

ZINC SUPPLEMENTATION AND IMMUNE HEALTH: A REVIEW

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ABSTRACT

Human zinc insufficiency has been identified as a major global nutritional issue since it was first identified in an Iranian male in 1961. In regions with high cereal consumption and low animal food intake, it is more common. Zinc absorption is largely dependent on its bioavailability, even if the diet may not necessarily be poor in zinc. The primary known inhibitor of zinc is phytic acid. Zinc deficiency is more likely to occur in infants, children, adolescents, pregnant women, and nursing mothers than in adults due to their higher zinc requirements. Growth failure occurs when there is a zinc shortage during growth periods. The organs most clinically impacted by zinc deficiency include the skeletal, immunological, gastrointestinal, central nervous, reproductive, and epidermal systems. It is commonly acknowledged that zinc is essential for human health. Because zinc is used to treat and prevent respiratory tract infections, it has received increased attention during the COVID-19 pandemic. Zinc use, however, may have undesirable side effects and could be hazardous when taken in excess, according to certain research. This review provides an overview of recent basic science and clinical research on zinc's potential as a direct antiviral and antiviral immunity booster. Over the past 50 years, a wealth of evidence has been gathered to show zinc's antiviral action against a wide range of viruses and through many pathways. These findings have led to the therapeutic use of zinc for viral infections like the common cold and herpes simplex virus, but there is still much to learn about the antiviral mechanisms and clinical benefits of zinc supplementation as a preventative and therapeutic treatment for viral infections. Additionally, zinc has been associated with antiviral capabilities against a wide range of viruses, particularly RNA viruses including SARS-CoV, respiratory syncytial virus, and rhinovirus. Numerous food items naturally contain zinc. For those who are unable to obtain the necessary daily intake through diet, it can be taken as a supplement. Clinical research has demonstrated the health benefits of using zinc supplements to treat deficiencies and guarantee the proper operation of zinc-dependent physiological processes. The significance of zinc supplementation and its function in immunity have been discussed in this review.

KEYWORDS: Supplements, Immunity, Respiratory Infections, Zinc, Nutrition and Micronutrients.

INTRODUCTION

An integral part of our physiology, the immune system aids in the defense against both internal and external dangers as well as infections. The immune system functions on three levels: immune cells, biochemical barrier, and physical barrier. Body hair, mucous membranes, and skin are examples of physical barriers. They prevent exterior dangers from getting inside the body. The biochemical barrier uses a variety of immune cells, such as macrophages, natural killer cells, non-

specific leukocytes, and cytokines, to discriminate between "self" and "non-self" in the event that the physical barrier is breached. T and B cells produce a more sophisticated and adaptive defense against the invaders. To neutralize the threat, these cells generate antibodies specific to the target.^[1,2] Over 300 enzymes and transcription factors depend on zinc for their structural and catalytic functions.^[3] It affects almost every cell in the body and is essential for the growth and operation of the immune system in particular.^[4,5] Interest

in the biochemical and clinical aspects of zinc nutrition has significantly expanded since zinc insufficiency was identified as a human health issue in 1961.^[6] The biochemical and physiological functions of zinc, metabolism (absorption, excretion, and homeostasis), zinc bioavailability (inhibitors and enhancers), human requirements, high-risk groups, consequences and causes of zinc deficiency, assessment of zinc status, and prevention strategies of zinc deficiency are all covered in this paper. We found reduced serum testosterone levels, oligospermia, decreased natural killer (NK) cell activity, decreased interleukin-2 (IL-2) production, decreased thymulin activity, hyperammonemia, hypogeusia, decreased dark adaptation, and decreased lean body mass in the experimental human model where only a mild zinc deficiency in males was induced by dietary means. Therefore, it is evident that human clinical, biochemical, and immunological activities are negatively impacted by even a slight zinc shortage.^[7,9]

Zinc and Immunity

The immune system is impacted by zinc in several ways.^[10] For neutrophils, NK cells, and cells mediating innate immunity to form and operate normally, zinc is essential. Zinc deficiency also affects macrophages. Zinc deficiency affects cytokine production, intracellular death, and phagocytosis. Zinc may play a part in preventing damage caused by free radicals during inflammatory processes because of its capacity to maintain membranes and act as an antioxidant.

