceted. For example, it can promote protein synthesis and manufacture of insulin; maintenance of cells and enzyme systems to work; the composition of a variety of enzymes, and helps to enhance the activity of a variety of enzymes, synthetic DNA; regulating body fluid pH; promote the formation of collagen to make hair, skin, nails and other healthy growth; help to enhance memory and improve mental, especially for fetal brain development has an important role; to maintain the normal function of the prostate [1]. There are

experiments which show that zinc testosterone secretion in animals has important implications. The lack of zinc in the human body partial eclipse will appear in anorexia, loss of appetite, smell and taste failure and other symptoms; causing decreased immune system, triggering the disease arteriosclerosis and anemia [2].

In pregnant women, the lack of zinc may lead to fetal brain cells decreases, and affect their mental development. Children's lack of zinc will hinder their normal growth and development, detrimental to intellectual development and reproductive system health. In adult males, zinc-deficiency may lead to prostatic hyperplasia, reducing the reproductive function of the system and affect fertility; and so on.

Zinc metabolism

Zinc is absorbed into the body through the small intestine, which also regulates whole-body homeostasis through changes in both the fractional absorption of dietary zinc and excretion of endogenous zinc in pancreatic juice and other gastrointestinal secretions [3] [4]. Some zinc is also lost from the body through urine, menstrual flow, semen, and sloughed skin, nails, and hair, although quantitatively these other routes of zinc loss are relatively small compared with gastrointestinal excretion [5]. As with intestinal excretion, the urinary elimination of zinc can be affected by zinc status [6], although this effect is less consistent and may only occur with more severe or prolonged dietary restriction. Fecal zinc excretion is also increased during diarrhea [7], which may contribute to zinc deficiency in areas with high rates of enteric infections.

The total body zinc content of adult humans ranges from about 1.5 to 2.5 g, most of which is found intracellularly, primarily in muscle, bone, liver, and other organs [8]. Approximately 90% of the body's zinc reserves turn over slowly and are therefore not readily available for metabolism. The remaining zinc comprises the so-called rapidly exchangeable pool of zinc, which is thought to be particularly important for maintaining zinc-dependent functions of human biological systems. The rapidly exchangeable zinc can move into and out of the plasma compartment within a period of about three days. The size of this pool is sensitive to the amounts of zinc absorbed from the diet, and a reasonably constant dietary supply is thought to be necessary to satisfy the normal requirements of zinc for maintenance and growth.

Less than 0.2% of the total body zinc content circulates in plasma, which has a mean concentration of approximately 15 μmol/L (about 100 μg/dl). Zinc is transported in plasma bound to albumin and, to a lesser extent, α2-macroglobulin and oligopeptides [9]. Because the concentration of zinc in tissues, such as muscle and liver, is approximately 50 times greater than that in plasma, small differences in uptake or release of zinc from these peripheral sites can have a profound effect on the plasma zinc concentration. For these reasons, plasma zinc concentrations do not indicate total body zinc stores reliably under all circumstances in individual subjects. For example, release of zinc from muscle tissue that is catabolized during starvation can result in transient, seemingly paradoxical, elevations in plasma zinc [10].

In contrast, consumption of standard meals, or glucose alone, induces a postprandial reduction in plasma zinc concentration, even though dietary zinc intake and tissue reserves may be adequate [11]. Other factors that influence plasma zinc concentration are hypoalbuminemia, which influences absorption and transport of zinc [10]; intestinal diseases that interfere with zinc absorption [12]; pregnancy [13]; infection [14] [15]; and other forms of stress, such as tissue injury imposed by surgery [16] and strenuous physical exercise [17].

Immune Function During Zinc Deficiency

The importance of zinc for proper immune function is best observed in zinc-deficient individuals. Zinc deficiency has been known for 50 years [18] and is associated with skin abnormalities,

hypogonadism, cognitive impairment, growth retardation, and imbalanced immune reactions which favor allergies and autoimmune diseases [19]. In the case of inherited malfunction of zinc homeostasis, as seen in Acrodermatitis Enteropathica, zinc deficiency can be lethal [20].

