GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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The biomedical importance of zinc and its use in treating COVID-19: An overview

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GSC Biological and Pharmaceutical Sciences, 2023, 25(01), 048–062

Publication history: Received on 14 March 2022; revised on 09 September 2023; accepted on 12 September 2023

Article DOI: https://doi.org/10.30574/gscbps.2023.25.1.0111

Abstract

Zinc deficiency makes us to realize the importance of zinc to human health becomes obvious. Even a mild zinc deficiency can impair hematopoietic and immune functions, leading to the destruction of pro-inflammatory phenotypes and redox metabolism. Although dysfunction of the immune system is the most obvious effect, zinc deficiency can destroy the function of many types of tissue cells. Decreased adhesion molecules and tight junction proteins and increased cell death lead to barrier dysfunction and possible organ failure. Zn deficiency, when combined, weakens the human body's resistance to pathogens while also increasing the risk of an overactive immune response that can cause tissue damage. The coronavirus disease (COVID-19) pandemic is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This has prompted scientists all over the world to work on finding new treatments for COVID-19. Aside from a weakened immune system, zinc deficiency causes several metabolic changes. The role of zinc in inhibiting covid-19, as well as the negative effects of zinc deficiency, are discussed in this review.

Keywords: Zinc; Zinc deficiency; Human health; Immune system; COVID-19; SARS-CoV-2

1. Introduction

Atomic number 30 in the periodic table indicates the chemical element zinc. It is a bluish coloration with smooth diamagnetic properties. It is the twenty-fourth most abundant thing in the Earth's crust and has a hexagonal crystal structure viewed in 5 steady isotopes. Zinc has a piece of prolonged information and was once significantly used in the historic world [1]. Zinc is concerned with a variety of organic processes. Zinc is required for the shape and catalytic characteristic of thousands of enzymes that alter the body's most vital metabolic pathways at the mobile and molecular levels [2]. Zinc regulates gene expression and is involved in signal transduction and neuronal transmission as a structural aspect of transcription factors [3]. Zinc is required for a range of cellular processes, including cell proliferation, differentiation, apoptosis, and keeping the integrity of mobile membranes [4]. Zinc is required for everyday growth and development, immune function, and cognitive function [5].

1.1. Zinc transporters

The zinc importer, Zrt- and Irt-like protein (ZIP), and the zinc transporter are two types of zinc transporter proteins (ZnT) [6] (Figure 1). The ZIP protein family transports zinc to the cytosol from the intracellular as well as extracellular compartments [7]. Zinc is transferred by ZnT from the cytosol to intracellular as well as extracellular compartments [8]. Any natural mutation in such proteins, or laboratory inhibition of these proteins' genes, reveals important information about zinc's function in the body. Similarly, the pathogenesis of many diseases is influenced by the mutation of these protein genes [9].

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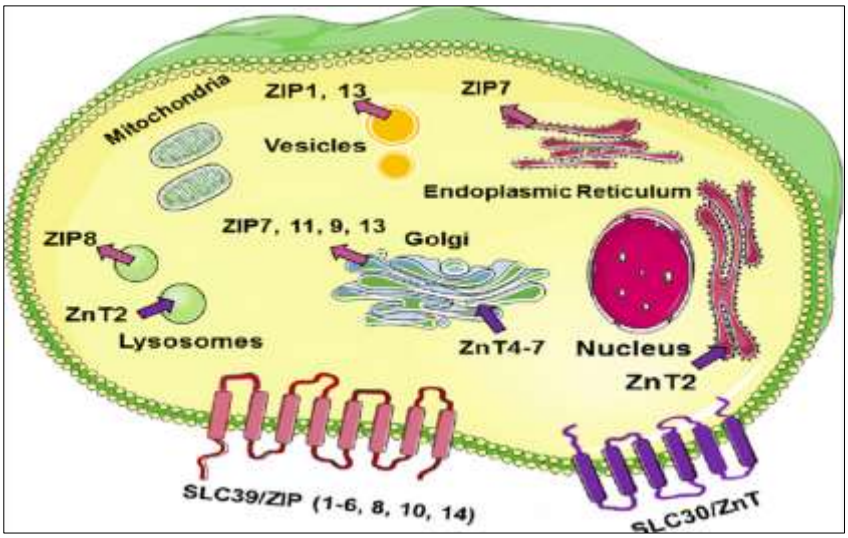


Figure 1 Zinc transporters ZIP and ZnT [10]

1.2. Zn metabolism

Zn is bound to and transferred by albumin (60%, low affinity) whereas transferrin in blood plasma (10 percent). Since transferrin also carries iron, too much iron may inhibit the ingestion of zinc [7]. Regardless of zinc intake, zinc concentrations are still relatively constant in the plasma. Zinc can be stored on reserves of metallothionein and carried by metal transporters of ZIP and ZnT family proteins [5]. In intestinal cells, metallothionein can adjust zinc absorption by 15–40% (Figure 2). Copper absorption is hampered by excess zinc because metallothioneins absorb both metals [11].

