J. Dhaka National Med. Coll. Hos. 2022; 28 (02): 39-44

Review Article

Zinc therapy: An emerging hope in the management of COVID-19

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Abstract:

COVID-19 global pandemic creates a great threat to entire healthcare system & disrupts the whole economy worldwide. There is no specific antiviral therapeutic option available for COVID-19 management still now. So, there is an urgent need to discover effective medicines, prevention and control measures to combat this novel corona virus infection. The preventive measure has been the mainstay to fight back the current COVID-19 infection. The host immune system plays pivotal roles against COVID-19 disease progression, similar to many other viral infections. The role of trace elements in boosting the human immune system are well established. Several vitamins such as vitamin A, B6, B12, C, D, E and folate; trace elements including zinc, iron, selenium, magnesium and copper play essential physiological roles in promoting the immune system. Zinc is a trace element that plays a role in stimulating both innate and acquired immunity. It is an indispensable trace element essential for a thorough enzymatic physiological process. Zinc, together with natural scavenger cells and neutrophils, are also involved in developing cells responsible for regulating nonspecific immunity. The benefit of zinc supplementation on the immune system function has been previously observed in non-COVID-19 patients. However, there is inadequate evidence to support the use of zinc in treatment of COVID-19. Therefore, this review will discuss about the efficacy and safety of zinc supplementation as preventive & therapeutic agent as well as adjunctive therapy in treating patients with COVID-19.

Keywords: Zinc therapy, COVID-19, Trace elements, Immunity, Pandemic.

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) creates a panic situation by producing 'The Coronavirus Disease 2019' (COVID-19) and emerged as a threat to public health worldwide.[1] Symptoms of COVID-19 manifest as a cluster of mild to severe respiratory symptoms. Severe COVID-19 amplifies the overall systematic inflammatory response in critically ill patients, increasing the risk of multi-organ dysfunctions, acute respiratory distress syndrome (ARDS), and mortality.[2] This inflammatory response is caused by the hyperactivation of chemokines and cytokines, prominently interleukin-6 (IL-6). Therefore, the dysregulation of cytokines was one of the targets for many treatment strategies in treating patients with severe COVID-19.[3]

To date, no specific pharmacological agents have proven efficacy against SARS-CoV; instead, host-directed therapies and supportive therapy are used.[4] The current treatment options for critically ill patients with COVID-19 include anti-viral agents, immunosuppressive agents, and immunomodulators.[5] However, the evidence about these treatment options' mortality benefit in critically ill patients with COVID-19 is conflicting.[6] Moreover, some mineral supplements and vitamins with immunomodulatory activity and antioxidant effects such as thiamine, vitamins C and D, zinc, and selenium use in patients with COVID-19 are investigated.[7]

Zinc is essential in maintaining human physiology and was first identified in an Iranian patient in 1961.[8] Zinc is a trace element; however, it remains a vital micronutrient for maintaining cellular physiology such as vision, taste perception, cognition, cell reproduction, growth, and immunity. Zinc deficits dampen equally innate and adaptive immune responses.[9] Zinc deficiencies are evident by oxidant stress, increased inflammatory process, and life-threatening situations, as well as premature cell death at the cellular and sub-cellular levels.[10] It has been reported that over 300 regulatory enzymes require zinc for their inhibition-activation processes.[11]

Furthermore, the sepsis process's signal transduction pathways are positively correlated to zinc deficiency.[12] Nuclear Factor Kappa B (NF-κB), a transcription factor known as the principal controller of the proinflammatory process, especially in infectious diseases, is also affected by zinc deficiency.[13] Additionally, NF-κB controls several characteristics of innate and adaptive immune purposes.[14] Moreover, common pathogenic microbes, including viruses, activate NF-κB, are remain raised among infected individuals. High NF-κB is related to marked pro-inflammatory effects, and high death rates among infected patients, especially aggressive infections, were instigating sepsis and septic shock, which could minimize with dietary zinc.[15]

Zinc is a trace element that plays a role in the development and function of the immune system exhibiting direct or indirect anti-viral properties.[16] High intracellular zinc levels were reported to stall the replication of coronavirus (SARS-CoV-2) and infuenza virus that caused the severe acute respiratory syndrome. Some reports demonstrate the synergistic effect of zinc with anti-viral therapy in SARS-CoV-2.[17]