Zinc deficiency can be classified by severity and is divided into severe or marginal zinc deficiency, respectively. Severe zinc deficiency is often observed because of malfunction of zinc uptake in the intestine. This is reported in patients suffering from chronic diarrhea, patients being treated with penicillamine, patients receiving parenteral nutrition without zinc, or following excessive alcohol consumption [21]. Patients present clinical symptoms such as lymphopenia, decreased ratios of T helper (Th) cells to cytotoxic T cells, decreased natural killer (NK) cell activity, and increased monocyte cytotoxicity. The most severe form of zinc deficiency observed in Acrodermatitis Enteropathica. This zinc malabsorption syndrome is inherited as an autosomal recessive condition and is due to a mutation of the intestinal zinc uptake protein ZIP4 [22]. Acrodermatitis Enteropathica is characterized mainly by diarrhea, weight loss, recurrent viral and bacterial infections, dermatitis, hair loss, and neuropsychological disturbances [23]. However, all observed symptoms can be corrected by high dose (1 mg/kg) zinc supplementation [24].

Marginal zinc deficiency is characterized by slight weight loss, rough skin, oligospermia, and hyperammonemia [25]. It is probably caused by nutritional zinc deficiency, often seen in vegetarians or vegans, due to the consumption of high levels of zinc-chelating agents in food originating from cereals, legumes, or plant parts. In these foods, lignin and phytates counteract zinc absorption by binding zinc and reducing its bioavailability [26] [27]. Nutritionally related marginal zinc deficiency is prevalent in the elderly population. Hence, a correlation between impaired immune function and zinc status is likely in older people [28]. Within the seventh decade of life, the human immune system undergoes dramatic age-related changes, termed “immunosenescence”. Associated with this condition is an increased incidence of inflammatory disease, most notably cardiovascular diseases, whereas the immunological response to vaccines is typically impaired [29].

The overall frequency of zinc deficiency worldwide is estimated to be higher than 20% [30]. Interestingly, zinc supplementation is already widely practiced and approved for clinical treatment of multiple diseases. Zinc has proven to be very effective for the treatment of pediatric diarrhea, saving millions of children’s lives in developing countries such as India [31]. The Food and Drug Administration (FDA) approved zinc supplementation for the treatment of Wilson’s disease, a genetic disorder in which copper builds up in the human body [32]. In the elderly population, age-related macular degeneration (AMD) is of frequent occurrence and AMD progress, which can result in blindness, can be treated successfully by zinc supplementation [33].

Furthermore, not only the very young or elderly benefit from zinc supplementation, as shown by studies with patients suffering from: (1) viral infections, e.g., the common cold, diarrhea, chronic hepatitis C, or human immunodeficiency virus (HIV); (2) bacterial infections such as shigellosis or Helicobacter pylori; (3) parasitic infestations such as acute cutaneous leishmaniosis or malaria; (4) autoimmune diseases such as Type 1 Diabetes Mellitus (T1DM) and Rheumatoid Arthritis; and (5) transplant rejections [34]. This widespread variety of clinical manifestations makes zinc deficiency a serious nutritional problem. However, to date, no reliable biomarker to assess zinc status exists. Thus, zinc deficiency is difficult to diagnose.

Overall, zinc contributes to the overall regulation of immune cell function, influencing several signaling pathways. Hereby, zinc acts in a direct manner by binding reversibly to regulatory sites in signaling proteins, or indirectly by

influencing enzymes such as phosphatases which are a component of and regulate signaling pathways [5]. Zinc homeostasis is essential for multiple aspects of the immune system including hematopoiesis, cell maturation and cell differentiation, cell cycle progression, and for the proper function of immune-cells [17]. During inflammation, adequate zinc status is essential since in acute phase responses zinc is transiently transferred from serum into organs, especially the liver, causing transient serum hypozincemia. This transient loss of serum zinc is eventually rebalanced during resolution of the inflammatory response. Here, zinc is probably released from tissue into serum. One proposed reason for this complex mechanism is to act as a danger signal for immune cells [9].

