



## **Immunomodulatory Effects of Zinc as a Supportive Strategies for COVID-19**

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### **Authors' contributions**

*This work was carried out in collaboration with all authors. All authors read and approved the final manuscript.*

### **Article Information**

DOI:10.9734/JPRI/2020/v32i1330577

#### **Editor(s):**

(1) Dr. Rafik Karaman, Al-Quds University, Palestine.

(2) Dr. Syed A. A. Rizvi, Nova Southeastern University, USA.

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(2) Marsida Krasniqi, University Aleksandër Moisiu Durrës, Albania.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/59328>

**Review Article**

**Received 08 July 2020**  
**Accepted 29 July 2020**  
**Published 01 August 2020**

### **ABSTRACT**

Coronaviruses 2019 (Covid-19) is a massive family of viruses that causes respiratory illnesses ranging from the common cold to the most severe conditions such as Middle East Respiratory Syndrome and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that represents the humanitarian crisis on a global scale. Currently, there are no therapeutic strategies approved by the U.S. Food and Drug Administration (FDA) to cure or prevent COVID-19. Global research efforts from around the world extrapolate the updates focusing specifically on the biphasic nature of Covid-19 that involve both innate and acquired immunity. Even though researchers around the globe are racing to invent a life-saving therapeutics and vaccines to tackle COVID-19, the only available venture is a supportive approach in rendering treatment to patients with severe and non-severe cases of COVID-19. Supplementation of several vitamins and trace elements showed the expected favorable impact on enhancing immunity in viral infection. Numerous studies prompted the value of zinc (Zn) supplementation that prevents the virus from entering cells by binding with protein in potentiating antiviral immunity, which is realized through different mechanisms, including the improvement in markers of immune function. Zinc is also an associated factor for several enzymes (needed for the activity for over 300 enzymes), transcription factors, and replication factors. Interestingly, low-level zinc results in dysfunction of all immune cells, subjects with altered zinc

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state have a high risk for infectious disorders, autoimmune disorders, and cancer. Several assumptions regarding immunomodulators of zinc remain unresolved. This review aimed to explore the hypothetical association of Zinc supplementation (the key immunomodulator) in association with a preventive and therapeutic role of treating patients with COVID-19.

*Keywords: Immunomodulator; zinc supplementation; supportive strategies; innate immunity; acquired immunity; COVID-19.*

## 1. INTRODUCTION

Worldwide Pandemic Coronavirus Disease (COVID-19) is caused by severe acute respiratory SARS-CoV-2. World Health Organization (WHO), on March 11, 2020, has recognized COVID-19 as Pandemic. According to the Johns Hopkins CSSE as of 5-07-2020, there were globally above 11,317,637 confirmed documented cases [1], WHO, as of 2-02-2020, half a million lives lost worldwide. COVID-19 represents the tremendous acute global health care challenges in the ways that it can be maddeningly tricky, experiencing unpredictable outcomes in any health care services. Some patients have severe debilitating conditions, while the rest of them barely feel ill, if at all. For, some it is mostly respiratory-related signs and symptoms, while others have nervous system-related illnesses such as loss of smell, a symptom documented between 20-80% of the infected COVID-19 patient. Severe illness may develop life-threatening vascular disorders added to the list [2].

The mortality rate differs from patients' age, country of origin, and by the presence of comorbid diseases [3]. Few people are more likely to fall ill than others to become seriously sick, which means that they might need hospitalized care or a ventilator to support them to breathe, or they might even die [4]. SARS-CoV-2 spread by direct contact such as touching an infected person or the contact objects, and fomites that the human has either touched or on which the expired droplets of virus from the person have landed, and it can remain live for days [5]. Every day we learn more innovative scientific global information about COVID-19. More importantly, people at risk for severe illness, older adults, and people with underlying medical conditions need to protect themselves from COVID-19. The essential element of zinc involved in several biological processes due to its role as a cofactor, signaling platform, and the element of structure. Zinc also plays a significant predominant role in the regulatory mechanism of

Carbohydrate and lipid metabolism, as well as in the reproductive, cardiovascular, and nervous system [6].

The researcher Walraven et al. speculated that zinc levels need to be tested for the hospitalized patients. Almost more than half of the patients missed at least one covariable test. It is also imperative to remember that a healthy diet supports in ensuring an adequate number of immune cells and antibodies, which are mandatory as the body mounts a response to infection. US dietary survey shows that people consume a diet that does not meet federal guidelines. Hence COVID-19 pandemic tends to put a lot more people at risk of food insecurity.

