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Short Communication

Immunomodulatory effects of zinc and its impact on COVID-19 severity

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ABSTRACT

The COVID-19 pandemic has led to severe financial, clinical, and societal repercussions and imposed more pressure on the healthcare system of many nations. COVID-19 impacts the immune system by causing a systemic inflammatory reaction, often known as cytokine release syndrome (CRS). COVID-19 patients had elevated levels of pro-inflammatory cytokines and chemokines. In this context, many dietary interventions have been utilized to mitigate the adverse effects of COVID-19 by regulating the excessive secretion of cytokines and chemokines. Zinc, an anti-inflammatory and antioxidant mineral in food with a well-established role in immunity, is now being employed in several clinical studies against COVID-19. Zn deficiency has been correlated with the increased production of pro-inflammatory cytokines. As a result, we will summarise zinc's immunomodulatory effects in this article. We will investigate how zinc deficiency might contribute to a poor prognosis of COVID-19 disease by altering the release of particular cytokines.

1. Introduction

The COVID-19 (Coronavirus Disease 2019) pandemic has claimed the lives of over 5.5 million people worldwide, along with causing severe problems to healthcare facilities and medical infrastructure [1]. Due to a lack of efficient therapeutic candidates, the world is having a difficult time battling this outbreak. Many research groups have developed COVID-19 vaccines such as mRNA vaccines, DNA vaccines, viral vector vaccines, virus-like particles (VLPs), recombinant vaccines, protein subunit-based vaccines, live attenuated and inactivated virus vaccines after a substantial amount of effort [2,3]. These vaccines are being employed to vaccinate people in various nations under national vaccination programs [4,5]. Various vaccines in use have demonstrated a high level of effectiveness, with varied protection values of up to 95% (70–95% range) in immunized persons against COVID-19 [6,7].

Because there are currently no approved medicines for the treatment of COVID-19, non-pharmaceutical strategies such as social distancing, public cleanliness, and the use of facial masks remain the best available options for the prevention of any possible outbreak [8]. In addition, various mutations have been identified and reported in its causative agent, i.e., SARS-CoV-2. Mutations in SARS-CoV-2 variants may alter the neutralizing activity of vaccine-elicited antibodies and monoclonal antibodies (MABs), resulting in a mild-to-significant loss of effectiveness. Furthermore, these viral alterations may significantly impact the dissemination capabilities of the virus, therapeutic efficacy, and diagnostic processes [9,10]. As a result, finding an alternative therapeutic regimen is critical at this time to reduce the negative repercussions of any future COVID-19 instances.

According to recent studies, certain nutritional supplements may be effective in COVID-19 patients. Higher-than-recommended daily doses of micronutrients, including vitamins and zinc, may have a beneficial effect, possibly lowering the viral load and length of hospitalization in patients with COVID-19 [11,12]. Surprisingly, a recent comprehensive analysis of randomized controlled trials discovered that relatively few research substantiates the favorable effects of zinc supplementation. As a result, zinc supplementation-based COVID-19 prevention or treatment treatments are currently speculative. However, if the outcomes of ongoing clinical studies are disclosed, the real conclusions can be revised and used to give improved treatment approaches to control SARS-CoV-2 infection [13].

It is important to consider that the micronutrients were shown to have immunomodulatory effects and to lessen the adverse effects of a

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variety of diseases. Hence, it is crucial to uncover that how deficiencies of micronutrients such as Zn and Selenium (Se) can lead to immune dysfunction and increased susceptibility to viral infections [8]. In viral diseases, micronutrients deficiencies have been associated with poor treatment outcomes. Undernourished people with the risk of or confirmed with COVID-19 can benefit from regular consumption of supplements and trace minerals to boost their immune response and build their resistance against viral infections. A recent study discovered vitamin D, zinc, and selenium deficiencies in COVID-19 patients with acute respiratory tract infections [8,14].

Recently, zinc has been identified as one of the critical micronutrients to provide supportive treatment in COVID-19 patients due to its immunomodulatory and antiviral properties. The efficacy and reliability of various treatments, such as hydroxychloroquine can be increased with zinc supplementation [15]. Moreover, improvements have been recorded in COVID-19 patients (clinical and symptomatic) treated with high-dose zinc [16]. Many studies have suggested that zinc supplementation can reduce the symptoms such as lower respiratory tract infection in patients with COVID-19. In addition, it has been postulated that the zinc may suppress viral uncoating, binding, and replication [11,17] which may help in the reduction of the viral load in severely infected patients with COVID-19. Apart from the anti-inflammatory action of zinc, antioxidant effects can also reduce the devastating consequences of COVID-19. As a result, the following section aims to look into the immunomodulatory effects of zinc.

2. Immunomodulatory effects of zinc

Zinc has been associated with the development and functional activity of various essential cells of the innate immune response, such as neutrophils and natural killer cells (NK cells). However, zinc deficiency may inhibit the production of cytokines and can significantly inhibit the adaptive and innate immune response [18]. There is no doubt that the balance of anti-inflammatory and pro-inflammatory cytokines is an essential component in the SARS-CoV-2 infection. Hence, zinc can play a crucial role in SARS-CoV-2 infection by regulating cytokine release. Moreover, a balance of Zn concentration in the human body is necessary for fighting against viral infection. In addition, zinc also helps in providing defense against the overactive immune system that causes severe allergies and autoimmune illnesses. Hence, zinc operates as a gatekeeper for the optimal functioning of immune cells and helps in providing an appropriate amount of immune response. In addition, the anti-oxidative characteristics of zinc can defend lung cells against free radicals induced harm amid inflammatory response [19] due to increased release of cytokines and chemokines.

