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Current Evidence on Role of Zinc in Immune Function

Review Article

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Abstract

Zinc is an important micronutrient and is listed as an essential trace element which is required to maintain the smooth functioning of the immune system. Zinc has a vital role in ensuring normal development of innate immunity, neutrophils, and Natural Killer (NK) cells and warrants smooth functioning of the cells modulating them. Zinc deficiency impacts the function of macrophages, T and B cells, and cytokine production. It acts as a second messenger in the immune cells and participates in various signaling pathways including activation of T cells via T cell receptor and by the cytokine interleukin (IL)-2 pathway. Zinc is required by the pathogens for survival, hence in case of an infection, host body limits the zinc in the milieu by altering zinc distribution. Zinc has also been linked with antiviral properties against a wide variety of viruses, specifically RNA viruses such as rhinovirus, respiratory syncytial virus, and SARS-CoV. Zinc is naturally available from a myriad of foods sources. However, it can be taken as supplements by people who are not able to meet the required daily amount through food. Clinical studies have proven the health benefit of zinc supplements to address the deficiency as well as to ensure zinc-dependent physiological functions run smoothly. In this review, the role of zinc in immunity and importance of zinc supplementation has been explored.

Keywords: Zinc; Immunity; Respiratory infection; Supplements; Nutrition; Micronutrient

Introduction

Immune system is an essential component of our physiology which helps in combating infections along with internal and external threats. Immune system works at three levels: physical barrier, biochemical barrier, and immune cells. Physical barriers include skin, mucous membrane, and body hair. They obstruct external threats from entering the body. If the physical barrier is breached, the biochemical barrier distinguishes between "self" and "non-self" to eliminate the "non-self" using a plethora of immune cells (e.g., macrophages, natural killer cells, non-specific leukocytes, cytokines). A more complex and adaptive response is generated by T and B lymphocytes against the invasions. These cells produce target-specific antibodies to neutralize the threat [1,2].

For the smooth functioning of this artillery, nutrition plays a critical role. Macronutrients and micronutrients are needed to have a healthy immune system and the protection it confers. Vitamins A, B2, B6, B12, C, D, and E; folic acid; beta-carotene; zinc; selenium; and iron are the required micronutrients to maintain the functioning of the immune system [2,3].

Zinc plays a crucial role in innate and adaptive immunity. Zinc deficiency manifests as thymic atrophy, lymphocyte count ≤ 1100 cells/μL, impaired immune response and mortality [4]. The estimated global zinc deficiency is between 17% to 20% [5]. The deficiency is more prominent in developing countries of Africa and Asia. It occurs mostly in the elderly, pregnant women, children from developing nations, vegans/vegetarians, and people suffering from chronic diseases (e.g., liver cirrhosis, inflammatory bowel disease) [6-8]. Even marginal or moderate deficiency of zinc can cause delay in wound healing, cause inflammation, and increase oxidative stress [9,10]. In this review, the role of zinc in immunity and importance of zinc supplementation has been explored.

Role of Zinc in Immunity

Zinc plays a critical role to ensure normal development of innate immunity, neutrophils, and NK cells and warrants smooth functioning of the cells modulating them. Macrophages are also impacted due to zinc deficiency. Functions like phagocytosis, intracellular killing, and cytokine production are impacted by zinc deficiency. The maturation and working of T and B cells are adversely affected due to insufficient zinc. Zinc has antioxidant properties and helps stabilize membranes thus preventing injury induced by free radicals [11].

Zinc acts as a second messenger in the immune cells [12]. Zinc participates in various signaling pathways including activation of T cells via T cell receptor and by the cytokine interleukin (IL)-2 pathway which is the major stimulus for T cell proliferation once activated [13-15]. Immune cells recognize the zinc deficiency before it is identified in the plasma [16]. The increased susceptibility to infections due to zinc deficiency is probably caused by zinc dependent alterations in chemotaxis, phagocytosis, respiratory burst and formation of neutrophil extracellular traps by innate immune cells [17-19].