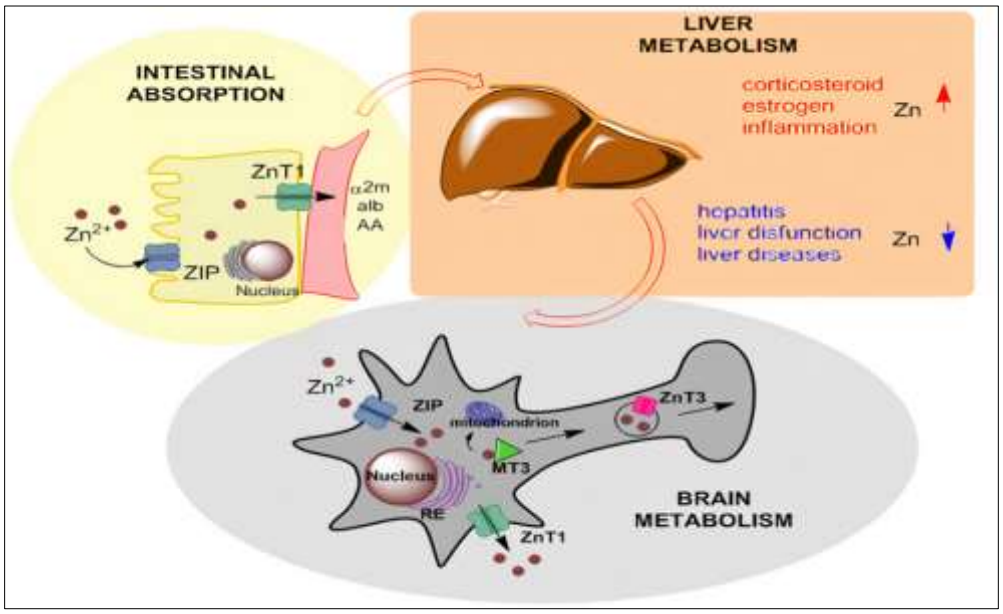


Figure 2 Generalized zinc absorption and metabolism [12]

1.3. Zn enzymes

Carbonic anhydrase (Figure 3) and Carboxypeptidase (Figure 4), two zinc-containing enzymes, are required for CO_2 regulation and protein digestion, respectively [5]. Carbonic anhydrase converts CO2 to bicarbonate in vertebrate blood, which is then converted back to CO_2 for exhalation through the lungs (Figure 1). Without the enzyme, a million times longer conversion would require a normal blood pH of 7 or a pH of 10 or higher. Throughout protein digestion, carboxypeptidase cuts down peptide linkages. The C=O zinc group makes a covalent bond to a terminal peptide, giving a positive charge to the carbon [13]. This helps to generate a hydrophobic pocket on the enzyme near the Zn that is

capable of digesting the nonpolar part of this protein. Zn has a structural function in zinc fingers. Zinc fingers are proteins that are found in various transcription factors and detect DNA basis sequences during transcription and replication of DNA. In transcription factor, by coordinatingly binding to 4 amino acids, each of a zinc finger's nine or ten Zn2+ ions contribute to the finger's structure [14]. The transcription factor binds to the DNA sequence by wrapping its fingers around the DNA helix. Histidine amino acids, cysteine, glutamic acid, and Aspartic acid have side chains that Zn ions bind to. The metal also possesses a flexible geometry of coordination, which allows proteins to easily modify conformation in biological processes [7]. In response to increases in intracellular zinc and other heavy metals, MTF-1 translocates from the Cytosol to the nuclear (cadmium and copper). Because the metal response components of this transcription factor are tied in with the proximal promoters, the transcription rate rises. The relevance of MTF-1 in zinc homeostasis, as well as mammalian physiology, is shown by the fact that mice with the knocked-out gene suffer serious liver deterioration and embryonic death. Following that, in the mouse that has a liver-specific conditional deletion of the gene MTF-1, researchers found another MTF-1 controlled zinc transporter gene, ZIP10. In the liver, MTF1 is a critical ZIP10component connected to cellular zinc homeostasis according to an experiment on isolated mouse hepatocytes. MTF-1 has physiologic significance, according to the findings, and can act as a ZIP10 repressor when cellular zinc levels are normal. Repression is removed by the depletion of cellular zinc as well as MTF-1, which allows transcriptional activation to increase ZIP10 [15]. The results also demonstrate that ZIP10 is a unique target for the investigation of dietary impacts in the liver and certain brain areas on zinc metabolism. ZIP transporters are considered crucial for the maintenance of homeostasis of cellular Zn, and zinc is supposed to perform secondary brain activities [5].

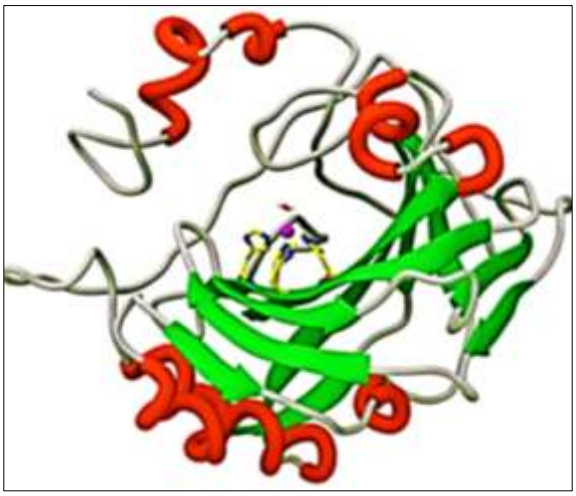
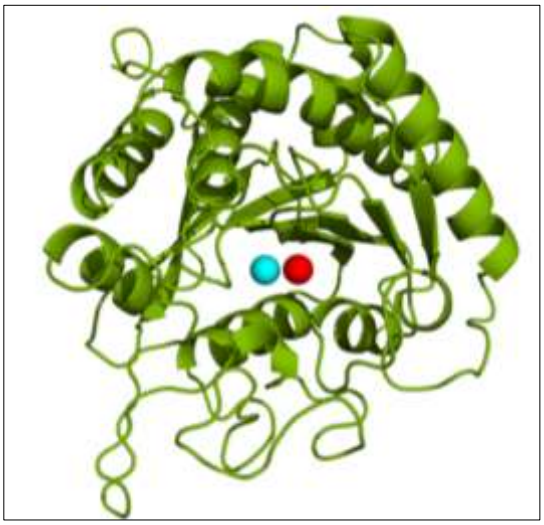