Zinc and Viral Infection

Zinc is an essential trace element that significantly impacts health, especially in maintaining immune physiology, growth, and development. Zinc is also considered an agent of antiviral immunity and an enhancer of both innate and acquired immunity.[18] Earlier studies reported that high dose zinc consumption has effectively boosted patients' immune systems with several viral diseases, including torquetenovirus (TTV), common cold (rhinovirus).[19] Apart from its effect on cellular division, differentiation, and rapid growth in humans, its role in preventing common cold and viral infections is underscored to date.[20] Increased susceptibility of viral infections has significantly been associated with zinc deficiency in the human body. Zinc-deficient individuals are more prone to severe viral infections like HIV and devastating outcomes in viral and bacterial co-infections. These include influenza-MRSA bacterial superinfection, S. aureus infections, and many more.[21] In light of the sudden onset of the COVID-19 global pandemic, there has been an increasing interest in searching for potential protective and therapeutic measures necessary to curb the uncontrollable spread of this virus.[22] Respiratory system pathology and oxygen saturation have improved with zinc supplements in clinical trials.[23] Notably, the elderly population that usually develops acute respiratory syndrome has lower serum Zinc levels. Similarly, 80% incidence of pediatric pneumonia is associated with low serum zinc levels.[24]

Anti-Viral Effects of Zinc on COVID-19

A possible clarification for the relevance of zinc in the treatment of COVID-19 conditions has been attributed to its immunomodulatory effect, antiviral property, as well as its ability to regulate the inflammatory response.[25] The possible mechanisms by which zinc might be effective in the therapy of COVID-19 are based on the previous evidence with other common viral infections and limited experience with COVID-19. Zinc has been found to refine and improve cilia's morphology and increase its length and beating frequency. It is also considered as a membrane stabilizer and helps to maintain cytoskeletal integrity.[26]

Zinc is proposed to prevent viral entry and block its replication by inhibiting the RNA dependent RNA polymerase (RdRp) of the virus. Zinc also minimizes the Sirtuin 1 (SIRT-1) induced angiotensin-converting enzyme 2 (ACE-2) receptors expression, decreasing the probability of viral binding ACE2 receptors.[27] Zinc also modulates the immune system and increases the production of IFNα production by leucocytes. Zinc, by increasing the levels of IFNα production, indirectly increases the synthesis of antiviral proteins like latent ribonuclease and protein kinase RNA-activated, which can degrade viral RNA.[28] Zinc has a well-known antioxidant action with reduced reactive oxygen species production and reactive nitrogen species.[29] It also exhibits anti-inflammatory action by inhibiting NF-κB signaling leading to decreased production of proinflammatory cytokine.[30] Zinc has been found to increase Natural Killer cells' activity, Cytotoxic T cells activity, and B Cell Receptor Signaling, along with increased production of antibodies. It also modulates regulatory T-cell functions and preventing hyperactivation of the immune system's hyperimmune response by modulating and balancing the cytokines.[31]

Generally, the role of Zinc as a stimulant of antiviral immunity coupled with its negative repercussions if deficient in the elderly persons or individuals with certain metabolic diseases like diabetes, obesity, or cardiovascular diseases has buttressed several hypotheses that claimed the use of zinc compounds might serve as an adjunct therapy in COVID-19 treatment.[32] However, some critics have challenged its consumption rate notwithstanding the positive effects

of using Zinc. It was suggested that 25–50 mg zinc per day is affordable and would not cause adverse effects than a higher intake of 200 to 400mg per day, triggering epigastric pain, lethargy, vomiting, nausea and fatigue.[33] Interestingly, zinc supplementation has been influential in reducing the replication of influenza virus, reduction of hepatitis in HCV infected patients, enhancement of response to antiviral treatment, improvement of both cutaneous and genital warts which are induced by human papillomavirus (HPV), and most notable is the significant reduction of prevalence in pneumonia, especially in developing countries.[34] Overall, these observations strengthen the fact that adequate zinc balance is essential to protect an individual from microorganisms, including viral infections. An uptake of up to 40mg per day of zinc as recommended will likely reduce the potential threat of the COVID-19 pandemic, resulting from the rise in the host resistance to viral infections. The efficacy, tolerability, and safety of combining zinc with CQ remain a viable option in conquering COVID-19.[35]