Since extracellular microorganisms are also dependent on zinc availability, zinc sequestration by the human immune system helps to combat invading pathogens. This is facilitated due to expression of pro-inflammatory acute phase proteins including interleukin (IL)-6, which upregulates expression of zinc binding peptides such as MTs and A2M [15]. In immune cells, on the one hand, increased intracellular zinc levels can intoxicate engulfed pathogens and act cytoprotectively by neutralizing reactive oxygen species (ROS) and nitrogen species (RNS). In general, zinc homeostasis and zinc signals are crucial to counteract inflammatory diseases, and the correlation of undernourishment with severe inflammatory diseases is accompanied by prolonged and severe forms of serum hypozincemia.

In the literature, it has been suggested that hypozincemia goes along with elevated inflammatory mediators, e.g., ROS, and antimicrobial peptides such as calprotectin or matrix metalloproteases (MMP), causing tissue injury, especially in liver, lung, and spleen [18]]. In general, cellular function, such as the intracellular killing of harmful pathogens, cytokine production as well as ROS production, are dependent on zinc and are impaired due to zinc deficiency. Zinc deficiency also adversely affects the maturation and function of T and B cells, which occurs through dysregulation of basic biological functions at the cellular level.

For T cells, a disturbed ratio of Th1 and Th2 cells in favor of Th2-driven allergic reactions is a well-known consequence of zinc deficiency [5]. Zinc flux and homeostatic zinc signals, as defined below, are highly important for adequate T cell differentiation, and this observed malfunction can be reversed by zinc supplementation. Moreover, the pro-tolerogenic immuno-reaction is triggered by long-lasting changes in intracellular zinc levels due to induction of regulatory T cells (Treg) cells and dampening of pro-inflammatory Th17 and Th9 cells. T cell development is strongly dependent on DC activation. Interestingly, zinc signals were recently shown to induce a tolerogenic DC phenotype in vitro and in vivo. Herein, zinc suppressed MHC-II expression and enhanced programmed cell death 1 ligand 1 (PD-L1) and PD-L2 expression resulting in the manipulation of the Treg/Th17 balance in favor of Treg cell development. Moreover, on the molecular level, zinc inhibits the IL-6-induced STAT3 signaling cascade essential for Th17 development. Another potential target of zinc-mediated Th17 manipulation might be found on the epigenetic level since several epigenetic enzymes as (de-)acetylases, and (de-) methylases are regulated in a zinc dependent manner. A malfunctioning adaptive immune system has been observed in the elderly population, whereby secretion of pro-inflammatory IL-6 is pathologically elevated, while T cell activation was reduced, as were responses to stimulation or vaccination. Interestingly, all these pathologies can be improved due to zinc supplementation, highlighting the significance of zinc for a well-balanced immunoreaction.

Regarding innate immunity, zinc deficiency leads to prioritization of maturation of innate immune cells such as monocytes. In this case, differentiation was promoted by the reduction in the concentration of intracellular free zinc. This was facilitated by induced expression of the zinc-binding

heterodimeric protein calprotectin. In general, calprotectin was also highly expressed in neutrophils. Recently, zinc deficiency has been shown to negatively influence critical neutrophil functions such as phagocytosis, oxidative burst, degranulation, cytokine production, chemotaxis, and neutrophil extracellular trap (NET) formation. These observations are in line with an impaired ROS production during zinc deficiency, which is needed for NET formation, and for intracellular killing of phagocytosed pathogens by neutrophils.

