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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. 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 a recent survey by WHO, zinc deficiency is found in most of the Indian population and zinc supplement is used commonly to enhance wound healing and treatment of pneumonia. The element is important in maintaining the healthy growth of the human body, especially for infants and young children.*

Key words: *Zinc, human health, Zinc deficiency*

I. Introduction

Zinc (Zn) is an essential nutrient for all forms of life and its importance lies in the fact that many body functions are linked to zinc containing enzymes(1). Zn as a trace element has indispensible role in human health and diseases. It has been insufficiently recognised by a number of experts as an important public health issue, especially in developing countries. It is the most abundant intracellular metal ion found in cytosol, vesicles, organelles and in the nucleus(2). However, even a small deficiency is a disaster to human health, so as such the number of biological functions, health implications and pharmacological targets that are emerging for zinc has evoked further interest regarding its status in human health and nutrition.

II. Dietary Sources of Zinc and Recommended Dietary Allowance

The best food sources of zinc include meat based products, especially the most abundant meat, such as chicken, lamb, beef, rabbit meat, oysters, scallops, blackfish, animal liver, and so on. Other sources of Zinc include, mushrooms, day lily flowers, edible fungus, cabbage, black sesame, black rice, dates, hazelnut, ebony and other vegetables, food crops and fruit, although fruits and vegetables are poor sources. Recommended daily allowance (RDA) varies from 5mg in infants to 15mg in adults(2). RDI (Recommended Daily Intake) and RDA numbers are a statistical estimate of the amounts that prevent individuals from manifesting deficiency signs and symptoms (Table 1).

Table 1
Zinc Requirements Daily Reference Intakes

Infants		Males	
0 - 6 months	2 (mg/day)	9 - 13 years	8 (mg/day)
7 - 12 months	3 (mg/day)	14 - 18 years	11(mg/day)
		19 - 30 years	11(mg/day)
		31 - 50 years	11(mg/day)
Children		51 - 70 years	11(mg/day)
1 - 3 years	3 (mg/day)	> 70 years	11(mg/day)
4 - 8 years	5 (mg/day)		
Pregnancy		Females	
< 18 years	13 (mg/day)	9 - 13 years	8(mg/day)
19 - 30 years	11 (mg/day)	14 - 18 years	9(mg/day)
31 - 50 years	11 (mg/day)	19 - 30 years	8(mg/day)
		31 - 50 years	8 (mg/day)
Lactation		51 - 70 years	8(mg/day)
< 18 years	14 (mg/day)	> 70 years	8(mg/day)
19 - 30 years	12 (mg/day)		
31 - 50 years	12 (mg/day)		

adapted from: Bhowmik et al(3)

III. Zinc metabolism

About 25-66% of dietary zinc is absorbed mainly from jejunum and ileum in a concentration dependent manner. The SLC39 proteins that are members of the broad ZIP (Zinc importer) family of metal ion transporters are implicated in zinc uptake across the plasma membrane of various cell types and SLC39A4 is specifically implicated in the uptake of dietary zinc into intestinal enterocytes[4]. Phytates (inositol hexaphosphate)–rich foods inhibit bio-availability while animal proteins improve zinc absorption. The total body zinc content has been estimated to be about 2.5 g in men and 1.5g in women. There is no specific zinc store. Zinc is present in all body tissues and fluids. The plasma pool, which is required for the distribution of zinc, represents less than two percent of the total body content. The major part of serum or plasma zinc i.e., about 57% circulates with albumin, remaining 40% with α2 globulin and 3% with amino acids. The serum zinc concentration is 16% higher than plasma because of dilution factor, disintegration of platelets and hemolysis .The normal serum zinc level is 70 – 125 µg/ dl and females have slightly lower values. Skeletal muscle accounts for approximately 60% of the total body content and bone mass about 30%. High concentrations of zinc are found in the choroid of the eye and in prostatic fluids. More than 95% of zinc exists intracellularly[2]. The intracellular zinc homeostasis is regulated by buffering metallothioneins (MT) and zinc transporters[5]. Zinc is lost from the body through the kidneys, skin and intestine. The endogenous intestinal losses can vary from 0.5 mg/day to more than 3 mg/day depending on zinc intake. Urinary and skin losses are of the order of 0.5-0.7 mg/day each and depend less on normal variations in zinc intake. Starvation and muscle catabolism increase zinc losses in urine. Strenuous exercise and elevated ambient temperatures can lead to losses by perspiration.

Toxicity of zinc occurs with long term exposure to 100-300mg / day (6-20 times recommended daily allowance). Symptoms include copper deficiency, impaired immune function, and reduction of HDL cholesterol levels. Acute toxicity results in vomiting, epigastric pain, lethargy and fatigue[1].

Functional activities of Zinc

Zinc is an essential component of more than 300 metalloenzymes participating in the synthesis and degradation of carbohydrates, lipids, proteins, and nucleic acids as well as in the metabolism of other micronutrients[2]. At the cellular level, the function of zinc can be categorised into Catalytic, Structural and Regulatory.