The primary mechanism (Zn homeostasis) is critically regulated by the coordinated function of Zn transporters and metallothioneins, which regulate the transportation, distribution, and storage of Zn. However, the exact physiological technique of the Zn-mediated immune system has been vastly unclear [7]. The upcoming chapters intend to explore the recent collection of scientific findings on the supportive strategies of the immunomodulatory effect of zinc (Zn) to deal with COVID 19, which could predominantly act on one of the preventive measures.

## 2. BACKGROUND TO HYPOTHESIS

Zinc possesses several antiviral effects which are realized through generating both innate and acquired (humoral) immune response, facilitation of the normal functioning and stabilization of cell membrane, inhibiting the entry of viral replication through the interference of the viral genome transcription, protein translation, polyprotein processing, viral attachment, and uncoating. Multiple antiviral effects of Zn demonstrated in a variety of viral species, including several nidoviruses, for which SARS-CoV-2 belongs. It suggests that Zn supplementation may be of benefit for prophylaxis and treatment of COVID-19 [3]. However, this review discusses mechanistically using the available information,

as relevant data on the effects of zinc against COVID-19 are absent to date.

The compromised immunoregulation of zinc deficiency is known for more than 50 years. The knowledge about the biochemistry of zinc has continued to grow, but recently in-depth awareness about molecular structure into the multiple aspects of zinc as a regulator of immunity studies have increased in numbers. Proteins of ZnT and ZIP (Zrt- and Irt- like proteins and zinc transporters) for transport and metallothionein for storage strictly regulate the availability of zinc. In vivo, Zinc deficiency alters the number and function of neutrophil granulocytes, monocytes, natural killer (NK), T, and B-cells. In this case, T cell functions and balance between the different subsets are particularly susceptible to changes in zinc status [8].

Although the function of the zinc as a crucial structural or catalytic component in 300 enzymes and transcription factors is well clear, there is a growing body of evidences that supports zinc's role as a second messenger in several cellular functions. The intracellular Zinc concentration can be altered by immune-related extracellular activation, and the subsequent crosstalk between zinc and signaling components accelerate the transduction of signaling pathways for immune homeostasis and functions. However, the opposite results also reported regarding the effects of Zn on the immune system of the body [9]. However, the underlying mechanisms of the zinc molecule still need to be paved with further detail to guarantee the beneficial effects of clinical zinc supplementation to patients suffering from distinct diseases [8]. Anti-inflammatory and antioxidant characteristics of zinc also have long been reported in several studies, along with the homeostatic mechanism of zinc [9].

Although the molecular mechanisms underlying the concentration-dependent effect of zinc are poorly understood, they probably involve the capacity of the intracellular buffer mechanism to absorb massive amounts of Zn and a breakdown of the system of Zn transportation. Collectively, these results strongly suggest that cellular Zinc levels can decide the threshold for the role of zinc in physiology and pathology of the immune response [9].

### 2.1 Hypothesis

The immunomodulatory effect of zinc as a potential supportive treatment strategy for

COVID-19 is stated as a hypothetical statement that "Supplementation of Zinc may provide a favorable potential impact in prophylaxis and treatment of COVID-19" since it possesses an immunomodulatory effect, which is evidenced through several mechanisms

### 3. ANTIVIRAL ACTION OF ZINC

Zinc possesses a protective role as a preventive and adjuvant treatment of Covid-19 through minimizing infection and inflammation, improving mucous clearance, and preventing lung injury caused by a ventilator, and modulating antiviral and antibacterial immunity. The anti-inflammatory effect created by the inhibition of NF- $\kappa$ B (nuclear factor kappa light chain enhancer of activated B cells) signaling and modulation of regulatory T-cell role limit the cytokine storm in Covid-19. Hence, the search for prophylactic and therapeutic antiviral properties of zinc is of dire need for the entire world [10]. The study on cell culture model reported that stimulation of several dependent enzymes of zinc and the factors of transportation was disastrous due to low-level zinc. Chronic deficiency increases the production of pro-inflammatory cytokines, influences the outcome of a large number of inflammatory, metabolic, neurodegenerative, and immune diseases [11].

Altogether, the available data concerning the immunomodulation effect of zinc proposed further study to explore the clinical evidences and to prove the conditional statement of the association with chloroquine (CQ) and Hydroxychloroquine (HCQ). Several theoretical investigations increased intracellular Zn<sup>2+</sup> concentration by (CQ) might modulate antiviral effect against SARS-CoV-2. In this perspective, zinc supplementation in the absence of CQ might produce similar effects without adverse side-effects of CQ treatment [12]. A similar effect observed in a study using zinc ionophores [13], and it is also interesting to note that a combination of CQ with zinc has an inhibitory effect on autophagy by the influx of Zn<sup>2+</sup> into the cell [14]. Hydroxychloroquine metaphorically make the cap on the vinegar, Greene says, preventing acid surroundings. Thus there is a proven rationale for how this drug might exert an antiviral effect [15].

