



Battle with COVID-19: Role of Vitamin D and Zinc as a Preventive Strategy

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Authors' contributions

Authors PR, BAAME and HEMM equally contributed to developing the study concept with the protocol of the manuscript until the completion of the whole process. All authors read and approved the final manuscript.

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ABSTRACT

The immune system protects us by producing antibodies against viruses and diseases. Currently, there is no cure in treating patients infected with COVID-19. Even though many nations declared extrapolate findings on the COVID-19 vaccine trial, this will require months to develop an effective vaccine successfully. Meanwhile, an immune-enhancing preventive approach can be considered in order to strengthen the immune system that would enhance the host's resistance to infection. Although the leading health authorities of national and international health institutions, the Centers for Disease Control and Prevention (CDCP), and the World Health Organization (WHO) consistently providing standard guidelines focusing on treatment, prevention, and promotion perspectives, this article discussed the promising alternative prophylactic solutions in enhancing host immunity with a highly valuable supplements Zinc, Vitamin D to protect human beings from COVID-19 pandemic disease.

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1. INTRODUCTION

A novel coronavirus (COVID-19) is a new disease that affects humans. Worldwide Pandemic Coronavirus Disease (COVID-19) causes severe acute respiratory SARS-CoV-2, reported first in Wuhan, China, in December 2019. Coronaviruses viruses are an unprecedented disease that is known to cause mild to severe illness [1]. Johns Hopkins CSSE as of 27-07-2020, there were globally above 16,540,137 confirmed documented cases [1]. COVID-19 represents an acute global health problem, where some patients have severe debilitating conditions. At the same time, the rest of them barely feel ill if at all [2]. The significant health concerns created by Coronaviruses are widespread, and unfortunately, the speed at which it spreads surpass at which any studies could explore the studies on immune boosters, including vaccination [3].

The COVID-19 pandemic crisis was a wake-up call to remind ourselves of the importance of maintaining better health as a preventive measure to the virus. Though several factors determine the status of each human health, bolstering the immune system has a predominant role and is used as the resilience of the healthy immune system towards such a crisis [4]. It is evident that balanced nutrition also impacts immunity; therefore, it has a substantial way to develop and strengthen the human system of immunity [5,6]. While collecting pieces of evidence on our battle against COVID-19, we might have witnessed plenty of scientific and clinical reports that demonstrated the only compelling sustainable way to improve our fighting mechanism is to boost the immune system [7]. As the pandemic situation continues, we need an analysis to understand which group is more at risk of developing severe illness or fatality issues from COVID-19. Researchers around the world had come up with the popular theory that COVID-19 patients suffer from fewer immune cells than healthy people. In the perspective synthesis of immunity, this paper discusses the benefits of vitamin D, zinc supplementation, and the necessity of a healthy lifestyle [4].

In recent months since the outbreak of COVID-19, the vitamin D role in preventing COVID-19 infection has been the substantial debate of the subject. The statement by "Joint Guidance on

Vitamin D in the Era of COVID-19" by bone and mineral research American society, the Endocrine Society, and the American Association of Clinical Endocrinologists as of July 10, 2020, stated that vitamin D is safe at a reasonable dosage which is vital for musculoskeletal health. To remember, the predominant cause for low-level vitamin D during this pandemic is due to individuals minimized their outdoor activities [8]. Vitamin D deficiency is an international health concern that affects more than a billion children and adults, and the consequences of low-level vitamin D in the body can be underestimated. There is a correlation between vitamin D and many conditions of acute and chronic illnesses, including pregnancy-induced hypertension, dental caries among children, periodontitis, autoimmune disorders, cardiovascular diseases, cancers of the colon, breast, ovarian, and prostate, type II diabetes mellitus, and neurological diseases [9]. Besides, Genomic and non-genomic effect is regulated by cells of vitamin D receptor (calcitriol receptor and NR111) and activation of the signaling molecule, respectively act as a factor of ligand-activated transcription [10,11].

Zinc (Zn) is a dietary trace mineral and is essential for maintaining and developing immune cells in both the general and specialized immune systems. Zinc deficiency results in the dysfunction of both humoral and cell-mediated immunity and increases susceptibility to infectious diseases [12]. An estimated 30% of the world's population is Zn deficient and inadequate intake, which contributes to 800,000 deaths worldwide, according to the World Health Organization (WHO). However, it is also recognized that Zn deficiency as a well-established nutritional problem is common in both underdeveloped and developed countries [13].