Besides cellular immune responses, zinc is also indispensable for proper RNA transcription, DNA synthesis, as well as cell survival. In relation to cell survival and apoptosis, adequate intracellular zinc levels are needed because apoptosis is triggered by zinc deficiency. Furthermore, cytokine function and secretion are adversely affected by zinc deficiency impairing

the function of the basic messengers of the immune system. Thus, zinc is crucial for the appropriate development and function of the whole immune system including innate as well as adaptive immunity, and the affected signaling cascades and networks are described in detail below.

Zinc and Health Benefits

Zinc plays a vital role in the maintenance of immune functions, including cellular and humoral immunity and zinc deficiency affects multiple aspects of innate and adaptive immunity. Changes in the intracellular concentration of free zinc control immune cell signal transduction by regulating the activity of major signalling molecules including kinases, phosphatases and transcription factors. Zinc deficiency is associated with profound impairement of cell-mediated immunity. Delayed lymphocyte stimulation response, decreased CD4+: CD8+ cells and decreased chemotaxis of phagocytes occur. Thymus atrophy also occurs and activity of serum thymulin – a thymus specific zinc dependent hormone involved in T cell functions is decreased. A mild deficiency of zinc causes an imbalance between T Helper1 and T Helper2 cell functions.

Production of T Helper1cytokines, in particular IFN-γ, IL-2 and tumor necrosis factor (TNF)-α are reduced, whereas production of the T Helper 2 cytokines IL-4, IL-6 and IL-10 are not affected. Lytic activity of natural killer (NK) cells and cytolytic T cells are also decreased. Zinc deficiency reduces circulating luteinizing hormone and testosterone concentrations, alters hepatic steroid metabolism, and modifies sex steroid hormone receptor levels, thereby causing male reproductive dysfunction. Zinc is necessary to maintain normal serum testosterone. Inadequate zinc levels prevent the pituitary gland from releasing luteinizing and follicle stimulating hormones, which stimulate testosterone production. Zinc also inhibits the aromatase enzyme that converts testosterone into excess estrogen. The testosterone to estrogen ratio in men declines with aging from about 50:1 to even as low as 10:1. Higher estrogen activity results in increased risk of heart disease, weight gain, and obesity. One reason for the progressive weight gain with age is that fat cells contain aromatase. More fat cells mean more estrogen which means more fat deposition. This is further aggravated by alcohol consumption, which lowers zinc and increases estrogen and so magnifies the problem. In addition to the impact on hormone levels, zinc also has been proven to help the body produce healthier sperm by increasing sperm count and motility. Zinc deficiency has been found to have a severe impact on the prostate gland. Zinc deficiency predisposes the prostate to infection (prostatis) which may lead to enlargement of the prostate gland (prostatic hypertrophy)(3).

Zinc as an antioxidant Zinc stabilises cytosolic Zinc/Cu superoxide dismutase which catalyses superoxide removal by virtue of zinc –histidyl-Cu triad acting as a proton donor during the oxidation cycle. It also inhibits the enzyme NADPH oxidases which catalyse the production of superoxide O2- from O2. Cytotoxic cytokines TNF- α, IL-1β and IL-8 which generate free radicals are also inhibited

by Zinc. The production of cysteine- rich metallothionein, an excellent scavenger of hydroxyl (OH-) radical is also induced by zinc.

Zinc and central nervous system In Alzheimer's disease abnormal excessive interaction of beta-amyloid 42 (Aβ42) with copper, zinc and iron induce peptide aggregation and oxidation resulting in neocortical Aβ precipitation(11). Zinc being an antagonist of the glutamate N-methyl-D-aspartate (NMDA) receptor exhibits antidepressant-like activity in rodent tests/models. Zinc also induces brain derived neurotrophic factor (BDNF) gene expression. Clinical observations have demonstrated serum hypozincemia in depression which was normalized by effective antidepressant treatment. Moreover the benefit of zinc supplementation in antidepressant therapy in both treatment of non-resistant and resistant patients has also been documented. Thus, zinc homeostasis is relevant in psychopathology and therapy of depression.