Similarly, the most persuasive evidence of advantages is the immediate initiation of zinc administration for common respiratory tract infection, which needed in 24 hours of the onset

of common cold [16]. Fortification of more commonly used foods such as bread with zinc salts may also be beneficial [17]. Furthermore, it was demonstrated that low-level zinc significantly associated with the predisposing factor that develops acute respiratory distress syndrome (ARDS) in human patients compared with healthy plasma zinc category patients and non-acute respiratory distress syndrome intensive care unit as a control group [18]. In parallel, these clinical findings ally with the experimental study that was performed among the rats of zinc deficiency [19]. Hence, further experimental evidences are strongly needed to explore the potential antiviral function of zinc in COVID-19 with the underlying mechanism.

#### **4. ZINC SUPPLEMENTATION AND VIRAL INFECTION**

The analysis and a more profound understanding of the investigation of zinc relevancy against several kinds of viral diseases and those scientific reports recommended that an appropriate dose of zinc potentiates the restoration of depleted cells and could improve the normal cell function [9]. The published study between 1966 and 2013, including three trials with children, 13 trials of adults up to 65 years consumed zinc continuously for minimum five days, within three days of their onset of cold symptoms showed the findings of less duration of specific symptoms including nasal congestion, nasal drainage and sore throat [20]. Despite several treatments, at times, warts become resistant to any number of medications. The recalcitrant viral warts can be treated with simple supplementation of oral zinc sulfate. It has been documented that at least 75% reduction in the number of warts, shown to be more efficient and safe [21]. It is believed that zinc therapy improves the condition of the liver, and it is effective in lowering the incidence of hepatocellular carcinoma [22].

Carefully designed investigation of COVID-19 patients data for the altered level of zinc, for instance resulting from the intake of vitamin c, organic compounds, the animal source of protein, phytate with zinc, and the zinc status altering medications such as HCQ had shed light on the immunomodulator significance of the observed covariation of low-level zinc cases and fatality in a different category of populations and its predicted defensive role. Trials are mandatory to discuss if the benefit of CQ and HCQ therapy depends on the specific factor of age, clinical

manifestation, and the response rate among the individual from different countries [23]. The specialist believed that repositioning (known drug usage for indication) with some medication is the best strategy that is considered as the most significant way for treating patients with the COVID-19 without delay. HQ is one of those drugs, which is an antimalarial medication [24].

Numerous approaches have been paid to invent and demonstrate the usefulness of already known antivirals, immunomodulators, monoclonal antibodies, and vaccines for treating COVID-19 [25]. The impressive new findings about the combination of CQ with zinc reported the zinc enhanced CQ cytotoxicity and induced apoptosis in A2780 cells. The zinc ionophore characteristics of the CQ specifically target on the element of extracellular penetration to intracellular lysosomes [14]. In vitro and clinical studies have also demonstrated the zinc activity and viruses [26]. Indeed it was further documented that zinc suppressed coronavirus RNA dependent and RNA polymerase (RdRp) function and zinc ionophores blocked the replication of coronavirus [27]. The combination of CQ/HCQ with zinc, along with other medications with an antibiotic like azithromycin (triple combination), constitutes an added option to succeed in a battle against Covid-19. The amendment of WHO (2020) supported clinical trial and other studies are mandatory to avail the advantages of using CQ or HCQ in combination with zinc, because of its availability, affordability, and its established indications [28]. Another study hypothesized that CQ/HQ with zinc might be the effective treatment in decreasing the COVID-19 morbidity and mortality than CQ/HCQ as a monotherapy [29].

Despite the earlier mixed results about zinc with CQ/HCQ, a recent record among 900 COVID-19 patients demonstrated the definite effect of triple medication therapy (HCQ, zinc sulfate, and azithromycin). The study entitled half given triple medication, and the remaining have received double drug combination. Patients who received triple-drug showed 1.5 times greater effect of recovery, and 44 percent were less likely to die compared to the treatment without zinc [30]. Unfortunately, there are no confirmative treatment protocol has been reported, and a few are undergoing clinical trials [31]. So evidence seeking to follow up research for scrutinizing COVID-19 patients' documents, including the micronutrient and the food consumption details, is mandatory to ensure the role of low-level zinc

in Pandemic COVID-19 and potentially find a new solution concerning zinc supplementation to COVID-19 [32].

