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A Review on the Role of Zinc in the Biological and Microbiological System

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ABSTRACT

Biological and antimicribiological role of bio metal zinc have been reviewed in this article. It has been found that zinc shows a number of biological and microbiological functions for example zinc is an essential component of a large number (>300) of enzymes participating in the synthesis and degradation of carbohydrates, lipids, proteins, and nucleic acids as well as in the metabolism of other micronutrients. Although, zinc-dependent biochemical mechanisms in physiologic functions have received extensive study, but a clear relationships have not been yet fully established. The role of zinc in biology can be grouped into three general functional classes, namely catalytic, structural and regulatory functions. Deficiency of zinc causes many disorder, like growth retardation, defective neurological and behavioral development in children, disturbance in male reproduction and pregnancy complications etc. Remarkable microbiological role of zinc have been reported by various researchers. Zinc has been proposed as a useful adjuvant for COVID-19 therapy due to its systemic antiinflammatory, antioxidant, immunoregulatory activity, as well as its role in respiratory protection

Introduction

Zinc is present in all body tissues and fluids.Now it is also considered as one of the important micro element in the biological system [1]. Total body zinc content has been estimated to be approximately 2.0 g for an adult [2]. Zinc is an essential component of a large number (>300) of enzymes participating in the synthesis and degradation of carbohydrates, lipids, proteins, and nucleic acids as well as in the metabolism of other micronutrients [3 - 5]. Zinc stabilises the molecular structure of cellular components and membranes and contributes in the maintenance of cell and organ integrity [6]. Further more, zinc has an essential role in polynucleotide transcription and thus in the process of genetic expression [7]. Its involvement in such fundamental activities probably accounts for the essentiality of zinc for all life forms [8]. Zinc plays a central role in the immune system, affecting a number of aspects of cellular and humoral immunity. The role of zinc in life has been reviewed by Frassinetti S. et al. [9]. The clinical features of severe zinc deficiency in humans are growth retardation, delayed sexual and bone maturation, skin lesions, diarrhoea, alopecia, impaired appetite, increased susceptibility to infections mediated via defects in the immune system, and the appearance of behavioural changes [2]. The effects of marginal or mild zinc deficiency are less clear. A reduced growth rate and impairments of immune defence are so far the only clearly demonstrated signs of mild zinc deficiency in humans. Other effects, such as impaired taste and wound healing, which have been claimed to result from a low zinc intake, are less consistently observed [10]. Zinc also plays an important role in the microbiological system. Zinc ion concentrations of 10^{-5} - 10^{-7} M are required for optimal bacterial growth of most microorganisms in vitro [11]. However, it is claimed that high zinc ion concentrations may have some antibacterial properties [12]. Thus various biological and microbiological roles of zinc are reviewed in this article.

Physiologic Functions of Zinc

Although, zinc-dependent biochemical mechanisms in physiologic functions have received extensive study, but a clear relationships have not been yet fully established. The role of zinc in biology can be grouped into three general functional classes, namely catalytic, structural and regulatory functions [5]

(i) Catalytic role of zinc: More than 250 different enzymes are now known which depend on zinc for their ability to catalyze biochemical reactions [13].

(ii) Structural role: Zinc plays an important role in the structure of proteins and cell membranes. A finger-like structure, known as a zinc finger motif, stabilizes the structure of a number of proteins. For example, copper provides the catalytic activity for the antioxidant enzyme copper-zinc superoxide dismutase (CuZnSOD), while zinc plays a critical structural role [14,15]. The structure and function of cell membranes are also affected by zinc.

(iii) Regulatory role of zinc: Zinc finger proteins have been found to regulate gene expression by acting as transcription factors (binding to DNA and influencing the transcription of specific genes). Zinc also plays a role in cell signaling and has been found to influence hormone releas and nerve impulse transmission [16].