Role of zinc in immunity

Zinc is essential for the proper growth of neutrophils, NK cells, and innate immunity as well as for the smooth operation of the cells that regulate them. Zinc deficiency also affects macrophages. Zinc deficiency affects processes including phagocytosis, intracellular killing, and cytokine synthesis. Lack of zinc has a negative impact on T and B cell development and function. Zinc has antioxidant qualities and aids in membrane stabilization, minimizing damage caused by free radicals.^[11] In immune cells, zinc functions as a second messenger.^[12] Zinc is involved in a number of signaling pathways, such as the cytokine interleukin (IL)-2 pathway, which is the primary stimulus for T cell proliferation once engaged, and the activation of T cells via T cell receptors.^[13-15] Before the zinc shortage is detected in the plasma, immune cells detect it.^[16] Zinc-dependent changes in chemotaxis, phagocytosis, respiratory burst, and the creation of neutrophil extracellular traps by innate immune cells are likely the source of the increased susceptibility to infections brought on by zinc shortage.^[17,19]

Dietary, medical, and physiological factors all impact zinc absorption.^[20-22] Zinc intake, protein quantity and quality (positive correlation), phytate and 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) are among the dietary factors influencing zinc absorption.^[23,24] Since the mucus layer and intestinal fluid are dynamic, their physiological state dictates the degree of zinc absorption. Furthermore, a favorable association between albumin content and zinc absorption has been shown.^[25] Chronic gastrointestinal illnesses, renal ailments, and hereditary predispositions including sickle cell anemia and zinc malabsorption syndrome can all be treated with zinc.

Viral infection and zinc homeostasis

Because intracellular and systemic zinc levels are strictly controlled, free zinc ions (Zn²⁺) make up a very small portion of total cellular zinc (about 0.0001%).^[26-28] Most zinc is still coupled to zinc-binding proteins such intracellular metallothionein proteins or serum albumin, from which it can be transported to transcription factors and zinc-binding enzymes when needed. Zinc transport is primarily mediated by two protein families: the ZIP [Zrt- and Irt-like proteins (SLC39A)] family of proteins, which carries zinc into the cytoplasm from extracellular sources or cellular organelles, and the ZnT [solute-linked carrier 30 (SLC30A)] family, which is in charge of zinc efflux outside the cell or influx into organelles.^[29] Well-established antibacterial immune responses include metal sequestration and toxic buildup. One excellent example is calprotectin, which binds and sequesters extracellular calcium and zinc to stop the growth of bacteria and fungi.^[30] On the other hand, intracellular Mycobacterium growth in macrophages can be inhibited by toxic endosomal zinc accumulation.^[31] Unfortunately, these mechanisms are little understood when it comes to viral infections, possibly due to their lack of effectiveness. For instance, calprotectin is not markedly elevated in response to viral gastroenteritis and has no demonstrated antiviral function.^[32]

Antiviral action, zinc homeostasis, and metallothionein

Small, cysteine-rich proteins called metallothionein have the ability to bind divalent cations like copper and zinc. Because they may bind and release metals from their thiol groups, metallothionein serve a variety of purposes as containers for a large portion of the labile intracellular zinc pool. These include participation in oxidative stress, apoptosis, and immunological responses, as well as the storage and transport of zinc ions and heavy metal detoxification.^[33] Four metallothionein isoforms (MT1–4) are expressed in humans, including the widely expressed MT1 and MT2 genes (MT1A, B, E, F, G, H, I, J, L, M, X, MT2A), as well as MT3 and MT4, whose expression is restricted and whose function is yet unclear.^[34] Significantly, MT1 and 2 gene expression is highly responsive to zinc, making it a perfect measure of a person's zinc status.^[35] Notably, metallothionein have traditionally been categorized as interferon stimulated genes (ISGs) despite their great zinc responsiveness^[36] Hundreds of antiviral genes are expressed when infected

cells and surrounding immune cells release IFNs, which are immunostimulatory cytokines. They have a variety of functions, such as direct antiviral activity, immune cell stimulation, and chemoattraction. We propose two methods of metallothionein induction in response to IFNs. Like MT1X and MT2A, the majority of ISGs have binding sites for STAT- or IFN regulatory factor (IRF) transcription factor-mediated expression.^[37,38] Other metallothionein, like MT1F and MT1G, are more responsive to zinc rather than having identified IFN regulatory areas in their promoters.^[39] The precise functions of metallothionein during viral infection are yet unknown due to their wide range of functions. However, research conducted both *in vitro* and *in vivo* has demonstrated unequivocally that viruses generate metallothionein. Metallothionein expression has been linked to zinc inflow or redistribution.^[40,41] viral infection, cytokine exposure, or oxidative stress.^[42] however the exact mechanisms are frequently still unknown. Measles virus,^[31] influenza,^[43,44] HIV,^[45] hepatitis C virus (HCV),^[46] and coxsackie virus.^[47] have all been linked to overexpression of metallothionein. Zinc seems to be the primary factor influencing the expression of metallothionein in HIV, which promotes viral persistence. Both intracellular zinc and MT1 gene expression are significantly elevated in HIV-infected monocytes.^[48]

Zinc in diarrhea

By stimulating ion absorption in enterocytes under basal conditions, zinc directly promotes transepithelial ion transport. The function of the gastrointestinal epithelial membrane barrier is also maintained by zinc. It reduces intestinal permeability, promotes enterocyte development and differentiation, and controls oxidative stress and inflammation.^[50,51] The World Health Organization has suggested zinc supplements as an adjuvant to oral rehydration salts (ORS) for the treatment of acute diarrhea based on clinical research.