The systemic and intracellular zinchomeostasis is strictly regulated to keep the free zinc ions (Zn2+) at a minimal fraction of about 0.0001% of total cellular zinc. Majority of zinc is bound to proteins such as serum albumin or intracellular metallothionein proteins. This helps in transfer of bound zinc to zinc-binding enzymes and transcription factors on need basis. Zinc transport is primarily facilitated by 2 groups of proteins: the ZnT [solute-linked carrier 30 (SLC30A)] family, which is responsible for efflux of zinc outside the cell or influx into organelles, and the ZIP [Zrt- and Irt-like proteins (SLC39A)] family of proteins, which performs the opposite role, transporting zinc into the cytoplasm from extracellular sources or cellular organelles. There are more than 30 human proteins accountable for zinchomeostasis. They collectively warrant that zinc does not become toxic (in the case of dietary excess), nor limited (in the case of dietary insufficiency). This balance when not maintained may result in zinc-induced copper deficiency if zinc intake is in excess and severe zinc deficiency if there is dietary insufficiency [7]. Zinc and copper are absorbed via the small intestine. Presence of excess zinc stimulates production of metallothionein, a copper and zinc-binding ligand, in enterocytes. These metallothionein proteins are further stimulated by the zinc to provide more zinc-binding sites in order to prevent zinc toxicity. Metallothionein proteins have high affinity for copper as compared to zinc, and increased metallothionein concentration in enterocytes leads to its preferential binding with copper. This hampers the absorption of copper into the systematic circulation, as the copper remains tethered inside the enterocytes, the metallothionein-copper complex is excreted via the feces, thus resulting in copper deficiency [20, 21]. Zinc absorption is affected by physiological, disease and dietary factors [4,22,23]. Dietary factors affecting zinc absorption include quantity of zinc intake, protein quality and quantity (positive correlation), phytate & fiber (negative correlation), calcium (negative correlation), iron (possible negative correlation), toxic cadmium levels (negative correlation), low-molecular weight ligands and chelators (positive correlation), amino acids (positive correlation), and organic acids (possible positive correlation) [22,23]. The physiological state of the mucus layer and intestinal fluid determines the extent of zinc absorption, since they are not static. Additionally, albumin concentration is also reported to have a positive correlation with zinc absorption [23]. Zinc can be used as therapeutic treatment in diseases like chronic gastrointestinal disorders,renal diseases, and genetic predispositions, such as sickle cell anemia and the zinc malabsorption syndrome [4].

Zinc in Diarrhea

Zinc causes a direct pro-absorptive effect on transepithelial ion transport by inducing ion absorption in enterocytes in basal conditions. Zinc also plays a role in maintaining gastrointestinal epithelial membrane barrier function. It stimulates enterocyte growth and differentiation, reduced intestinal permeability and keeps a check on oxidative stress and inflammation [24], Based on the clinical studies, WHO has recommended zinc supplement for managing acute diarrhea as an adjunct to oral rehydration salts (ORS) [25].

Zinc in Infectious diseases

Zinc is essential for the host as well as the invading pathogen. A competition ensues for securing zinc which the pathogen requires for survival, multiplication and thus causing the disease. As a defense mechanism, the host's body tries limiting zinc in the milieu of the pathogen by altering the zinc distribution. One of the ways of achieving this is locking 99.9% of zinc within the cells of the host, thus locking out the pathogen from gaining direct access. Secretion of inflammatory cytokines like IL-6 up regulates ZIP14 expression within hepatocytes leading to zinc getting accumulated in the liver bound to metallothionein. Zinc concentrations can be altered on an extracellular level by releasing some antimicrobial peptides from the S100 family. Macrophages kill phagocytose pathogens like *Histoplasma capsulatum* by depriving it of zinc by reducing the phagosome zinc content. They kill tuberculosis (which is caused by Mycobacterium) with intoxication of excess amounts of zinc and copper.

Metallothioneins, the small protein molecules responsible for storage and transfer of zinc, play a role in heavy metal detoxification, immune response, apoptosis, oxidative stress, and are classified as interferon stimulated genes (ISGs). Metallothionein inductions occur as a response to interferons (IFNs). IFNs stimulate an influx of zinc into the target cell which in turn promotes metallothionein expression. In vitro and in vivo studies have proved that metallothioneins are induced by viruses which are subsequently ascribed to zinc influx or redistribution. Metallothionein upregulation has been noted as a retort to various viruses like measles, influenza, HIV, hepatitis C, and coxsackie virus, among others [7]. Zinc has been studied in various clinical trials. A particularly positive association of zinc supplements and respiratory infections has been observed. Zinc deficiency has been associated with pneumonia in pediatric patients. Early symptom resolution and prevention of respiratory infections was reported when zinc supplements were taken by the patients [8].

