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Review Article

Role of Vitamin-C, Vitamin-D and Zinc in Covid-19 Pandemic

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Abstract

The world is caved under the grips of the COVID-19 pandemic, caused by the SARS-CoV-2 virus, which has mutated to allow human-to-human spread. COVID-19 infection is accompanied by symptoms like fever, dry cough, fatigue, severe pneumonia, respiratory distress syndrome, and in some instances death. This affects the immune system by producing a systemic inflammatory response, or cytokine release syndrome. Patients have shown a high level of pro-inflammatory cytokines and chemokines. While there is no presence of widely available treatment for COVID-19, nutrition plays a key role in maintaining homeostasis in the physiological systems including immunological function. Micronutrient supplementation improving immunity and preventing the onset of severe symptoms. Of all the nutrients, zinc, Vitamin-C, and Vitamin-D supplementation in immunity have been investigated in this review as these have the most evidence for immunological support and decrease the morbidity and mortality rates in patients. Evidence suggests that these micronutrients play an immune-modulatory role and the medical literature show that the subjection of the above-mentioned micronutrients can palliate viral respiratory infections, lower the continuance and rigorousness of symptoms, reduce the rate of hospitalization, need for an ICU or ventilator, length of stay in ICU and increase the frequency of discharge from hospital.

Keywords: COVID-19; Supplementation; Antiviral; Hospitalization; Chemokines; Cytokines; Immune-modulatory

Introduction

Currently, the new coronavirus SARS-CoV-2 is causing a massive epidemic of coronavirus [CoV] infection over the world, posing a substantial threat to global healthcare. It was originally discovered in late 2019 in a group of individuals with pneumonia symptoms in Wuhan, China. Initially, it was known as 2019 nCoV but was later renamed by the World Health Organization as COVID-19. The virus can be communicated from human to human through respiratory droplets, contact, and fomites [1,2].

This disease has a wide range of clinical symptoms, including asymptomatic infection, moderate upper respiratory tract infection, and severe pneumonia with respiratory failure, which necessitates hospitalization with sub-intensive or critical care [3,4]. The US Centers for Disease Control and Prevention [CDC] gave a list of SARS-CoV-2 symptoms which include fever or chills, cough, difficulty in breathing or shortness of breath, fatigue, aches in muscle or body, headache, loss of taste or smell, sore throat, runny nose, congestion, nausea or vomiting, and diarrhea.

As of now, there are no recognized treatments for COVID-19 but the best current techniques for reducing the risk of COVID-19 are by practicing social distancing, public cleanliness, and wearing facial masks. Some vaccines have also been developed with 70-81%

efficacy but the body's immune system is proved to be the best defense against the COVID- 19 because it provides natural power to the body to fight against pathogens such as viruses, bacteria, fungi, protozoan, and worms [6] and defy infections. As long as the immune system is functioning efficiently, the chances of infections such as COVID-19 will be unheeded.

Nutrition plays a key role in maintaining homeostasis and the health of various organs and physiological systems of an organism, including immunological function [7,8]. On the other hand, inadequate nutrition is thought to have a negative role in the onset of infection caused by the virus by weakening the immune system, which further raises the chances of infections as well as the risk of morbidity and mortality. Therefore, viral infections raise demand for various vitamins and minerals, including Vitamin-C, D, and zinc [9-11]. Higher-than-recommended daily doses of these micronutrients may have a favorable effect, potentially lowering SARS-CoV-2 virus load and duration of hospital stay. These nutrients are well-known for their antioxidant properties and immunomodulatory effects. Immune dysfunction and increased vulnerability to pathological infection can occur from deficiencies of these nutrients [12-14]. So, the functions of Vitamin-C, D, and Zinc in the prevention and treatment of the coronavirus are discussed below.

Vitamin-C

Role in immunity

Vitamin-C, a water-soluble vitamin also known as Ascorbic acid, has antioxidant properties. It plays a crucial role in the defense function or immunity by scavenging reactive oxygen species [ROS], hence, protecting biomolecules like proteins, nucleotides, and lipids from oxidative damage and dysfunction. Vitamin-C gets accumulated in leukocytes, in concentrations of 50– 100-fold higher than in the plasma during the infection, Vitamin-C which exists in leukocytes is utilized rapidly. Multiple signaling pathways involving pro-inflammatory transcription factors, such as nuclear factor κB [NF-κB], can be disrupted when the balance between antioxidant defense and oxidant production is disrupted and when the level of oxidants is increased it causes the activation of NF-κB which trigger a signaling cascade, and which leads to further production of oxidative species and inflammatory mediators. NF-κB plays a role in inflammatory reactions, disease development, and viral infection. Inhibition of NF-κB may be used as a treatment for viral infections [15,16].