Figure 3 Carbonic anhydrase [16]



[Image source: https://proteopedia.org/wiki/index.php/Carboxypeptidase]

Figure 4 Carboxypeptidase

1.4. Zinc homeostasis

Survival needs the capability, despite changing external conditions, to sustain a continuous interior state. In an organism, if the nutritional flow is balanced, known as homeostasis, and if the nutrient is continuously retained, as during growth, reproduction, or lactation, it is called homeorhesis [17]. In the gastrointestinal system, Zinc excretion as well as absorption, particularly small intestine, pancreas, and liver elegantly control systemic zinc homeostasis. Zinc absorption changes along with excretion in the gastrointestinal tract are the key processes used to maintain zinc homeostasis [18]. Extremely low or high zinc intakes cause changes in renal excretion as well. Zinc redistribution in tissues and cells has a significant role to play in maintaining zinc homeostasis. It is critical for normal function to maintain cellular zinc nutrition constant state, also known as homeostasis. Primarily Zinc homeostasis is maintained by zinc absorption changes as well as intestinal excretion from endogenous in humans along with animals [19]. The endogenous excretion in the gastrointestinal tract and changes in zinc absorption work together. Endogenous excretion appears to shift quickly in response to changes in intake that are just above or below ideal. Zinc is slower to absorb, but it can cope with significant intake variations. In situations of extremely low zinc consumption or extended marginal intakes, secondary homeostatic adaptations may exacerbate gastrointestinal abnormalities. Secondary alterations involve changes in urinary zinc excretion, shifts in zinc turnover in plasma, and perhaps eager retention of zinc released into other functional tissues from chosen tissues such as bone [20]. Zinc influx into cells and efflux out of cells, cellular compartmentalization, as well as storage, are all involved in maintaining cellular zinc homeostasis. A wide proteins range, involving zinc-binding proteins and zinc transporters are involved in these processes. Zinc transporters are found on the plasma membrane and the organelles' membranes [21]. Two distinct yet interacting types of zinc transportation proteins that have till now been discovered are the Zin Importers (SLC39/ZIPs) as well as the Zinc Exporters (SLC30/ZnTs) [8]. Zinc is transferred from the extracellular or intracellular organelles into the cytosol via the ZIP family (ZIP1 to ZIP14). Several proteins, involving zinc-binding proteins and zinc transporters, are involved in these processes. Zinc transporters are found on the plasma membrane and the membranes of organelles. Two distinct yet interacting types of zinc transportation proteins that have till now been discovered are the Zin Importers (SLC39/ZIPs) as well as the Zinc Exporters (SLC30/ZnTs). Zinc is transferred from the extracellular or intracellular organelles into the cytosol via the ZIP family (ZIP1 to ZIP14). ZnT1 is part of the ZnT family that exports zinc from the cytosol to intracell or extracellular organelles. ZnT1 is a ZnT10 family member. In general, ZIPs regulate cytosolic zinc levels positively and ZnTs negatively, whereas ZnTs regulate organelle zinc levels positively and ZIPs negatively. The cell contains almost no free zinc, and Dynamic cell activities need a continuous movement of zinc from one area to another, or from one location to another [22]. The major intracellular zinc reservoirs are metallothioneins (MTs) and glutathione (GSH). MT proteins are classified into four isotypes: MT-I to MT-IV. The structure of MT consists of two categories of zinc/thiolate one binding to three categories of zinc ions and the other top four. One MT molecule may bind up to seven Zinc ions under physiological requirements and is the main zinc reservoir [14]. Zinc is a major role in both MTs and GSH which regulates several cellular processes and transferring to apoproteins to functional zinc proteins. Certainly, zinc-binding proteins such as pyridoxal kinase, thermolysin, alkaline phosphatase, carbonic anhydrase, estrogen receptors, along with zinc finger peptides have been shown to accept oxidatively released zinc from MT in cell-free systems [23]. Signal transduction, second messenger metabolism, protein phosphorylation, and gene expression are just a few of the cellular functions that these proteins and peptides play [24].

1.5. Zinc Deficiency in Humans

The signs of zinc deficiency are growing retardation, a lack of appetite, and a decreased immune function. The signs of zinc deficiency are loss of hair, diarrhea, delayed sexual maturation, impotence, male hypogonadism, and skin and eyes diseases. Other signs include loss of weight, delayed injury, abnormality in the taste, as well as mental lethargy. Because most of these symptoms are non-specific or other health issues might be misinterpreted, a medical check is needed to determine whether a zinc deficiency occurs [26].

Zinc nutritional condition with laboratory testing is difficult to evaluate because it is found in a variety of proteins and nucleic acids throughout the body. Zinc deficiency is most frequently evaluated by plasma or serum zinc levels, however, due to strong homoeotic control mechanisms this level doesn't necessarily represent cell Zinc status. Zinc deficiency can have clinical effects even if there are no abnormal laboratory indices. Clinicians consider zinc deficiency symptoms as well as risk factors (for example insufficient caloric intake, digestive diseases, and alcoholism). When determining the need for zinc supplementation, consider factors including impaired growth in children as well as infants [27,5].

Severe Zinc Deficiency: It is one of three types of zinc deficiency. A severe zinc deficit may be fatal after complete zinc less parenteral feeding, following penicillamine treatment, and in individuals with acute alcoholism as has been shown in acrodermatitis enteropathica (AE). Bullous Pustular dermatitis, intercurrent infections, mental disturbances, alopecia, and diarrhea due to cell-mediated immune deficiency are some of the clinical manifestations of severe zinc

deficiency; if zinc deficiency cannot treat properly, it can be fatal. A mutation in the ZIP-4 zinc transporter produces AE, leading to zinc malabsorption [28,29].