Catalytical: Various enzymes depend on zinc for their ability to catalyze vital chemical reactions within body. Zinc dependent enzymes can be found in all known classes of enzymes.
Structural: Zinc plays an important role in the structure of proteins and cell membrane. The structure and function of cell membranes are also affected by zinc. Loss of zinc from biological membranes increases their susceptibility to oxidative damage and impairs their functions.
Regulatory: Zinc finger proteins have been found to regulate gene expression by acting as transcription factors. Zinc also plays a role in cell signaling and has been found to influence hormone release and transmission of nerves impulse.

Zinc is a constituent of both DNA and RNA polymerases and influence the activity of thymidine kinase and ribonuclease[2]. Some other important zinc-containing enzymes are carbonic anhydrase, alcohol dehydrogenase, retinene reductase, alkaline phosphatase and lactate dehydrogenase[6]. More than 2000 zinc-dependent transcription factors are involved in gene expression of various proteins. It is thus involved in virtually all aspects of cellular and molecular biology as catalytic, structural and regulatory cofactor[5].

Zinc deficiency

a) Primary zinc deficiency syndromes may be due to diets poor in zinc[6]. Acrodermatitis enteropathica, characterized by the triad of dermatitis, diarrhoea, and alopecia occur as autosomal recessive disorder due to mutations in the gene (SLC39A4) that codes the zinc transporter protein, ZIP4. It also can occur in an acquired form in exclusively breast-fed infants due to mutation in the zinc transporter gene SLC30A2 (ZincT-2), responsible for transfer of zinc from serum to breast milk, in their mothers[4,7].
b) Secondary or conditioned zinc deficiency occurs in various conditions like malabsorption syndrome, cirrhosis of liver , chronic renal disease, total parenteral nutrition, sickle cell disease, diabetes, malignancies, other chronic disorders and drug therapy with penicillamine, anticonvulsants and ethambutol[2].

Zinc deficiency affects many organ systems, including the integumentary, gastrointestinal, central nervous system, immune, skeletal, and reproductive systems. Zinc deficiency results in dysfunction of both humoral and cell-mediated immunity and increases the susceptibility to infection. Disturbances in nucleic acid metabolism and protein synthesis may account for some features of zinc deficiency. Relative excess of dietary nitrogen secondary to zinc deficiency can cause anorexia and impaired taste. Zinc status may affect function of

growth hormones, gonadotrophins, sex hormones, prolactin, thyroid, corticosteroids and insulin. Growth retardation occurs because of disruption of function of insulin like growth factor which mediates the cellular effects of growth hormone. Delayed sexual maturation and impotence as well as hypogonadism and hypospermia can occur. Increased synthesis of prostaglandin especially PGE-2 which occurs in zinc deficiency may result in diarrhoea, alopecia, acro-orificial skin lesions, glossitis and nail dystrophy may also be manifested. Mental changes in the form of apathy, depression and change in behaviour have also been noted. Delayed healing of wounds, burns and decubitus ulcers also occur. Eye lesions including photophobia and lack of dark adaptation, conjunctivitis, corneal opacities, macular degeneration and night blindness have been documented[(2)]. The optimal therapeutic dosage that is required to reverse the symptoms of zinc deficiency is still unclear, and the pharmacologic zinc dose should be adapted to the actual requirements to avoid negative side effects on immune functions. In dermatitis caused by low dietary zinc, treatment with elemental zinc supplementation at the dose of 0.5-1 mg/kg/day is recommended[(7)].

IV. 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[(8, 9)].

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 O_2^- from O_2. 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[(10)].

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[(12,13)].

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[14].

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[15]. 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[16].

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[18, 19]. 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[20].

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[21].

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 treatment[22]. Zinc supplementation has proved to decrease hepatic encephalopathy and blood ammonia levels[23,24]. 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[25].

V. Zinc in Skin diseases

Oral APC (methionine-based zinc complex with antioxidants) thrice daily for 12 weeks given to patients with mild to moderate facial acne vulgaris has been found to be effective and well tolerated[26]. Shampoos containing zinc pyrithione provide clinical benefits for treatment of scalp seborrheic dermatitis[27]. Oral zinc sulfate supplementation has been used as an useful adjuvant therapy with encouraging results in patients with alopecia areata[28]. Topical 10% zinc sulphate solution 3 times daily for 4 weeks has been found to be a very effective and safe modality for treatment of plane warts[29]. Intralesional injection of 2% zinc sulphate has proved to be beneficial as local therapy for viral warts, especially the recalcitrant form[30]. Necrolytic acral erythema (NAE), a distinct skin entity distinguished by its acral location, typical clinical and histopathologic

feature is strongly associated with chronic hepatitis C virus (HCV) infection though it may occur independently. Topical zinc in the form of divalent zinc ions has also been reported to provide photoprotection through its antioxidant role[31,32,33].

VI. 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. Concurrent 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. There are still avenues for further research particularly controlled clinical trials to establish the potential use of zinc as a preventive and therapeutic agent for a wide range of diseases in human.

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