Metabolism and Absorption of Zinc

Zinc is absorbed in the small intestine by a carrier-mediated mechanism [6]. Under normal physiologic conditions, transport processes of uptake are not saturated. The fraction of zinc absorbed is difficult to determine because zinc is also secreted into the gut. Zinc administered in aqueous solutions to fasting subjects is absorbed efficiently (60-70%), whereas absorption from solid diets is less efficient and varies depending on zinc content and diet composition [7]. Generally, 33% is accepted as the average zinc absorption in humans [6 - 8]. More recent studies have suggested different absorption rates for different population groups based on their type of diet and phytate. Zinc absorption is concentration dependent and increases with increasing dietary zinc up to a maximum rate [7 - 9]. In addition, zinc status may influence zinc absorption. Zinc deprived humans absorb this element with increased efficiency, whereas humans on a high-zinc diet show a reduced efficiency of absorption [10]. Zinc is released from food as free ions during digestion. These liberated ions may then bind to endogenously secreted ligands before their transport into the enterocytes in the duodenum and jejunum [7 - 9]. Specific transport proteins may facilitate the passage of zinc across the cell membrane into the portal circulation. With high intakes, zinc is also absorbed through a passive paracellular route. The portal system carries absorbed zinc directly to the liver, and then released into systemic circulation for delivery to other tissues. About 70% of the zinc in circulation is bound to albumin, and any condition that alters serum albumin concentration can have a secondary effect on serum zinc levels.

Interactions with Other Essential Metals

Taking large quantities of zinc (50 mg/day or more) over a period of weeks can interfere with copper bioavailability. High intake of zinc induces the intestinal synthesis of a copper-binding protein called metallothionein. Metallothionein traps copper within intestinal cells and prevents its systemic absorption [15]. Supplemental (38-65 mg/day of elemental iron) but not dietary levels of iron may decrease zinc absorption [17]. This interaction is of concern in the management of iron supplementation during pregnancy. High levels of dietary calcium impair zinc absorption in animals, but it is uncertain whether this occurs in humans. One study showed that increasing the calcium intake of postmenopausal women reduced zinc absorption and zinc balance [18].

Deficiency of Zinc

Zinc is required for many biochemical processes and functions. One of its most important role is supporting our immune system, which protects us from pathogenes, infections, and diseases. Zinc also plays a role in carbohydrate breakdown (which supplies energy) as well as growth, division and reproduction of our cells [19]. Severe zinc deficiency has also been reported in individuals undergoing total parenteral nutrition without zinc, in those who abuse alcohol, and in those who are taking certain medications like penicillamine [20].Zinc deficiency is usually due to insufficient dietary intake, but can be associated with malabsorption, acrodermatitis enteropathica, chronic liver disease, chronic renal disease, sickle cell disease, diabetes, malignancy, and other chronic illnesses [21]. Groups at risk for zinc deficiency include the elderly, children in developing countries, and those with renal insufficiency.Clinical outcomes include depressed growth, diarrhea, impotence and delayed sexual maturation, alopecia, eye and skin lesions, impaired appetite, altered cognition, impaired host defense properties, defects in carbohydrate utilization, and reproductive teratogenesis [22]. Mild zinc deficiency depresses immunity [23] It is now recognized that milder zinc deficiency contributes to a number of health problems, especially common in children who live in developing countries. An estimated 2 billion people worldwide are affected by dietary zinc deficiency [24]. In children it causes an increase in infection and diarrhea which resulted in death. In fact, zinc deficiency has been estimated to cause more than 450,000 deaths in children under the age of 5 annually, comprising 4.4% of global childhood deaths [25]. The WHO advocates zinc supplementation for severe malnutrition and diarrhea [26]. Zinc supplements help prevent disease and reduce mortality, especially among children with low birth weight or stunted growth [26].

Common Diseases Associated with Zinc Deficiency

(i) Growth retardation

Delays in linear growth and weight gain, known as growth retardation or failure to thrive, are common features of mild zinc deficiency in children. Meta-analyses of growth data from zinc intervention trials have confirmed the widespread occurrence of growth-limiting zinc deficiency in young children, especially in developing countries [27 - 29]. Although the exact mechanism for the growth-limiting effects of zinc deficiency are

not known, research indicates that zinc availability affects cell-signaling systems that coordinate the response to the growth-regulating hormone (IGF-1) [30].

(ii) Defective neurological and behavioral development in children

Low maternal zinc nutritional status has been associated with diminished attention in newborn infants and poorer motor function at six months of age. Maternal zinc supplementation has been associated with improved motor development in very low-birth-weight infants [31]. Additionally, zinc supplementation in children was associated with better neuropsychological functioning, but this was observed only when zinc was provided with other micronutrients [32].