Moderate Level of Zinc Deficiency: Delayed wound healing, abnormal dark adaptation, mental lethargy, poor appetite, skin changes, hypogonadism, and growth retardation are a few moderate symptoms of zinc deficiency in humans. Nutritional factors, chronic renal ailment, sickle cell illness, malabsorption, as well a few other debilitating diseases have all been linked to moderate zinc deficiency [28,30].

Marginal Zinc Deficiency: An experimental protein diet based on soybean caused a mild zinc deficiency in healthy human volunteers. Except for zinc, the diet met every suggested dietary allowance for protein and essential macro-and micronutrients [28,28,30]. Intake of zinc has been limited to 3 to 5 milligrams per day. Zinc RDA for adults is 12-15 mg per day.

1.6. Immune Function in the Presence of Zinc Deficiency

Zinc deficiency is very harmful to the human immune system [32]. Subclinical zinc deficiency impairs cellular mediators of innate immunity involving macrophage and neutrophil phagocytosis, natural killer cell activity, oxidative burst generation, as well as complement activity, to name a few. Increased susceptibility to infection is a result of these changes [33]. Zinc, *In vitro* studies and research on zinc-deficient individuals, is necessary for both cell-mediated and humoral immunity. Reducing lymphocyte counts (lymphopenia) and poor growth of lymphocytes are all typical signs of zinc deficiency, increased apoptosis, decreased proliferation, and thymic atrophy [34]. Experimentally generated zinc-deficient patients showed reduced serum thymulin activity, poor T cell activity, and natural cell killers, and lower IL-2 and interferon levels [35]. Zinc deficiency has a particularly negative impact on infection defenses. The skin's barrier functions, as well as gastrointestinal and pulmonary tracts, are harmed, and most immunologic cells' function, development, or both, are negatively impacted [36]. Zinc supplementation can help to converse the negative zinc deficiency effects, such as impaired development of immune cells, a weakened T-cell-mediated immune response, along the reduction in an oxidative burst, among other things [37]. Zinc supplementation has a wide range of potential benefits, including anti-inflammatory and immunomodulatory properties, allergy and autoimmunity prevention, and allogeneic reactions suppression [38]. A deeper knowledge of the molecular actions of zinc and their regulated management could provide a helpful tool in the future for tailored regulation of the immune system with minimum adverse effects [7].

1.7. Zn intake recommendations

Consumption of dietary references published by the National Academy of Institute of Medicine by the Food and Nutrition Board (FNB) includes recommendations of Zn intake [26]. For zinc Table 1 shows the current RDA (Recommended Dietary Allowances). However, the Zn intake differs in Pregnant and lactating women.

Table 1 Zn intake recommendations

Age	Male (mg)	Female (mg)
0-6 months	2*	2*
9-12 months	3	3
1-3 years	3	3
4-8 years	5	5
9-13 years	8	8
14-18 years	11	9
19 years and above	11	8

(* Adequate Intake); [Table source: https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/]

1.8. Groups at risk for Zn deficiency

Zinc deficiency affects people belonging to different ages and based on their lifestyle. A few of the Groups at risk for zinc deficiency and the mechanisms that cause it are listed in table 2.

Table 2 Groups at risk for zinc deficiency and the mechanisms that cause it [39]

Category	**Mechanism**
Elderly	Epigenetics, a reduction in dietary intake, and a decrease in absorption.
Children	Specifically, malnutrition and vulnerable populations in the developing world.
Vegetarian	Consumption of zinc-rich foods is low, and phytate levels in the diet are high (zinc chelation)
Vegan	
Diet high in cereal grains	Higher phytates in diet (zinc chelation)
Alcoholics	Malabsorption as well as increased excretion
GI tract disease	E.g., malabsorption increased excretion and reduced dietary intake

- Pregnant and lactating women: Pregnant females are more likely to be zinc deficient due to increased fetal zinc needs, specifically those who begin pregnancy with low levels of zinc. Zinc reserves in the mother may be depleted by lactation. As a result, the RDA for zinc in lactating and pregnant women is higher than in other women. The purpose of this study has been to look at the interrelationships between trace elements such as zinc, copper, and iron in blood samples from pregnant women. Copper levels were found to be considerably greater in iron-deficiency anemia than in non-iron deficiency anemia and were also higher in non-anemic pregnant women than those of non-anemic non-pregnant women [controls]. When compared to other groups, the zinc level in iron deficiency anemic pregnancy was significantly lower. There is evidence that pregnancy affects blood trace element levels. This could be due to competitive inhibition of trace element absorption in the intestine, or it could be a result of hormonal changes [estrogen, insulin] throughout pregnancy [5, 41].
- Breast-fed babies: In breast-fed babies, zinc deficiency is a rare disease caused due to low zinc levels in their mother's milk. Early newborns acquire a zinc deficit more often than full-term infants, because, despite their high zinc requirements, they do not have enough body reserves for zinc and are unable to absorb zinc from the stomach. In the first four to six months of life breast milk contains an adequate amount [2 mg/day] of zinc, but not enough for babies 7-12 months of old who require 3 mg/day. Children 7-12 months of age should take in addition to breast milk suitable food or formula containing zinc. Few children with mild-to-moderate growth failure and zinc deficiency have seen an improvement in their growth rate after taking zinc supplements [5,42,43].
- People with gastrointestinal diseases: Digestive disorders and Gastrointestinal surgery like short bowel syndrome, Crohn's disease, as well as ulcerative colitis, can reduce zinc absorption whereas rising endogenous zinc losses, mainly from the gastrointestinal tract [5, 44].
- Vegetarians: Phytates, found in whole-grain bread, legumes, cereals, as well as other foods that are bound to Zn whereas preventing it from being absorbed. As a result, Zinc bioavailability in grain and plant meals is lower than that of animal foods, however, there are still good sources of zinc for many grains and plant foods [5,43].
- People with sickle cell disease: According to the findings of a large cross-sectional survey, the low plasma zinc level of 44% of children with sickle cell disease might be caused by higher dietary needs and/or poor nutritional status. Zinc deficiency is also common in adults with sickle cell disease, affecting 60–70% of them. It has been demonstrated that zinc supplementation helps children with sickle cell anemia to develop more quickly [5,45].
- Diarrhea: Excessive zinc loss is also a result of chronic diarrhea. In Southeast Asia, South America, Africa, and India malnourished children have less and shorter infectious diarrhea following a group randomized controlled trials analysis, due to zinc supplementation. In such studies, children were given 4–40 mg of zinc acetate, zinc gluconate, or zinc sulfate per day. Similar results have been found in a meta-analysis published in 2008 and 2007 evaluation of a zinc supplement to prevent and cure diarrhea both reported similar findings. However, in children zinc supplementation effects on diarrhea with adequate zinc levels, which is the case for the vast majority of children, are unknown. Short-term zinc supplementation (20mg/day, or 10mg for 6 months infants, for 10days to14 days) is now recommended by the WHO and UNICEF to treat acute childhood diarrhea [5,46].
- Alcoholics: As the use of ethanol decreases the absorption of the gut and increases the excretion of urine zinc, around 30-50 percent of alcoholics are deficient. Furthermore, numerous alcoholics consume a limited variety and amount of food, resulting in insufficient zinc intake. Acrodermatitis enteropathy is an influencing form of acrodermatitis. Zinc supplement is an efficient therapy for enteropathy acrodermatitis, a recessive autosomal disease caused by an inborn metabolic mistake in zinc. Pustular dermatitis, diarrhea, and nail dystrophy are all