The immune system is effective against several chronic diseases and viruses; indeed, it requires some time to get familiarized with the enemy of viruses. Besides, growing evidences suggest that the COVID-19 pandemic has caused stress, which can undermine the importance of regular exercises, relaxation strategies, self-care, and social awareness that would be facilitated with better sleep [14]. This paper tries to reveal the disrupted homeostasis that affects the immune system and also discusses the combination of vitamins and minerals (Vitamin D and Zinc) as

prophylaxis. The comprehensive approach of healthy lifestyles added to the discussion to keep our body fit battle against these coronaviruses.

2. VITAMIN D AND COVID-19

Historical evidence to support the immune system has been established and demonstrated its specific role through several studies in addressing the needs of multiple micronutrients vitamin D, C, and Zinc. There have been researched papers written on Vitamin D mechanisms, and it has been found that Vitamin D has several platforms by which it reduces the risk of viral infection. Although many controversial reports exist, using the available findings of clinical trials, it has been proven that supplementing with vitamins and minerals might modulate and reduce the risk of getting an infection [15].

The report of epidemiological studies pointed out the factor that vitamin D deficiency would increase the susceptibility to risk and mortality due to coronavirus infection [16]. A large body of data from scientific communities and mainstream media showed the relationship between vitamin D and COVID-19. It linked the low-level vitamin D with respiratory infections, which suggested low-level vitamin D is more likely one among the causative factors in Covid-19 infection and risk factors. A randomized controlled 25 eligible trials documented that vitamin D supplementation decreased the acute respiratory infection among the study group. Vitamin D levels have also shown protective benefits among the participants who received daily supplementation. It was found that either daily or weekly supplementation have shown the more robust baseline data of 25-hydroxyvitamin D level [17].

The essential role of vitamin D that interplays with the cells of the immune system, such as B and T lymphocytes, macrophages, neutrophils, and dendritic cells, tends to decrease the secretion of cytokines (Pro-inflammatory), and enhances the release of cytokines (anti-inflammatory) [18]. Worldwide countries such as Spain, Italy, and India have a high prevalence of vitamin D deficiency, where age-specific highest fatality rate exist [19,20]. Low-level vitamin D is also prevalent in these nations, as compared to other nations. Shortage of B cell memory and divergent innate immunity are more likely to create a cytokine storm that is also observed among COVID-19 patients [21]. A similar study emphasized the importance of the

supportive therapy of vitamin C, and D, along with zinc supplementation to battle coronaviruses [22].

There are retrospective studies that demonstrated the association between vitamin D and COVID-19, while others did not find the association though variables are adjusted. However, there is a correlation found between vitamin D levels and the risk of acute viral respiratory infection (ARTI), and pneumonia has shown positive, including findings showed an inhibitory effect of viral replication or immunomodulatory impact. Vitamin D supplementation against ARTI discussion in a meta-analysis quoted the unusual cofactor renin-angiotensin system (RAS) mechanism that led patients of infected COVID-19 patients to have cardiovascular diseases and increased lung infection. Hence it is conceivable that Vitamin D could suppress cytokines storm and can promote RAS. Thus, vitamin D deficiency needs to be considered during this pandemic crisis to maintain circulating 25(OH)D at an optimum level [23]. Covid-19 infected patients with the symptom of pneumonia rapidly progresses into chronic respiratory illness, and septic shock, consequently followed by several organ failures, and approximately 10% of them face fatality [24,25]. In northern Italy, study analysis showed that most of the COVID-19 (96.5%) infected people fatality attributed to comorbid conditions such as hypertension (69.9%), diabetes (31.8%), and ischemic cardiomyopathy (28%) [26].

Most importantly, patients admitted in the Intensive care unit significantly have an increased serum level of granulocyte colony-stimulating factor (GSCF), IP 10, and TN, which indicate a cytokine storm, an underlying reason for the disease severity [27]. A study by Daneshkhah et al. showed the possible correlation of high C-reactive protein with severe Covid-19. Researchers associated this link to explore the crucial role of vitamin D in lowering the risk exposed to cytokine production and chronic inflammatory conditions of daily admitted, recovery, and deceased patients data with COVID-19. Daneshkhah also documented that cytokine storm can seriously damage lungs, which would lead to ARDS as an end-stage complication that might kill most of the COVID-19 patients. Destruction of the lungs has been observed as a complication, not the virus [28]. Several studies validated the pathogenesis of cytokine peak in order to modulate the immunity of the COVID-19 infected patients.