Zinc and diabetes Zinc deficiency occurs in patients with type II diabetes mellitus because of impaired zinc absorption and hyperzincuria. Hyperzincuria is proportional to proteinuria and correlates with the mean serum glucose concentration.

Zinc in wound healing Zinc-dependent matrix metalloproteinases augment autodebridement and keratinocyte migration during wound repair. Zinc confers resistance to epithelial apoptosis through cytoprotection against reactive oxygen species and bacterial toxins possibly through antioxidant activity of the cysteine - rich metallothioneins. Zinc deficiency delays wound healing as a result of decreased nuclear factor(NF) kB activation. It also reduces expression of proinflammatory cytokines including interleukin(IL)-1β and tumor necrosis factor (TNF-α). The deficiency may cause decreased neutrophil infiltration during early stages of wound healing. Oral zinc supplementation is beneficial in treating zinc-deficient leg ulcer patients, but its therapeutic role in surgical patients remains to be seen. Topical administration of zinc appears to be superior to oral therapy due to its action in reducing superinfections and necrotic material via enhanced local defense systems, collagenolytic activity and the sustained release of zinc ions that stimulates epithelialization of wounds in normozincemic individuals.

Zinc and ageing The role of zinc in healthy aging is particularly important as it prevents neoplastic cell growth. It is also involved in mitotic cell division, DNA and RNA repair(17). Many studies have confirmed decline of zinc levels with age. Most of these studies do not classify the majority of elderly as zinc deficient, but even marginal zinc deprivation may contribute to immunosenescence. At molecular level, the intracellular zinc homeostasis is altered because high metallothioneins (MT) are unable to release zinc and some zinc transporters deputed to zinc influx (ZIP family) are defective leading to low intracellular zinc content for immune efficiency. Consequently, physiological oral zinc supplementation demonstrates the potential to improve immunity and efficiently downregulates chronic inflammatory responses in the elderly. Also following zinc supplementation in an elderly population, the incidence of infections is found to be significantly lower. Also plasma zinc levels are significantly higher and generation of TNF-α and oxidative stress markers are significantly lower in the zinc-supplemented group than in the placebo group.

Zinc and cancer Zinc has been ascribed roles in the metabolism and interaction of malignant cells particularly in apoptosis. It is involved in structural stabilization and activation of cytochrome P53 that appears to be an important component of the apoptotic process and also in activation of certain members of the caspase family of proteases. Zinc exerts a positive beneficial effect against chemically induced preneoplastic progression in rats and provides an effective dietary chemopreventive approach to disease in vulnerable section

of population with family history of carcinoma.

Zinc and liver disorders Zinc deficiency is also associated with acute and chronic liver disease. Zinc supplementation protects against toxin-induced liver damage and is used as a therapy for hepatic encephalopathy in patients refractory to standard treatmen. Zinc supplementation has proved to decrease hepatic encephalopathy and blood ammonia levels. Supplementation of zinc in chronic Hepatitis-C-Virus infected patients has been shown to reduce gastrointestinal disturbances, weight loss, hair loss and mild anaemia.

Zinc and HIV Long term zinc supplementation of 12-15mg/day as adjuvant has been reported to decrease likelihood of immunological failure and diarrhoea in HIV-infected patients with poor viral control. Decreased serum zinc levels have been associated with more advanced disease and increased mortality in HIV patients.

CONCLUSION

Zinc is an essential trace element which is involved in many fundamental activities of cellular metabolism that accounts for its essentiality to all life forms. A large number of studies have elucidated the significant role of zinc as an intracellular signalling molecule playing very important role in cell-mediated immune functions and oxidative stress with very wide clinical ramifications. Zinc deficiency present in many chronic disorders needs correction to obviate complications and increased morbidity. Mild to moderate zinc deficiency may be common in the developing countries but the public health importance of this degree of zinc deficiency is not well defined. It is therefore suggested that status of zinc should be assessed in relevant clinical situations.

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