symptoms of zinc deficiency. Atrophy of the brain cortex causes irritability and emotional disturbances. The disease's severity is appropriate [5,47].

2. Zinc and its antiviral properties

Zinc's efficacy as an antiviral agent has been studied extensively *In vitro*. Furthermore, zinc levels are often far greater than the physiological level needed for antiviral action. For example, zinc levels in human plasma vary from 10 to 18 M, while antiviral zinc can reach mM [46, 48]. Intracellular zinc concentrations range from tens to hundreds of micrograms, but zinc-binding proteins like metallothionein's significantly reduced free zinc concentrations to picomolar to low nanomolar levels. Even though zinc's antiviral properties are virus-specific, it appears that the availability of zinc ions has a key role to play in zinc's antiviral efficacy [49]. In this paper, we are discussing the function of zinc as an anti-virus, encompassing both in-vitro mechanical and clinical testing on a human basis. Zinc reduces infection and inflammation, improves mucous clearance, prevents ventilator-induced lung injury, and modulates antiviral as well as antibacterial immunity, all of which are beneficial in the prevention and treatment of Covid-19 [49,50].

3. Zinc and COVID-19

The 2019 NOVEL CORONAVIRUS OF DISEASE (COVID-19) has been caused by the SARS-CoV-2 virus that may cause a severe respiratory illness [51]. The connection between the SARS-spike CoV-2 (S protein) receptor-binding field and the peptidase area of angiotensin-conversion enzyme 2 (ACE2) was discovered in a recent study as crucial for viral entrance into host cells. 1 ACE2 inhibitor was recommended as a possible treatment for COVID-19 due to the significant connection between ACE2 and SARS-CoV-2 infections [52,53]. We think that the trace mineral zinc is already a safe potential ACE2 inhibitor that might decrease SARS CoV-2's capability of infecting cells. Given the extensive usage of zinc supplements that are safe and available in moderate dosages and that have no prescription, we consider that it is urgent to verify if zinc may be used for prophylactic treatment in the form of COVID-19 [43].

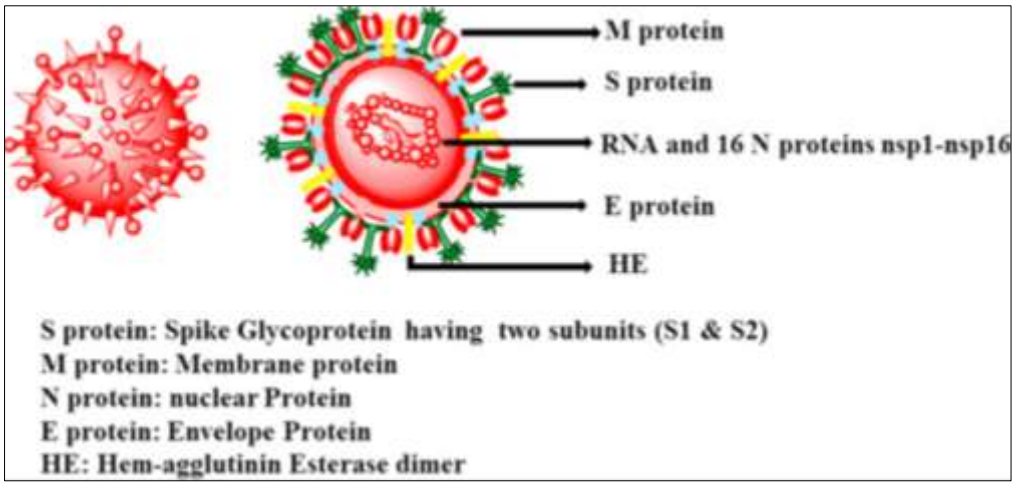


Figure 5 Structural elucidation of SARS-CoV-2 [56]

The enveloped, positive-strand SARS-CoV-2 RNA virus is around 80 percent similar to the SARS-CoV virus which resulted in the 2002-2003 outbreak of SARS. At that time the researchers found a viral infection mechanism connection between the S protein of SARS-CoV with ACE2. 4 ACE2 is an integral membrane protein of type I found in the intestine, heart, kidney, and lungs on the surface of the epithelial cells and is defined by the zinc-binding domain HEXXHE. In the upper respiratory tract cells and oral epithelial cells, ACE2 was also detected. This may explain why SARS-CoV-2 is so infectious and why symptoms such as pneumonia and diarrhea are so prevalent. COVID-19 is so common. Whilst ACE2 is a metallopeptidase of zinc the exogenous zinc impacts its activity is little studied. According to research, zinc impeded the capacity of ACE2 to dose-dependent metabolize the substrate from levels up to 10mM, which means zinc can block the interaction between the proteins of SARS-CoV-2 S and ACE2 [54, 55, 57].