Impaired Immune System Function

Adequate zinc intake is essential in maintaining the integrity of the immune system [33], specifically for normal development and function of cells that mediate both innate (neutrophils, macrophages, and natural killer cells) and adaptive (B-cells and T-cells) immune responses [34 - 35]. Moreover, zinc plays a structural role in the antioxidant enzyme, CuZnSOD. Zinc deficiency adversely affects a number of immune functions, resulting in decreased production of certain cytokines; reduced activation of zinc-dependent enzymes and transcription factors; and decreased activity of thymulin, a zinc-dependent thymic hormone important for T-cell function [36]. Consequently, zinc-deficient individuals are known to experience increased susceptibility to a variety of infectious agents [37]. It is estimated that diarrheal diseases result in the deaths of over 1.8 million children under five years of age in developing countries annually [38]. The adverse effects of zinc deficiency on immune system function are likely to increase the susceptibility of children to infectious diarrhea, and persistent diarrhea contributes to zinc deficiency and malnutrition. Research indicates that zinc deficiency may also potentiate the effects of toxins produced by diarrhea-causing bacteria like E. coli [39]. Zinc supplementation in combination with oral rehydration therapy has been shown to significantly reduce the duration and severity of acute and persistent childhood diarrhea and to increase survival in a number of randomized controlled trials [40-41]. The World Health Organization and the United Nations Children's Fund currently recommend zinc supplementation as part of the treatment for diarrheal diseases in young children [42].

Male reproduction

The results of meta-analysis of 2600 infertile men and 867 controls demonstrated that infertility is associated with significantly lower seminal plasma Zn levels, whereas Zn supplementation significantly increased semen volume, sperm motility, and improved sperm morphology [43]. Correspondingly, a significant correlation between seminal plasma Zn levels and reduced risk of asthenozoospermia was observed in another metaanalysis [44]. Correspondingly, a number of studies addressed the efficiency of Zn supplementation for improvement of semen quality and male fertility. Zn supplementation (220 mg daily) for 3 months resulted in a significant increase in semen volume, sperm motility, and morphology, and was associated with increased high- and low-molecular weight Zn binding ligands [45]. The results of meta-analysis performed by Salas-Huetos et al. in 2018 demonstrated that Zn supplementation is capable of increasing total sperm concentrations and sperm motility [46].

Pregnancy Complications

It has been estimated that 82% of pregnant women worldwide are likely to have inadequate zinc intakes. Poor maternal zinc nutritional status has been associated with a number of adverse outcomes of pregnancy, including low birth weight, premature delivery, labor and delivery complications, and congenital anomalies [47]. However, results of maternal zinc supplementation trials in the developing countries have been mixed [31]. Although some studies have found maternal zinc supplementation increases birth weight and decreases the likelihood of premature delivery, A recent systematic review of 20 randomized controlled trials found that zinc supplementation during pregnancy was associated with a 14% reduction in premature deliveries; the lower incidence of preterm births was observed mainly in low-income women [48].

Age-related Racular Degeneration

A leading cause of blindness in people over the age of 65 in the US is a degenerative disease of the macula, known as age-related macular degeneration (AMD). The macula is the portion of the retina in the back of the eye involved with central vision. Zinc is hypothesized to play a role in the development of AMD for several reasons: (1) zinc is found at high concentrations in the part of the retina affected by AMD, (2) retinal zinc content has been shown to decline with age, and (3) the activities of some zinc-dependent retinal enzymes have been shown to decline with age. Recently, a randomized, double-blind, placebo-controlled trial in 74 AMD patients reported that supplementation with 50 mg/day of zinc monocysteine for six months improved measures of macular function, including visual acuity, contrast sensitivity, and photorecovery [49]. The AREDS formulation containing antioxidants, zinc, and copper is currently the standard of care for AMD patients [50].

Role of Zinc in Diabetics

Moderate zinc deficiency may be relatively common in individuals with diabetes mellitus [51]. Increased loss of zinc by frequent urination appears to contribute to the marginal zinc nutritional status that has been observed in diabetics [52]. Although supplementation with zinc reportedly improves immune function in diabetics, zinc supplementation of 50 mg/day adversely affected control of blood glucose in insulin-dependent (type - 1) diabetics in one study [53]. Presently, the influence of zinc on glucose metabolism requires further study before high-dose zinc supplementation can be advocated for diabetics [15].