Backman believes that the significant role of vitamin D not only improves our immune system but also protects the system from becoming dangerously overactive. Hence it is understood that the appropriate level of vitamin D will protect all human beings against getting severe illnesses, including fatality from COVID-19. The analysis shows that it could cut the mortality rate into half, and it will never prevent an individual from getting COVID-19 infection, but it will reduce risk and prevent fatal conditions in those infected cases. It is difficult to predict the doses that would be beneficial; however, it is proven that low-level vitamin D is harmful, and this piece of information is helpful to protect vulnerable groups [29].

Yet it is essential to elucidate that lymphopenia has been associated with severe cases of COVID-19 [30], and there was a recent report by Ruan et al. that a significant lower lymphocyte count was found among non-survivors of COVID-19 [31]. In-vitro study explored the role of vitamin D in respiratory homeostasis either by stimulation of antimicrobial peptides or by interference mechanism of replication of viruses. Therefore people with a higher risk of low-level vitamin D need to be supplemented with vitamin D to maintain an optimal circulating level of 25(OH)D (75-125 nmol/L) [32,33]. Eight observational studies in a meta-analysis demonstrated the association between vitamin D deficiency and community-acquired pneumonia [34]. Danceret et al. hypothesized vitamin D deficiency in an experimental model with ARDS, resulted in profused epithelial damage, including exaggerated inflammation of alveolar cells and found that vitamin D has a tremendous trophic impact also affect >600 genes. They concluded that low-level vitamin D is one of the causative factors for developing ARDS [35].

It is not surprising that the patients with COVID-19 have been observed with a high level of cortisol because any kind of persons' sickness causes a change in cortisol. However, according to the new study by the National Institute for Health Research suggested the level of cortisol could predict which patients infected with COVID-19 are at a higher risk of dying. COVID-19 patients with a cortisol level of 744 or less had a chance of survival for an average of 36 days. The level above 744, survived only for 15 days [36]. The limbic system creates emotional stress that places a unique role in stimulation, which results in the weakness of an individual immune system. Fear is the most

predominant feeling that human beings experience during this pandemic situation will completely disintegrate our homeostasis [37]. Thus, Zinc has a crucial role, which could help in stabilizing serum cortisol levels, and it is essential, safe, and useful to consider as a prophylactic therapy.

Currently, COVID-19 represents the robust global humanitarian crisis where little is known about the protective strategies of this infection. WHO committee on an emergency basis declared COVID-19 outbreak is an anticipated lengthy duration and insisting on the importance of national, regional, and global level efforts. Therefore, we need a platform towards preventive measures that can minimize the risk of infection, transmission, progression, and risk that are desperately required [38].

3. BENEFITS OF ZINC AND COVID-19

In developing countries, according to the WHO, zinc deficiency is currently the fifth leading cause of mortality and morbidity that affects approximately one-third of the population globally. Zinc deficiency contributes to 16% lower respiratory tract infections, 18% malaria, and 10% diarrheal diseases. Nevertheless, globally severe Zc deficiency is rare; mild to moderate deficiency is prevalent worldwide [39]. Zinc establishes an essential immune system, which zinc flux and zinc homeostasis control the adequate function of innate as well as adaptive immunity [40].

Zinc regulates immune function, and the human body needs Zinc to activate T lymphocytes [39]. Low-level Zinc 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 [41]. 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. The striking effect here is the essential element of Zinc involved in several biological processes due to its role as a cofactor, signaling platform, and the element of structure. [42]. Despite its benefits, deficiency can severely impair immune system function [43]. Generally, micronutrients play an essential role in maintaining adequate immune activity, and when impairment or imbalance can adversely affect the immune system, that would enhance the

susceptibility to various bacterial and viral microorganisms [4,43].

Surprisingly the new data published in science in August 2020 with possible rationale as to why COVID-19 can be fatal to some? The research knows it by Mateus J et al., who determined common cold infections generate immunity that is similar to the response by SARS-CoV-2-COVID-19. Therefore it raises the concerns that previous infection with milder SARS-CoV-2 could make COVID-19 infection less severe. The author demonstrated a range of potential pre-existing cross-reactive nature of comparable affinity to SARS-COVID-19 and the viruses causing the common cold [44]. Zahi N et al. and Read SA et al. discussed the pattern of immune receptors, which recognizes the viral infection and how it influenced the various inflammatory process [39,45].