Zinc is a trace mineral that has been linked to the treatment of the common cold due to its ability to inhibit viral replication and attachment to the nasopharyngeal mucous. Zinc appears to alter the effects of several respiratory pathogens *In vitro*, including rhinovirus, respiratory syncytial virus, and SARS-COV.[58].

Zinc has anti-inflammatory properties, inhibits NF-KB signaling, and regulates T cell function, all of which help to keep the cytokine storm to a minimum. Zinc was shown to have antiviral properties *In vitro* by inhibiting SARS-CoV RNA polymerase [59]. Indirect evidence suggests that zinc may reduce angiotensin-converting enzyme 2 activity (ACE2), a SARS COV-2 receptor. Inhibiting caspase-3,-6, and 9, also improves the cell's resistance to apoptosis. Zinc's antiviral properties are also linked to zinc-binding proteins called metallothionein's (MTs), which store and transport zinc [60, 61].

In vitro, RNA-dependent RNA polymerase against SARS CoV was already found to be inhibited by zinc. Furthermore, as large intracellular zinc concentrations are difficult to develop, administering preventive zinc alone may not work with SarCoV-2. When coupled with zinc ionophores, including chloroquine (hydroxychloroquine), chloroquine (hydroxychloroquine) will improve cellular absorption and will hence be more likely to reach adequate intracellular level levels. This combination has been already studied as a preventive scheme in a randomized clinical study [61]. Adding zinc sulfate to hydroxychloroquine and azithromycin during hospitalization did not result in a reduction in stay length, the average inspired oxygen fraction, or maximum inspired oxygen fraction in univariate analysis, an average flow rate of oxygen, a maximum flow rate of oxygen, and mechanical ventilation duration. Following the time adjustment of zinc treatment, it was found that zinc sulfate was added in hydroxychloroquine and azithromycin linked with decreased mortality or hospice transition in patients who did not have an ICU level, but this was not significant in ICU patients. This observation could be linked to the suggested action mechanism in COVID-19 for zinc sulfate. Zinc *In vitro* has been demonstrated to decrease RNA polymerase SARS-CoV activity dependent upon RNA. As a result, zinc has a significant role to play in preventing the virus from progressing to serious disease, but once the cytokine storm, or abnormal production of systemic immune mediators, begins, zinc may not be effective for a long time. If used early in the presentation with COVID-19, their outcomes suggest that zinc sulfate and hydroxychloroquine may have a therapeutic synergistic mechanism. Despite the interest in zinc sulfate as a prevention therapy, their findings do not support a prophylactic benefit in the absence of a zinc ionophore. To help answer this question, a zinc sulfate prophylactic strategy should be evaluated [35, 62-65].

The RNA sequences of SARS-CoV, as well as SARS-CoV-2, are strikingly similar. In 2005, the mechanism of SARS-CoV infection was identified in great detail. Both of these viruses are thought to have the same mechanism, which has led to the advancement and knowledge application in SARS-CoV-2 study. The SARS-CoV virus primarily infects the lungs. Angiotensin-converting enzyme (ACE) 2 is a virus receptor found in the lungs, primarily in the endothelium, alveolar cells along vascular epithelial cells (pneumocytes—type II). Both SARS-CoV, as well as SARS-CoV-2, utilize their envelope spike proteins for infecting mammalian cells. Both viruses require the envelope's spike (S) protein to infect the envelope's cells, and those spike proteins have an amino acid homology of 76.5% and an almost similar 3D shape to attach to the spike(S) envelope protein receptors of ACE-2. Nevertheless, SARS-CoV-2 has a greater affinity than SARS-CoV for receptors, which might explain the enhanced pathogenicity. ACE-2-binds SARS-CoV and SARS-CoV-2 cause the serine-2 serine transmembrane (TMPRSS2) to be activated and cells may be accessed. The activation of TMPRSS2 could be to blame for COVID-9's fatal conditions. Furthermore, ACE is a significant RAS (renin-angiotensin system) component. RAS is involved in hypertension pathogenesis and such complications that accompany it. Endothelial dysfunction can also lead to hypertension. As a result, RAS modulation and ACE inhibitors are important for treating hypertension. ACE is a protein that transfers angiotensin I to angiotensin II (vasoconstrictor). Angiotensin II maintains vascular tone and cardiac functions by degrading bradykinin (a vasodilator). ACE is a zinc metallopeptidase that requires zinc for the catalytic activity of the enzyme. The enzyme includes a g-atom of zinc per mole of protein. As a consequence, Zn has a vital role in heart function and can also contribute to viral infection prevention [66-69].