Evaluation of Zinc effectivity & toxicity in COVID-19 management

There are quite a few published studies that illustrate the efficacy of zinc therapy in managing COVID-19 patients. Many individuals globally consume zinc tablets, vitamin C and B because of immune booster effects and combating COVID-19 and its antiviral effect.[36]

However, a recent pre-print United States-based retrospective analysis utilizing electronic medical records found that patients treated with hydroxychloroquine and azithromycin with the addition of zinc sulfate had a higher recovery rate. Interestingly, additional input of zinc sulfate was claimed to be associated with lower mortality rate, need for hospital care, and less invasive ventilation requirements. However, this association remained null when observed among Intensive Care Unit (ICU) patients.[37] These associations should further be studied in different clinical trials and laboratory tests to provide more robust shreds of evidence. Preventive measures by zinc supplement should be accompanied by a standard of care among COVID-19 patients. Henceforth more double-blind controlled clinical trials should be conducted to confirm the effectiveness. Generally, zinc should be prescribed as an optimal zinc supplement. This is because the recommended intake depends on particular conditions or specific illnesses. Acute zinc toxicity could lead to nausea, vomiting, abdominal cramps, persistent diarrhea, and other gastrointestinal abnormalities like hematemesis, haematuria, and renal syndromes. At the same time, chronic overdose manifests as sideroblastic anemia, neurological disorders, granulocytopenia, myelodysplastic syndrome, and copper deficiency.[38]

Furthermore, there have been no reports of deaths or significant life-threatening adverse drug reactions related to zinc supplementation.[39] Therefore, both preventive and therapeutic doses should be determined for COVID19 patients considering age, gender, and comorbidity to avoid further consequences. As there is some zinc-related toxicity; thereby, an individual should seek health professional advice before zinc supplementation. However, these supplementary medicines are sold as over-the-counter products without prescription. Oral zinc supplements are likely to be recommended in arresting the burden of COVID-19. This is due to its oral bioavailability and because zinc participates in protecting the body from viral and bacterial infections and improving immunity.[40]

Therefore, vigorous clinical studies should commence urgently to validate the therapeutic efficacy of orally administered dose and investigate its limitations. It is noteworthy, although SARS-CoV-2, influenza, and rhinoviruses employ distinct cellular receptors, angiotensin-converting enzyme-2 (ACE2) present in the oral cavity and upper airway's epithelium further suggests reasons to initiate oral zinc therapy. Unless a comprehensive study is conducted with scientific approval of oral zinc therapy for COVID-19 patients, nobody should take it as self-prescribed. This is to avoid overdose leading to substance abuse and worsen the patient's condition.[41] It should also be investigated and see if the elevated level of oral zinc helps combat SARS-CoV2 and mitigate the intensity, complications, and duration of COVID-19. All efforts should continue until the globally approved vaccination process is concluded. The nutritional therapy, particularly zinc considering its antiviral and immunity-boosting potency, should be further investigated in order to recognize its possible role in prophylactic as well as an adjuvant during treatment against SARS-CoV-2.

Conclusion

COVID-19 is a great challenge to the entire healthcare system as there is no specified antiviral treatment option to date. That's why, preventive and control

measures, or discovery of appropriate medicine should be available to fight the disease back. The host immune system plays pivotal roles against COVID-19 disease progression, similar to many other viral infections. The micronutrient zinc is found to strengthen both the innate and adaptive immunity. The antiviral effects of zinc have been reported in several viral diseases by boosting the immune systems. Furthermore, zinc augments the normal physiological process by facilitating epidermal, gastrointestinal, central nervous, skeletal, and reproductive systems in the human body. Altogether, zinc inhibits the entry of virus in the human cell, inhibits the viral replication process, viral interaction with human cell, and viral uncoating. However, double blind controlled clinical trials should be conducted on zinc therapy considering its antiviral and immunity boosting potency to recognize its possible role in therapeutic, prophylactic as well as adjuvant therapy against COVID-19.

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