Zinc is an essential micronutrient for the chemotactic activity of innate immune cells such as NK (Natural killer) cells and neutrophils. Zinc has a significant role in recruiting neutrophils and positively affects the phagocytic activity of antigen-presenting cells (APCs). Zinc deficiency can lower lymphocyte counts and hampers the efficient functioning of $CD4^{+}$ and $CD8^{+}$ T cells. Nevertheless, intake of zinc increases the number of T cells and NK cells and the production of IL-2 and soluble IL-2 receptors. These Zinc immunomodulatory effects can help suppress coronavirus synthesis, replication, and transcription [11,20]. In addition, zinc can interfere with viral multiplication and protein translation, giving antiviral benefits and pharmacological properties [21].

Zn is well known for its anti-inflammatory activities, but it is essential to consider that zinc also possesses antioxidant and membrane stabilizing activities [22,23]. Therefore, immune cell survival might be hampered by zinc deprivation, which also impacts essential processes like phagocytosis, target cell death, and cytokine synthesis. Preclinical studies have shown that Zn deficiency leads to the thymus and lymphoid tissues degeneration [24] as well as reductions in the processes of Th (T helper) cells [25]. In addition, the cytotoxic effects of $CD8^{+}$ T cells can be impaired due to the lesser concentration of zinc in the human body [21,26]. Zn deficiency causes immune system dysfunction, as indicated by thymus degradation, lymphopenia, and impaired immunologic response of lymphocytes [22,27,28]. Immunodeficiency, along with the significant reduction in the lymphocytes, can be resulted from Zn deficiency, which is characterized by a considerable decrease in growing B cell compartments inside the bone marrow [27–29]. Furthermore, the optimum concentration of zinc can increase the IFN-α effect [25,30], which can be employed to reverse the reduction of IFNs secretion by SARS-CoV-2 proteins [23,30,31]; hence the zinc deficiency can lead to poor prognosis of the COVID-19 disease [23].

In vitro studies have shown that Zn deficiency can lead to the increased production of IL-6 and IL-1, which are the crucial cytokines in the initiation of cytokines release. In addition, higher expression of intercellular adhesion molecule 1 (ICAM-1) has been reported, which is vital for leukocyte extravasation of CD86 [31]. Reduced plasma Zn levels can be associated with increased IL-6 and ICAM-1 gene expression in splenocytes [26,31]; hence, Zn supplementation may be beneficial in reducing inflammatory cytokines, particularly IL-6 and IL-1. In addition, zinc can enhance the secretion of IFN type-1 cytokines [11,32], which is suppressed in patients with severe COVID-19. Beneficial cytokines such as IFN type-1 and IL-7 are essential to generate an appropriate immune response to apparent viral infection [33]. On the other hand, IL-6 and TNF-α are considered harmful cytokines [33,34], which have been reported higher under zinc deficiency [31].

Patients with COVID-19 who had lower zinc levels on arrival to the hospital had a greater mortality risk [35]. As a result, it has been proposed that transient zinc deficiency during SARS-CoV-2 infection can lead to hyperinflammation. Zinc's anti-inflammatory response, on the other hand, has been demonstrated by a reduction in IκB kinase response, modification of T-cell function, and NF- κB signaling, as well as a drop in pro-inflammatory cytokines [36]. Furthermore, zinc therapy has been shown to reduce inflammatory cytokines (IL-1 and IL-6), enhancing type-I IFN response [37]. Hence, using zinc supplementation along with other therapeutic regimens can be proven as a more effective strategy to combat viral infections like SARS-CoV-2 [23,38].

3. Conclusion and future perspective

Many studies have demonstrated that boosting the immune response with micronutrients during SARS-CoV-2 infection can help to reduce viral load and reduce the risk of hospitalization. Supplementing increased doses of micronutrients like vitamin D and zinc during COVID-19 infection may be beneficial. Zinc deficiency can lead to increased levels of specific crucial pro-inflammatory cytokines such as IL-6 and IL-1. At the same time, Zinc supplementation can induce the type I IFN immune response, which has been considered critical in reducing the excessive release of cytokines, a key characteristic of patients with severe COVID-19. Aside from the fact that nutritional supplementation is usually cost-effective, research has linked zinc, vitamin D, and vitamin C to anti-inflammatory and anti-oxidative properties. A lack of these nutraceutical supports has been linked to the poor prognosis of the COVID-19 disease.

Till now, more than 50 clinical trials have been reported with the goal of using zinc supplementation as a therapeutic or preventative approach. The results of ongoing clinical trials will be critical in validating the efficacy of zinc as an alternative strategy to treat SARS-CoV-2 infection. Furthermore, more research is needed to determine the optimal dosage of micronutrients like zinc to prevent people from COVID-19 or ease symptoms. In order to further understand the effect of diet on illness outcomes, other critical immunomodulatory micronutrients must be investigated.

Ethical approval

This article does not require any human/animal subjects to acquire such approval.

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Author contribution

Manish Dhawan: Conceptualization, Data Curation, Visualization, Writing - Original Draft, Writing - review & editing. Talha Bin Emran: Writing - Original Draft, Writing - review & editing. Priyanka: Writing - Original Draft, Writing - review & editing. Om Prakash Choudhary: Conceptualization, Writing - Original Draft, Writing - review & editing. All authors critically reviewed and approved the final version of the manuscript.

Registration of research studies

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Guarantor

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Consent

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Declaration of competing interest

All authors report no conflicts of interest relevant to this article.

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