A study demonstrated that zinc lozenges shed light on how Zinc can inhibit coronavirus replication by the inhibition of RNA synthesis. It was observed that the oral cavity with Zinc coat, were somewhat active with short-term use at mitigating the duration of rhinovirus infections, especially at doses greater than 75 mg zinc daily. [46]. Moreover, studies explored that zinc treatment could support restoring the phagocytic ability of the macrophages [47]. The linked data of 1996-2019 from a hospital measured the zn level of the patients admitted at the hospital with a median of five days. The study included 318 adults with a median age of 71 and admitted by ambulance. Study findings found that severity of illness due to infection, inflammation, and presence of bleeding had an association with zn deficiency, and the author concluded that zn deficiency has a nature of the potential worst outcome [48]. Besides, dietary Zn also contributes its influence on the immune system that, at low concentrations of Zinc, it serves as an essential nutrient and functions as a metal cofactor for several enzymes, and high concentrations are relatively nontoxic [49]. It is well evident that Zinc will not hurt the human body in any way; there is a crystal clear benefits.

Altogether, the current clinical trial compared supplementation of Zinc sulfate 220 mg orally two times a day among the patients of COVID-19 who had been on hydroxychloroquine and azithromycin. The study has shown improvement in the level of lymphocyte count at baseline [50]. The critical novel information concerning the combination of Chloroquine (CQ) with Zinc documented the Zinc induced 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 [51]. Despite the absence of clinical guidelines and recommendations, considering the preventive approach that is vital during any pandemic crisis, and prevention is better than cure. Hence a prophylactic approach needs to be considered.

4. ANTI-VIRAL PROPERTIES OF ZINC

Zinc having the nature of anti-viral properties it is one of the micronutrients that could be taken to reduce the intensity of COVID-19 infection and perhaps lessen the respiratory tract infection for its anti-viral properties. Supplementation of Zc against rhinovirus infection, or "common cold" viruses, including the influenza virus, has shown promising anti-viral effects with reduced disease burden. Evidences mounted on Zc supplementation on reducing the in vitro replication of influenza causing viruses, the likely impact of nanoparticles Zc oxide, and inhibition of replication of syncytial virus [52]. During a pandemic crisis, a robust attempt to use Zinc to decrease disease burden is worth trying to. More significantly, consuming around 25-50 mg zinc in a day is affordable, and less likely to impact human toxicity, as >200 to 400 mg in a day of zinc consumption has shown to enhance adverse effects, including nausea, vomiting, epigastric pain, lethargy, and fatigue [53].

This opinion-based mechanistic discussion of the existing published information by Velthuis AJ et al. focused on the benefits of maintaining adequate Zinc to reduce COVID-19 associated illnesses load Of clinical significance, severe acute respiratory syndrome (SARS). Furthermore, zinc supplementation in developing countries among children significantly reduced the prevalence of pneumonia. Despite How Zinc exerts its anti-viral effects are not yet apparent, scientific papers have raced its endeavors in revealing the inhibitory role of viral-binding mucosa in prohibiting subsequent replications of viruses. In vitro studies have proven that Zinc could induce the generation of anti-viral interferon (IFN)- and IFN- to exert anti-viral effects. Besides, Zinc could also suppress inflammatory events [54].

Zinc induced anti-virus activity may be enhanced for Tcell division, maturation and differentiation, lymphocyte response to mitogens, programmed cell death of lymphoid and myeloid origins, gene

transcription, and biomembrane function. Zinc-binding activity of human metapneumovirus (M21) protein was found to incorporate zinc ions, although the specific roles of the zinc-binding activity in viral replication and pathogenesis remain unclear. The pathogenic process or viral pathogenesis is the process by which an infection leads to disease that pathogenic mechanisms of viral disease include viral entry, local replication, and spread to organs and shedding of disease site [41].

Accordingly, the Zinc induced Zn²⁺ ion coordinated activity results in regulation of viral growth and may lead to virus death in host cell-virus interaction during the pathogenesis process. So viral prevention is a significant objective in human health. One attractive approach to prevention is the inhibition of virus replication [48]. In a recent study by Nahla et al. described the global prevalence of zinc deficiency using a conditional statement between zinc supplementation and the impact on treating COVID-19 patients. It was also mentioned that micronutrient supplementation at an optimal level would not create an adverse effect [4].

5. CONCLUSIONS

Of concern, Vitamin D and Zinc deficiency are globally more prevalent primarily among the vulnerable group of population. The concerns that COVID-19 predominantly affect older people and the individual with comorbid conditions. Whenever the global health pandemic threatens human beings, health authorities are consistently advising all groups to continue social distancing, better hand hygiene practices, and the etiquette of coughing techniques. The public needs to take the necessary initiatives to boost the immune system by meticulous attention by adopting healthy lifestyles. Nevertheless, the government also needs to educate the people to create awareness about the optimal functions of the immune system, physical and psychological health, and promote the quality of life. In summary, regulatory agencies must consider investigating further to consider Zinc and Vitamin D supplementation and shall implement it through public health activities in distributing supportive medications to promote the well-being of the public.

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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