Zinc was discovered for improving and refining the morphology of cilia, as well as increasing their frequency and length of beating. It also acts as a membrane stabilizer and aids in the maintenance of the cytoskeletal system. The tight membrane junctions of proteins including claudin-1 and ZO-1 are increasing in expression to enhance the respiratory epithelial barrier function. The respiratory epithelial lining is further protected by improved antioxidant function, as well as the suppression of caspase activation and apoptosis. Zinc is supposed to stop viral entrance as well as replication by inhibiting RNA polymerase, which depends on the RNA (RdRp). Zinc also decreases the expression of angiotensin-converting enzyme2 (ACE-2) receptors, produced by Sirtuin 1(SIRT-1), reducing the probability of viral binding to the ACE2 receptors. Zinc also affects the immune system as well as causes leucocytes to produce more interferon (IFN). The synthesis of antiviral proteins such as latent ribonuclease and protein kinase RNAs is increased by zinc, which can cause viral RNA degradation through increased production of IFNs. Zinc was shown for increasing the activity of Natural Killer cells, B Cell Receptor Signaling, and Cytotoxic T cells, as well as the production of antibodies. By modulating and balancing cytokines, also affects the regulatory activities of T-cells, limiting the hyperactivation of hyperimmune response to the immune system [18,70-73].

COVID and zinc Mechanical ventilation may be needed as a supportive treatment for 19 patients with ARDS (acute respiratory distress syndrome). Human patients with ARDS have lower plasma zinc levels than non-ARDS ICU as well as healthy controls. Moreover, though mechanical ventilation is required to help ARDS patients, this exacerbates lung injury by activating signaling pathways activated by mechanical stress. Zinc along with its downstream target protein MT (metallothionein) was found to be important in improving tolerance to mechanical ventilation-induced lung injury, according to the findings. Zinc deficiency increases lung injury and lowers MT levels in mice, according to in vivo studies. Pneumonia and zinc- Inadequate zinc levels in the blood were proposed as a pneumonia risk, as well as numerous studies showed that zinc can shorten the illness duration. Zinc supplementation significantly reduced fatalities from severe pneumonia, according to Srinivasan et al., but did not affect recovery time. Brooks et al. found that supplementing 20 mg of zinc daily for seven days reduced recovery time and improved symptoms in patients with severe pneumonia in a double-blind placebo-controlled trial. Roscioli et al. looked into the effects of zinc and how it regulates airway function. Zinc is required for the functional integrity of the airway epithelium, and zinc deficiency promotes apoptosis of airway epithelial cells, according to the study. Overall, zinc supplementation can ease inflammation of the airway and destruction of cells caused by massive infection and mechanical ventilation as well as zinc supplementation can minimize airway inflammation and inflammation caused by severe infection 32, 74-77].

4. Zinc deficiency and COVID-19

Zinc supplementation may help with COVID-19 treatment and improve the effectiveness of medications like remdesivir, dexamethasone, and ribavirin. When COVID-19 patients are admitted to the hospital, the vast majority of them have a severe zinc deficiency [72].

Zinc deficiency affects hematopoiesis and disrupts the balance of innate and adaptive immune cells, primarily affecting lymphoid cells. A zinc deficiency could set the stage for cytokine release syndrome. Zinc deficiency and vascular complications: a possible link between multiple organ complications. The history of zinc deficiency has been linked to the rapid progression of respiratory diseases. During zinc deficiency, epithelial barrier integrity is disrupted, allowing severe acute respiratory syndrome-Coronavirus-2 and co-infections to take hold. Wound healing and tissue regeneration are slowed by pre-existing Zn deficiency. Zinc deficiency is a precursor to virus-induced neuronal damage and sensory loss [46, 72].

All COVID-19 samples were tested for serum Zn levels, which were then assigned to survivors or non-survivors. The EPIC cohort has been used to determine the serum Zn laboratory reference range in healthy European teenagers. In this regard, EPIC data had been utilized to calculate the 95 % interval of the observed concentrations with a lower limit of 642.5 g/L (Zn deficit), representing the lowest 2.5 percent of Zn values. The majority of COVID-19 patients' samples fell below the Zn deficiency threshold. Non-survivors' samples had lower Zn levels than survivors' samples, with some values signifying severe Zn deficiency. Especially, few of the survivors' samples had a Zn status that was not suppressed, which was higher than the control EPIC cohort's median [46,77].

At the European Society of Clinical Microbiology and Infection Diseases (ESCMID), the recently concluded Conference of Dr. Güerri-Fernández and his colleagues has presented retrospective analysis data on zinc mortality in patients admitted to hospitals in Spain. A total of 8 percent (21 patients) of the 249 patients studied died. The researchers discovered that COVID-19 patients who died had a significantly lower plasma zinc level (43 lg/dl) than those who survived (63.1 lg/dl). After controlling for a variety of factors, the researchers found that the rise in plasma zinc of each unit resulted in a 7 percent reduction in-hospital mortality at the time of admission to the hospital. In addition, the significance of maintaining sufficient zinc balance was demonstrated in patients with plasma zinc levels of less than 50 lg/dl at the time of admission, 2.3 times greater than those with plasma zinc of 50 lg/dl at the time of admittance. Incomparable research, the levels of serum zinc in COVID-19 patients are lower than those in healthy controls [56, 78-80].

Zinc deficiency affects both kinin-kallikrein and renin-angiotensin systems, whose dysfunction is an important COVID-19 pathophysiology mechanism, potentially exacerbating COVID-19 symptoms. Zinc deficiency causes ACE2 dysfunction, which increases its enzymatic activity and, while not proven, may be responsible for increased SARS-coV-2 binding. Zinc deficiency causes ACE2 dysfunction, which could exacerbate COVID-19-induced ACE2 downregulation. Both systems are affected by ACE2 dysfunction, which increases des-Arg9-bradykinin, angiotensin II, and Lys-des-Arg9-bradykinin, as well as increased vasoconstriction, pro-inflammatory, along with prothrombotic effects. Furthermore, Zinc deficiency affects the function of cathepsin L, leading to a deficit of bradykinin at the infection site as well as reduced vasodilatory activity. Finally, the deficiency of zinc impedes activation of the contact system by blocking endothelial cell binding HMWK, prekallikrein, and FXII binding to endothelial cells, resulting in increased FXII accumulation along with bradykinin deficiency [83, 85].