## 5. ZINC DEFICIENCY

High prevalence of zinc deficiency among particular categorical populations, mainly elderly, is considered to be of a vulnerable high-risk group to deficiency, and its impact on specific clinical perspectives is considered as a significant issue [33,34]. In the case of community-acquired pneumonia and older adults, the Serum level of zinc is 15% lower, which is associated with severe pneumonia as evaluated by confusion, urea, respiratory rate, blood pressure (CURB-65) scores [35]. Zinc is the crucial element that has a significant role in its immune system, which is mandatory for the innate and adaptive functions of the immune system. Any deregulation that occurs within each cell deregulate our normal body function that can be seen in many diseases such as infections and inflammations of any of the body systems, including allergic reactions, autoimmune disorders, and cancers. Low-level zinc has the negative influences upon molecular, cellular, and systemic levels of hematopoiesis [36]. Zinc deficiency in humans and cell culture models activates macrophages and microcytes by enhancing the oxidative stress that generate inflammatory process [37].

Zinc in the blood and serum gets transported as albumin-bound in the blood. A low level of albumin of the susceptible subjects would need correction. There is a zinc related viewpoint to modulation of COVID-19 may include zinc ions in the anatomical pattern of viral proteins [38]. Documented reports through several studies demonstrated the crucial role of zinc in limiting the incidence of the illness, especially for older adults. The daily recommended dose of zinc is 9.5 mg for the men and 7.5 mg for the women. The older adults need up to 20 mg/day [39]. A randomized, double-blinded placebo-controlled trial study among children hospitalized with Lower respiratory tract infection (ALRTI) demonstrated faster recovery and short stay at the hospital with zinc supplementation [40].

A prospective study among 82,297 women of 33-60 years of age at baseline from 1980 to 2004 in the Nurses' Health Study, identified 6030 cases of Type 2 Diabetes mellitus (T2DM). During those 24 years follow up, they confirmed intake of zinc but not dietary source was significantly

related to with a lower risk of type 2 DM [41]. A recent hospital-based double-blind study also explored the outcome of supplementing zinc that had shown the faster recovery of clinical symptoms among children with pneumonia. This study added the recommendation that zinc therapy, along with antibiotics, could reduce the drug resistance in multiple antibiotic treatments [42].

Hence, the current supportive studies revealed an association of zinc with pneumonia among the elderly, as well as the associated risk factors of respiratory failure, ventilator-induced injury, and sepsis-related issues. It was also indicated that zinc supplementation was well-tolerated with no adverse reports.

## 6. PROPHYLACTIC ROLE OF ZINC AGAINST COVID-19

Several studies documented zinc lozenges as effective in reducing the misery stage of common colds. Currently, there is a critical question many are asking: can zinc lessen the duration of or even minimize the severity of illness and thereby lessen the impact of COVID-19?. The updated Cochrane review in 2013 demonstrated 18 clinical trials that involved 1781 participants from all age groups had shown that zinc in the form of lozenges or syrup- prohibit the replication of viruses, that cause the common respiratory infections and lessen the average days of infection when consumed within 24 hours of the initiation of any symptoms at a dose of above 75 milligrams a day. Snopes.com a dedicated website to confirming internet myths diagnosed after his words, which were twisted by many and reposted with overemphasized claims such as zinc being a "silver bullet" against COVID-19 [43].

Following infections due to COVID-19 older people are at a significantly increased risk with severe consequences. Recent statistics as of WHO reports (2020) 95% of the death occur among the people older than 60 years. More than 50 of the deaths were people aged 80 and above. There are reports that eight out of ten fatalities occur in individuals with at least one underlying comorbid conditions, particularly diabetes, hypertension, and cardiovascular diseases. The study report on zinc supplement showed increased plasma concentration of antioxidant power and decreased the plasma concentration of inflammatory cytokines and liquid peroxidation biomarkers in elderly subjects. The results imposed the findings that zinc is

effective in downregulating CRP (C Reactive Protein) levels in the elderly stated that zinc supplementation (45 mg elemental zinc as gluconate) daily was effective in lowering plasma CRP concentration. Zinc not only modulates cell-mediated immunity but is also an antioxidant and anti-inflammatory agent. Researchers studied in the 1930s to produce protamine zinc insulin to control the blood sugar in diabetic patients. Zinc is crucial for the pancreas and the regulation of blood glucose. Addition of zinc to insulin *in vitro* extended the duration of insulin action [44].