Zinc in infectious disease

Through both direct and indirect processes, zinc has been associated with antiviral capabilities against a wide range of viruses, particularly RNA viruses like SARS-CoV, respiratory syncytial virus, and rhinovirus.^[52] Zinc's antiviral qualities can be demonstrated by: preventing the virus from fusing with the host cell's membrane, preventing the release of viral particles, interfering with the translation and processing of the virus's proteins, upsetting the stability of the viral envelope, and impairing the virus's polymerase activity.^[53-55] By preventing the virus from entering the cell, zinc is thought to protect the cellular membrane.

Zinc exhibits antiviral immunity and maintains the integrity of the mucosal membrane by controlling the proteins of the tight junction structure of the mucosal layer. By changing the proteolytic processing of RNA-dependent RNA polymerase and replicase polyproteins, zinc interferes with the viral replication pathway.

Therefore, it is suggested that zinc may change COVID-19's RNA production^[56] Zinc has been shown to be beneficial in combating the SARS-CoV-2 (COVID-19) virus. For the virus to display its viral characteristics, the host cell's metabolism is necessary. With the use of the zinc ionophore pyrithione, *in vitro* research has demonstrated that zinc cations block SARS-CoV RNA polymerase, indicating an antiviral characteristic against the virus. Zinc ions have also been shown to reduce angiotensin-converting enzyme 2 (ACE2), which the virus needs to enter host cells.^[57,58] A zinc shortage is common, particularly in older people. Supplements may be a useful strategy to correct the zinc deficit and eventually lessen the worldwide burden of COVID-19 because establishing zinc is difficult.^[59] There have been no fatalities or major, life-threatening side effects linked to zinc supplementation. Before taking such supplements, medical specialists should be consulted because zinc-related toxicity has been documented. Since zinc supplements are provided as over-the-counter products, standardized doses for both therapeutic and preventive purposes should be developed and recommended from a COVID-19 perspective.^[60]

Role of zinc in respiratory infection

Numerous investigations have demonstrated that zinc and certain zinc-dependent proteins support immunological control and antiviral defense in the respiratory system. In addition to preventing acute respiratory distress syndrome (ARDS) and ventilator-induced lung damage, zinc has been suggested to lower the viral titer after influenza infection, lower the respiratory syncytial virus (RSV) load in the lungs, and shorten the duration of viral pneumonia symptoms. Significant alterations in the lung's epithelial layer can result from zinc deprivation, potentially due to increased apoptosis, FasR signaling, and IFN γ and TNF α .^[61] Numerous publications have demonstrated the beneficial effects of zinc supplementation in respiratory infections.^[62,63]

Zinc and transcription factors

Zinc-finger-bearing transcription factors control both the innate and adaptive immune systems in humans. Zinc can therefore be expected to play both a direct and an indirect role in modifying intracellular signaling. Because they have a zinc-finger domain, crucial transcription factors including GATA-4/-5/-6 and KLF-4/-5 may be zinc-regulated targets during the formation of innate immune cells.^[64,65] Additionally, a crucial transcription factor for the formation of iNKT cells is the promyelocytic leukemia zinc finger. PU.1 transcription factor expression is critical for lineage commitment in myelopoiesis.^[66] Numerous transcription factors that contain zinc fingers have been found in relation to the adaptive immune system. Several transcription factors, including the zinc-finger transcription factors GATA-3 and Zbtb7b (Thpok, cKrox), are crucial for the proper differentiation into CD4+ T cells throughout T cell development.^[67,68] Furthermore, Th1 and Th2

subpopulation differentiation depends on GATA-3.^[69,70] The zinc-finger-containing KLF family, such as KLF-2/-3 in B cells, KLF-2/-13 in NKT cells, and KLF-2/-4/-10 in T cells, generally plays a significant role in immune cell differentiation.^[71] Thus, it is not unexpected that zinc-dependent KLF-10 regulation is one of the factors driving Treg differentiation.^[72]