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Table 1: Role of Zinc in Immune System.

Immune function	Zinc's role
Physical and biochemical barrier	Maintaining integrity of skin and mucosal membrane. It acts as a cofactor for metalloenzymes essential for repair of cell membrane
Immune cells	Zinc helps in maintaining or boosting the cytotoxic activity of NK cells Central role in cellular growth and differentiation of immune cells that have a rapid differentiation and turnover Increases the phagocytic activity for *E. coli* and *S. aureus* via peritoneal macrophages It expands phagocytic capacity of monocytes
Antimicrobial effect	Involved in complement activity; role in IFNγ production
Roles in inflammation,antioxidant effects, and effects in oxidative burst	Anti-inflammatory Modulates cytokine releaseby diminishing the development of pro-inflammatory Th17 and Th9 cells and influencing the generation of cytokines such as IL-2, IL-6, and TNF-α Antioxidant activity confers protection against ROS andreactive nitrogen species Influences activity ofantioxidant proteins
Differentiation, proliferation and normal functioning of T cells	Zinc induces proliferation of cytotoxic T cells It is involved in Th1 cytokine production and subsequently in Th1 response Essential for intracellular binding of tyrosine kinase to T cell receptors, required for T cell development,differentiation,and activation Induces development of Treg cells and is thus helps maintaining immune tolerance
Antibody production and development	Involved in antibody production (particularly IgG)
Responses to antigen	Involved in antibody response Essential for maintaining immune tolerance (i.e., distinguishing between "self" from "non-self")

IFN, interferon; IL,interleukin; NK, natural killer; ROS, reactive oxygen species; TNF, tumor-necrosis factor; Tregs, regulatory T cells.
Adapted from: Gombart et al., 2020

Table 2: Indian Council of Medical Research (ICMR)–Nutrient Recommendations for Zinc (mg/dL) [38].

Lifestyle	Category	EAR(mg/d)	RDA(mg/d)	TUL(mg/d)
Men	Sedentary	14.0	17	40
	Moderate			
	Heavy			
Women	Sedentary	11.0	13	40
	Moderate			
	Heavy			
	Pregnant	12.0	14.5	40
	Lactation 0 – 6 months 7 – 12 months	12.0	14	40
Age Group				
Infants	0 – 6 months	-*	-*	4
	6 – 12 months	2.0	2.5	5
Children	1 – 3 years	2.8	3.3	7
	4 – 6 years	3.7	4.5	12
	7 – 9 years	4.9	5.9	12
Boys	10 – 12 years	7.0	8.5	23
Girls	10 – 12 years	7.1	8.5	23
Boys	13 – 15 years	11.9	14.3	34
Girls	13 – 15 years	10.7	12.8	34
Boys	16 – 18 years	14.7	17.6	34
Girls	16 – 18 years	11.8	14.2	34
Elderly Men	≥60 years	14	17	-
Elderly Women	≥60 years	11	13.2	-

EAR, Estimated Average Requirement; RDA, Recommended Dietary Allowance; TUL, Tolerable Upper Limit
*Adequate Intake (AI)

Zinc has been linked with antiviral properties via direct and indirect mechanisms against a wide variety of viruses, specifically RNA viruses such as rhinovirus, respiratory syncytial virus, and SARS-CoV [27]. Zinc can exhibit its antiviral properties by: inhibiting fusion of virus with the membrane of the host cell, blocking release of viral particle, disrupt the virus' protein translation and processing, destabilize the viral envelope, and hamper the polymerase function of the virus [27-29]. Zinc is hypothesized to preserve the cellular membrane by blocking the virus' entry. Zinc regulates proteins of tight junction structure of the mucosal layer, thus exhibiting antiviral immunity and preserving the mucosal membrane integrity. Zinc disrupts the viral replication pathway by altering the proteolytic processing of RNA-dependent RNA polymerase (RdRp) and replicase polyproteins. Hence, it is being implied that zinc might alter the RNA synthesis of COVID-19 [27].

Zinc has been seen in a favorable light against SARS-CoV-2

(COVID-19) virus. The virus is dependent on the metabolism of the host cells to exhibit its viral properties. In vitro studies have shown that zinc cations inhibit SARS-CoV RNA polymerase with assistance from zinc ionophore pyrithione, thus suggesting an antiviral property against the virus. It is also indicated that zinc ions decrease the angiotensin-converting enzyme 2 (ACE2) which is required by the virus to enter the host cells [28, 29].