Considering the severe nature of the contagious, life-threatening, and negative impact on the affected COVID-19 patients and health care systems globally, the conditional statement of zinc supplementation that has a potential prophylactic and active treatment role requires the dire necessity of testing in humans [3]. A similar study emphasized the importance of the supportive therapy of zinc supplementation along with vitamin C, and D to fight with coronaviruses. It was also proposed to do the clinical trial of zinc with the antimalarial drug as these drugs can inhibit pH-dependent steps of coronavirus replication by increasing pH in intracellular vesicles and interfere with the virus entry into cells [45].

Even though many hospitals have adopted HCQ based treatment for COVID-19 under the establishment of clinical protocols, there are no definite recommendations about the well-established safety profile. The authors of the recent study stressed the necessity Amid pandemic COVID-19 with a high mortality rate, the challenges of health systems, and the devastating impact on the economy worldwide, a fast remedy is crucial. A preventive strategy with the appropriate medicine is the crucial factor in any pandemic crisis [46,47].

## 7. EFFECT OF ZINC AND RISK GROUPS

The correlation between zinc deficiency and risk groups in the perspectives of COVID-19 infection, inflammation, and sepsis need to be addressed. Approximately fifty percent of the COVID-19 infected people died due to bacterial and fungal coinfections, which underlined the significance of preserving the immune role by zinc supply[11]. Clinical improvement of Human Papillomavirus infection (HV) treated with zinc in the form of CIZAR (zinc chloride and citric acid anhydrous) was associated with apoptotic cell death of various cancer cells by enhancing intracellular zinc concentration. E6/E7 protein is

down-regulated by intracellular zinc accumulation through transcriptional factors—a study using CIZAR to treat cervical carcinoma cells where p53-dependent apoptosis did not happen after CIZAR treatment. Irrespective of HPV infection, CIZAR stimulates apoptosis by activating the p53-independent route by upregulating the p21waf1, that is the downregulation of c-Myc.

Most importantly, CIZAR induced apoptosis through activation of the independent pathway and the death-signal pathway of mitochondria in cervical carcinoma regardless of HPV-infection [48]. A similar clinical study reported the induction of p53, p21 and apoptosis by silencing the NF90/NF45 (Nuclear factor) complex in human papilloma virus-transformed cervical carcinoma cells [49]. The mechanism by which zinc down-regulates E6, E7 expression is not known.

Recent developments in nanotechnology (zinc nanoparticles) have been demonstrated its efficiency as an antimicrobial against different wide range of human pathogens. The study on the inhibitory effect of PEGylatedZnO-NPs on the H1N1 influenza virus revealed the higher anti-influenza activity, including lower cytotoxicity. This research experiment demonstrated the inhibitory properties that occurred due to nanoparticles that act against the influenza virus [50]. The promising clinical benefit of zinc (ZNP) nanoparticles evaluated by a recent study using SEM and TEM image confirmed that ZNP disintegrates the membrane of the cell to get accumulated in the cytoplasm where they react with biomolecules causing cell apoptosis that leads to cell death [51,52].

In summary, center for disease control and prevention has consistent evidence on the risk group who are severely getting ill from COVID-19, such as chronic kidney diseases, chronic obstructive pulmonary disease, Obesity (BMI of 30 or higher), immune-compromised state, severe cardiac disorders, sickle disease, and type 2 diabetes. As mentioned earlier, the clinical trial has been registered to test zinc supplementation alone [53] and in combination with other drugs such as CQ. There are many many more risk factors published along with the hypothetical representation of zinc by the growing body of researches. Nevertheless, during this challenging time, prevention is better than cure, and the prophylactic measures need to be taken.

## 8. CONCLUSION

The widespread impact of COVID-19 or SARS-Cov-2 has created significant health concerns around the world. The transmission and the speed at which COVID-19 spread, unfortunately, appears to be surpassing the speed at which zinc supplementation studies can produce the definite answers. Global statistical updates along with the available evidences indicate that older people and the people with comorbid diseases are undoubtedly more at risk from the severe ramification of such infections. Global prevalence of low-level zinc and its significant role in human health and, most importantly, its immunomodulatory impact, we hypothesize that Zinc supplementation may provide a favorable impact in prophylaxis and treatment of COVID-19. In the perspectives of the incidence of COVID-19 and its adverse outcome, there is still a significant inquiry concerning zinc supplementation: however, it is an immunomodulator that will not hurt in any way, and there might be the supportive benefit due to its anti-inflammatory effect.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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