5. COVID-19 and zinc supplementation

Zinc supplementation in COVID-19 patients may help to slow the progression of the disease by reducing ROS and improving the immune response to the infection [86].

A range of effective supplemental studies concentrating on respiratory tract infection supports our argument about the prevention and treatment of COVID-19 by zinc supplementation. Zinc supplementation with prophylactic was more efficient in the majority of instances than treatments [46,87]. Coronavirus infections cause up to 30% of all common respiratory infections, also known as the "common cold." Studies demonstrate that administration of zinc lowers the intensity, frequency, and duration of the common cold depending upon the dose, zinc component, and starting time after early symptoms [88]. Most importantly, zinc supplementation of children has been shown to have significant benefits in several studies, reducing pneumonia-specific mortality by 15% and pneumonia morbidity by 19% in developing countries [89].

Zinc can increase the cytotoxic activity of natural killer (NK) cells that attack cells in their plasma membrane with abnormal or unusual proteins. The NK cells are removed as well as destroyed by neutrophils and macrophages, that relocate to infected regions and employ phagocytosis to eliminate infected areas. In NK cells, infected areas are killed. Zinc also works as an anti-inflammatory agent in addition to being involved, in particular IgG, by inducing the formation of Treg cells to maintain immunological tolerance and blocking the development of pro-inflammatory Th17 and Th9 cells [46,86]. The micro-array study of population alterations in t-lymphocytes reveals variations in the expression of several genes associated with the proliferation, survival, and responsiveness of T-cells in mild zinc deficiency. In particular, the shortage of zinc among the elderly is quite prevalent, and diagnosis is challenging owing to a lack of clinical symptoms and accurate biochemical indicators and a lack of a particular and reliable zinc biomarker [86]. Numerous factors are determining how much zinc has to be eaten every day, including age, sex, weight, and the quantity of phytate in your diet. In the United States, the DRI recommends adult diets of 11 mg per day for men and 8 mg per day for women, respectively intakes of food and nutrition. In addition to a reduced dietary zinc intake, several variables linked to aging, such as intestinal absorption, medicinal interactions, and subcellular processes, may endanger its effectiveness. Zinc supplementation should be evaluated on an individual basis, taking into account zinc deficiency cases, low dietary intake, as well as diseases associated with zinc deficiency. According to studies that looked at different doses and durations of zinc supplementation, 20-40mg per day looks to be an effective and safe dose. It's important to note that these values aren't universally agreed upon [5, 85-89].

Superoxide dismutase is a cell cytosol that defends against oxidative stress that is located in the mitochondria and requires zinc as a cofactor. In contrast, excess zinc promotes cell oxidative stress. A narrative review revealed enough evidence that several viruses including influenza (10 mg/kg body weight, 600 mg/d total), have shown antiviral action of zinc [79]. For both innate and acquired antiviral responses, zinc is also necessary. The authors concluded, however, that there is a need for further study of the antiviral processes and the clinical advantages of zinc additional therapy for viral infections. According to the current study, the elderly is at risk for zinc deficiency that makes them more susceptible to infections like pneumonia [89]. In this group, zinc supplementation (i.e., elemental zinc, 30 mg/d) may be sufficient for improving reduced infection and risk immune function. Zinc has been shown to impede binding and elongation in Vero-E6 cells of the SARS coronavirus RNA-dependent polymerase (RdRp) template. Though oysters have the highest zinc content per serving, lentils, beans, sesame seeds, pumpkin seeds, nuts, red meat, and poultry are the most common sources of zinc [87, 88].

5.1. Limitations and Risks of Zinc Supplementation

Zinc salts like Zn-picolinate, Zn-sulfate, Zn-acetate, and Zn-gluconate can be prescribed as adjuvant therapy. Each salt, however, has a different amount of elemental Zn. Zn-sulfate, for example, contains about 23% elemental Zn, so a 220mg Zn sulfate tablet would be needed to get 50 mg of Zn. It's important to remember that the recommended daily Zn allowance varies depending on an individual's age, gender, and health. The daily recommended allowance of elemental Zn for healthy adults is usually 15–30 mg. Despite the positive effects of zinc on immune response, long-term high-dose zinc consumption leads to a reduction in high-density lipoprotein cholesterol levels, copper deficiency, anemia, and genitourinary complications risk [5, 79, 80].

6. Conclusion

Without a doubt, the use of zinc as the treatment COVID-19 is supported by a variety of published research. The intracellular content of free zinc in COVID-affected cells and tissue should also be increased for zinc to exert its intended therapeutic action. The quantity of zinc needed to therapeutically impact COVID 19 patients is not yet known. There is

no definitive understanding. Differences in zinc bioavailability induced by varied formulations, dosages, and administration modalities, especially problems that impact oral zinc bioavailability, like preexisting zinc insufficiency. In patients with COVID19, randomized controlled trials (RCT) should be considered, particularly in combination with an ionophore (such as HCQ). Zinc is important in many aspects of life. The immunomodulatory role of Zn is readily apparent during infection. If combined with chloroquine, Zn supplementation has a significant role to play in treating COVID-19 patients in the present SARS-CoV-2 pandemic, such as adding immune-boosting effects to antiviral drugs and halting the SARS-CoV-2 replication in infected cells. In light of this discussion, a Zn supplement in the form of a suitable Zn-salt can be given orally.

Compliance with ethical standards

Acknowledgments

The authors of this paper would like to express their gratitude to the RSST trust in Bangalore for their ongoing support and encouragement.

Disclosure of conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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