Zinc possesses anti-inflammatory properties and helps balance the immune response through an infectious disease. COVID-19 throws the immune system out of harmony induced by hyper-inflammation due to production of pro inflammatory cytokines such as IL-6, C - reactive protein (CRP), TNF-α, and IL-1β. The cytokines thus produced (IL-6, C - reactive protein (CRP), TNF-α, and IL-1β) cause the cytokine storm. Cytokines, Reactive Oxygen Species (ROS), and nitrogen species recruit a large number of activated immune cells. These together cause the destruction of the lung tissue which may permanently damage the lungs and can prove fatal. If the anti-inflammatory response falls short of expectation, systemic inflammation, and organ failure are anticipated [29]. Although, it cannot be conclusively suggested in zinc's favor, it is recommended to initiate supplements containing zinc, vitamin D, and selenium to restore deficiencies in case of COVID-19 infection [30].

Zinc deficiency is widely prevalent, especially in the elderly. As establishing zinc is challenging, supplements can prove to be a beneficial approach to address the deficiency and ultimately reduce the global burden of COVID-19 [31]. Zinc supplements have not been associated with any serious life-threatening adverse reactions or deaths. Since zinc-related toxicity has been reported, opinion from healthcare professionals should be sought before such supplements are taken. From COVID-19 perspective, standardized doses for prevention and therapeutic purpose should be established and advised since zinc supplements are sold as over-the-counter products [32].

Role of Zinc in Respiratory Infections

Various studies have shown that zinc and some zinc-dependent proteins aid in anti-viral defense and immune regulation in the respiratory tract. Zinc has been proposed to reduce the viral titer following influenza infection, decrease respiratory syncytial virus (RSV) burden in the lungs, reduce duration of viral pneumonia symptoms, and prevent acute respiratory distress syndrome (ARDS) and ventilator-induced lung damage. Zinc deficiency can cause substantial changes in the epithelial layer of the lungs, possibly through up-regulation of IFNγ and TNFα, enhancement of FasR signaling, and enhancement of apoptosis [33].

Beneficial effects of zinc supplementation in respiratory infections are supported by the results of many reports [34, 35].

Dietary Zinc and Supplements

Zinc is listed as an essential trace element [36]. The recommended dietary allowances (RDAs) for zinc for age 0-6 months for both males and females is 2 mg. For children between 7-12 months and 1-3 years, 3 mg is recommended for both genders. For ages 4-8 years and 9-13 years, 5 mg and 8 mg are recommended, respectively. For male population above and equal to14 years, 11 mg is the recommended RDA. In females aged 14-18 years, 9 mg and for females above 19 years, 8 mg are recommended RDA. Pregnant women between 14-18 years need 12 mg and for pregnant women above and equal to 19 years of age 11 mg is the recommended RDA. For lactating women, 13 mg is recommended for women between 14-18 years and 12 mg for women above and equal to19 years of age [37].

Zinc is naturally available from a myriad of foods sources. The highest zinc content is present in shellfish (74 mg per serving). The second highest source is red meat. Zinc bioavailability is relatively high in animal sources. The reason for such vast difference is absence of phytic acid which inhibits absorption of zinc and the presence of certain amino acids that enhance absorption. Vegetarian food sources include beans, nuts, and whole grain products [36,37]. The Dietary Guidelines for Americans recommend inclusion of zinc rich food items in the diet of infants starting at about 6 months especially in infants fed human milk [39].

Elderly individuals (above ≥ 65 years of age), children and adolescents, pregnant and lactating women, vegetarians, alcoholics, and infants born premature or having low birth weight are at a risk of developing zinc deficiencies. Diseases or disorders increasing risk of zinc deficiency include malnourishment, persistent or severe diarrhea, malabsorption syndromes, inflammatory bowel disease (e.g., Crohn's disease,ulcerative colitis), Chronic kidney disease, Sickle cell anemia, and patients who have undergone gastric by-pass surgery [36], Zinc deficiency is often discovered after infants are weaned off breast milk, and can be due to acrodermatitis enteropathica, a rare, autosomal recessive inherited disorder of zinc metabolism, or an acquired deficiency. These infants present with diarrhea, failure to thrive, and skin lesions as a result of impaired gastrointestinal zinc uptake and can be corrected using oral supplements [40].