The Herpesviridae

Zinc's impact on HSV-1 and -2 has been investigated for more than 40 years. In vitro research indicates that zinc inhibits nearly every stage of the viral life cycle, including viral polymerase function.^[73] protein synthesis and processing,^[74] and free virus inactivation.^[75,76] A more recent study utilizing the zinc ionophore pyrithione showed a decrease in HSV replication from decreased NF- κ B activation by interfering with the protein ubiquitination pathway, despite the fact that these investigations were conducted more than 20 years ago.^[77] Unfortunately, the mechanism by which zinc reduces HSV infection cannot be definitively demonstrated by any current experimental data. However, in vivo research in humans and mice has demonstrated a notable decrease in the burden of infection and illness. HSV-2 infection was significantly reduced in mouse experiments using intravaginal zinc inoculation in liquid^[78] or gel^[79] form. Numerous human topical zinc application trials have shown a^[78] markedly decreased duration of infection (outbreak) and recurrence.^[80,81] Free zinc may in fact coat HSV virions, preventing infection, according to the effectiveness of topical administration and in vitro findings.^[82,83] It is necessary to investigate this molecular mechanism further.

Additional respiratory tract illnesses include metapneumovirus, coronavirus, and influenza

The antiviral properties of zinc against other respiratory viruses have not been thoroughly studied. The addition of the zinc ionophore pyrrolidine dithiocarbamate.^[84] dramatically inhibits influenza (PR/8/34) replication in vitro, possibly via inhibiting the RNA-dependent RNA polymerase (RdRp), as was proposed thirty years ago.^[85] Similarly, zinc reduced the binding and elongation of the severe acute respiratory syndrome (SARS) coronavirus RdRp template in Vero-E6 cells.^[86] Furthermore, it was demonstrated that zinc salts inhibited the respiratory syncytial virus, even when zinc was merely incubated with HEp-2 cells before to infection before being withdrawn.^[87] The scientists speculate that by blocking viral membrane fusion, this suggests an inhibitory mechanism akin to HSV. However, neither the suppression of other elements of the viral life cycle nor changes in intracellular zinc levels were measured.

Togaviridae

Similar to flaviviruses, togaviruses are mostly arthropod-borne viruses like Chikungunya, Western horse encephalitis, and Semliki Forest viruses. Viral infection is caused via receptor-mediated endocytosis, which is followed by the release of particles into the cytoplasm

and the fusion of the virus and endosomal membranes.^[88] Zinc has been demonstrated to effectively prevent the membrane fusion of Sindbis and Semliki Forest viruses using liposome.^[89] red blood cell,^[90] and BHK-21.^[91] cell model systems. By attaching to a particular histidine residue that is visible on the viral E1 protein at low endosomal pH, zinc ions prevent membrane fusion.^[92]

Unfortunately, the large concentration of zinc (>1 mM) used in this model raises questions about its in vivo relevance. Interestingly, vesicular zincosomes, which are believed to function as intracellular zinc storage vesicles, contain enriched zinc.^[93] Zincosome fusion to viral endosomes may prevent important stages of the viral life cycle, such as togavirus membrane fusion, in a manner akin to how macrophages prevent intracellular Mycobacterium spp.

Retroviridae: HIV

Because of their special reverse transcriptase (RT), which enables the integration of retroviral DNA into the host genome, retroviruses are named for their capacity to transcribe RNA into DNA. The integrated provirus is a significant obstacle to virus treatment approaches, especially for HIV-1, and can subsequently create a latent infection that lasts the host's entire life.^[94] Zinc has also been found to suppress retrovirus RTs, much like viral RdRps,^[95,96] In 2011, Fenstermacher and DeStefano showed that Zn²⁺ cations can displace Mg²⁺ ions from HIV-1 RT, encouraging the creation of an extremely stable replication complex that is also very sluggish and inefficient.^[97] With the exception of molecular simulation studies that discovered the zinc-binding sites at the catalytic aspartate-25 residue,^[98] zinc has not received much attention since it was demonstrated to inhibit the HIV-1 protease in 199.^[99] and to impede viral transcription in 1999.^[100] Given its antiviral characteristics, it may seem paradoxical that HIV can also promote zinc influx into monocytes.^[101]

CONCLUSION

Zinc has a crucial function in human health, as evidenced by the strict regulation of zinc homeostasis both intracellularly and systemically. Despite making up just around 10% of the human proteome, zinc can trigger a number of signaling cascades, including the antiviral response, depending on whether it is free or attached to a protein. Trials using creams, lozenges, and supplements with high free zinc concentration confirm in vitro research that suggests free zinc may have strong antiviral effects. Zinc insufficiency has been linked to a variety of illnesses, however its exact source and effects are still unknown. Immune response changes brought on by prior zinc deficiency make people more vulnerable to infections. Zinc may be useful in preventing and combating COVID-19, according to recent research. Therefore, it is essential to consume enough zinc each day, which can be accomplished by taking zinc supplements. To establish standardized doses for

medicinal and preventive purposes, more research may be necessary.

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