Role of Zinc in HIV/AIDS

Sufficient zinc is essential in maintaining immune system function, and HIV-infected individuals are particularly susceptible to zinc deficiency. In HIV-infected patients, low serum levels of zinc have been associated with a more advanced stage of the disease and also with increased mortality [54, 55]. In one of the few zinc supplementation studies conducted in AIDS patients, 45 mg/day of zinc for one month resulted in a decreased incidence in opportunistic infections compared to placebo [56]. A placebo-controlled trial in 231 HIV-positive adults with low plasma levels of zinc (<0.75 mg/l) found that zinc supplementation (15 mg/day for men and 12 mg/day for women) for 18 months reduced the incidence of immunological failure by 76% and the rate of diarrhea by 60% [57].

Microbiological Role

Zinc ion concentrations of 10-5-10-7 M are required for optimal bacterial growth of most microorganisms in vitro [11]. However, it is claimed that high zinc ion concentrations may have some antibacterial properties [12]. Results of the study reveals that zinc acetate has an antibacterial effect on S.aureus, S.epidermidis and P.aeruginosa. Although the inhibitory activity of zinc acetate on P.aeruginosa was statistically significant, this effect was more evident on S.aureus and S.epidermidis than on P.aeruginosa (P<0.05). In a study by Södeberg et al. [12], it was found that gram-positive bacteria were the most susceptible bacterial group to zinc ion but gram-negative aerobic bacteria were usully not inhibited even at the highest concentration (1024 µl/ml). Although it is not clear why zinc exhibits different bacterial affinity with gram-positive and gram-negative bacteria, it may be ascribed to the difference in the protein constituents of their cell walls [11]. Zinc oxide (ZnO) nano/microparticles have been studied as antibiotics to enhance antimicrobial activity against pathogenic bacteria and viruses with or without antibiotic resistance. They have unique physicochemical characteristics that can affect biological and toxicological responses in microorganisms. Metal ion release, particle adsorption, and reactive oxygen species generation are the main mechanisms underlying their antimicrobial action [58, 59]. Nanoparticles of zinc metal oxides lead to the production of ROS (reactive oxygen species) upon interaction with bacteria [60]. The metal ions released by the nanoparticles affect the respiratory chain and inhibit some enzymes. This leads to the formation and accumulation of singlet oxygen, hydroxyl radical, hydrogen peroxide, superoxide anions, and other ROS. ROS can cause damage to the internal components of bacteria, such as proteins and DNA [61].

Zinc Excess Disorder and Toxicity

The immediate acute effects of overdose of this trace mineral are metallic taste in the mouth, headache, epigastric pain, lack of appetite, nausea, vomiting, abdominal pain, diarrhea and related gastrointestinal distress [62]. Zinc overdose suppresses copper and iron absorption and leads to nutritional deficiency of these trace minerals, anemia and neurological problems [63]. Neutropenia, a condition of an abnormally low number of neutrophils (white blood cells) may also result due to excess and overdose of the zinc. In a trial on elderly men, an intake at 80 mg/day has shown increased urinary complications and hospitalizations.Taking excess of this mineral in the form of supplements may cause its elevated levels in prostate gland and may increase the risk factors of enlarged prostrate gland or prostate cancer [64]. Suppression of immune response, loss of smell sense, decrease in high-density lipoprotein (HDL) and renal failure are some of the adverse effects of chronic overdose with its supplements. Isolated outbreaks of acute zinc toxicity have occurred as a result of the consumption of food or beverages contaminated with zinc released from galvanized containers. Signs of acute zinc toxicity are abdominal pain, diarrhea, nausea, and vomiting. Metal fume fever has been reported after the inhalation of zinc oxide fumes. Specifically, profuse sweating, weakness, and rapid breathing may develop within eight hours of zinc oxide inhalation and persist 12-24 hours after exposure is terminated [14, 15].

Zinc and Covid-19 pandemic

Since December 2019, the world community are facing a massive outbreak of COVID-19 infection caused by SARS-CoV-2 coronavirus. During less than two years, more than 163 million people worldwide are infected by COVID-19 with more than 3.3 million patients deceased [65]. COVID-19 predominantly affects respiratory system causing viral pneumonia that is associated with systemic inflammation, endothelial dysfunction [66] and immune dysregulation. Zinc was proposed as a useful adjuvant for COVID-19 therapy due to its systemic antiinflammatory, antioxidant, immunoregulatory activity, as well as its role in respiratory protection [67].

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