Zinc supplements are available in various pharmaceutical formulations like tablets, capsules, and lozenges. The supplements contain zinc salts in the form of gluconate, sulfate, and acetate [37]. Zinc supplementation in children is associated with reduction in all-cause childhood mortality. Zinc supplements reduce incidence of diarrhea and the associated morbidity [41,42]. Fortification with zinc can be an effective strategy to rectify deficiencies in at-risk populations but the evidence is insufficient. Zinc supplementation has been proven to meet the dietary requirements in vulnerable groups of infants, children, adolescents, and pregnant women [41]. Clinical studies have concluded that giving zinc supplements as a preventive measure in at-risk populations increases children's weight gain and promotes linear growth [5]. Medical dosage of zinc i.e. >40 mg/d of elemental zinc may be useful for managing the nutritional status and supporting optimal levels of zinc. The medical dose of zinc has been proven to be safe, but the posology may vary depending on specific physiopathology. High zinc intake for longer duration may inhibit its absorption. Zinc supplements can help with various clinical situations like infections, liver diseases, and disorders of the central nervous system, cancers, and heart diseases [43].

Zinc is known to play a pivotal role in metabolic syndrome development, inflammation suppression, scavenging free radicals, modulating insulin, regulating cytokines, lipid metabolism, confirmed via various clinical studies. Zinc supplements have been proven to help in regulating blood pressure, blood glucose, serum cholesterol, and low-density lipoproteins (LDL) [44].

Clinical Evidence

Numerous clinical studies have explored the effects of zinc supplementation in various age groups for its role in infections and as a general nutrient supplement.

Zinc sulphate monohydrate at a dose of 3 mg/kg given twice a day for 10 days orally along with standard antibiotics to neonates in intensive care units with clinical symptoms of sepsis, significantly reduced the mortality rate as compared to the group that did not receive the supplement. The study was conducted at Jawaharlal Institute of Postgraduate Medical Education & Research, Pondicherry, India in between from September 2013 to December 2016 on 203 neonates [45]. In another single-arm, open-label, study on pediatric population (aged 6 months to 5 years), 465 healthy children with and without zinc deficiency were given zinc syrup 5 ml (containing 20 mg zinc sulfate) once daily, for 14 days. Zinc supplementation was associated with a 48% reduction in the acute upper respiratory infection (AURI) episodes and 68% reduction in the acute lower respiratory infection (ALRI) episodes in the zinc deficient children [46].

In a community based, double-blind randomized controlled trial, efficacy of high zinc biofortified wheat flour was evaluated in children (aged 4-6 years) and non-pregnant, non-lactating woman of child-bearing age (WCBA) against low zinc biofortified wheat flour, in Delhi, India. The mean zinc levels did not differ between the two groups. However, beneficial effect of the high biofortification was observed in self-reported morbidity indicators such as reduction in days with pneumonia and vomiting, days with fever, days with ear discharge in both children and WCBA [47].

In a placebo-controlled study on 53 elderly patients with zinc deficiency, zinc supplements (30 mg/day for 3 months) were evaluated. The group receiving the supplements achieved a significant increase (16%) in serum zinc levels. However, for participants with zinc serum levels of ≥60 mg/dL did not notice further climb to ≥70 mg/dL. A significant increase in anti-CD3/CD28, phytohemagglutinin-stimulated T cell proliferation, and peripheral T cells was also reported with the supplement [48].

Conclusion

Zinc is an essential trace element and plays a vital role in ensuring optimal functioning of the immune system. Zinc deficiency is associated with increased risk of infections and inflammation, especially in at-risk population. Zinc supplements provide medical dosage of zinc to meet the RDA which may prove particularly useful in vegetarians and in populations at a risk of developing zinc deficiency. Zinc supplements have a certain health benefit to address the deficiency and thus ensure zinc-dependent physiological functions run smoothly. However, the interactions between the micronutrients may hamper the overall benefits of the supplements. Excess quantities consumed via zinc supplements may lead to toxicity and copper deficiency. Recent studies in COVID-19 have teased a beneficial role of zinc in preventing and fighting the infection. It is hence vital to meet the daily dietary requirement of zinc which can be achieved by zinc supplements. Further studies may be warranted to establish standardized doses for prevention and therapeutic purpose.

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