Role in symptoms related to COVID

Vitamin-C appears to be protective against avian coronavirus infection in both *in vitro* and *in vivo* investigations, and various human trials have found that Vitamin-C probably decreases susceptibility to respiratory infections caused by viruses and pneumonia [17]. Double Nobel Laureate Linus Pauling blighted his career-ending by encouraging high doses of Vitamin-C in curing common colds [18]. A meta-analysis comprising of 44 studies that used mega doses of Vitamin-C initiating with 200 mg/day concluded that there has been a diminution in the continuance of common cold in adults and children, which might be associated with the immune system supporting the role of Vitamin-C as well as its role in reducing the severity of symptoms [19].

Johnston., *et al*. [20] evaluated the effect of supplementation of Vitamin-C [1g for 8 weeks] on the symptoms of respiratory tract infections in men with avitaminosis C [≤45 μmol/L]. From the study, they found that about acute respiratory infections, the administration of Vitamin-C decreased the score for respiratory symptoms of pneumonia in censoriously sick individuals [21]. Vitamin-C is probably an adjuvant to acute respiratory distress syndrome, lowers the deleterious consequences of sepsis associated with acute pulmonary dysfunction, and decreases the occurrence of pneumonia by approximately 80% [22]. An *in vivo* study involving 12 healthy males demonstrated that pretreatment with Vitamin-C can lower the amounts of IL-6 generated by a vasoconstrictor endothelin-1 [ET-1] by lowering vascular dysfunction [23]. Additionally, increased ET-1 expression is also related to pneumonia, pulmonary hypertension, interstitial pulmonary fibrosis, and acute respiratory distress syndrome [24].

Role in severity of COVID

Studies of vitamin-C have exhibited heterogeneous results for the treatment of hospitalized patients and severely ill patients on mortality, duration of stay in the ICU, and continuance of mechanical ventilation [25]. In the USA randomized controlled trial was conducted among 167 patients suffering from sepsis-related ARDS showed that giving Vitamin-C (~15 g/day) for 4 days may decrease the mortality rate in these patients [26]. According to a meta-analysis of 18 controlled clinical trials administration of this vitamin orally or intravenously cut down both the time of detaining in ICU by 7.8-8.6% [$p \leq 0.003$] and the continuance of mechanical ventilation by 18.2% [$p = 0.001$] [13]. When compared to individuals who

did not incur Vitamin-C intravenously, those who received mega-doses of this vitamin had a shorter ICU detaining and required less mechanized ventilation, also quicker recovery. Importantly, the patient was also using other medicines: hydroxychloroquine, azithromycin, colchicine, and zinc sulfate [27] whereas prior evidence supporting the efficaciousness of -low to moderate dose Vitamin-C [alone or in a cocktail with additional antioxidants] in severely ill patients is minimal. Recent reviews and meta-analysis of 11RCTs showed no grounds of mortality in 9 trials or any secondary outcomes but it shows a non-significant positive relationship between the intravenous administration of high doses of Vitamin-C and decrease in mortality [28].

Despite the limitations of this study with COVID-19 patients, many of the findings point to the need for a more thorough examination into the application of Vitamin-C in the treatment of this disease., since this micronutrient plays a significant role in the development, maintenance, and expression of the immune response, factors which affect the risk and the severity of viral infection, such as COVID.

As a result, supplementing with Vitamin-C can help prevent and boost immunological responses in those who are low in micronutrients and are at risk of this viral infection. To that purpose, Vitamin-C supplementation in COVID-19 patients is being studied in several clinical trials (Table 1).

Trial Number	Study design	Intervention	Eligibility criteria	Primary outcomes	Country
NCT04264533	Randomized, triple blinded, parallel design. Phase 2	24 g/day vitamin C for 7 days	COVID 19 in ICU patients, ≥ 18 years old. Diagnosed as serious or critical SARI	Ventilation free days	China
NCT04323514	Uncontrolled longitudinal, open-label, single-groupstudy	10 g intravenous vitamin C along with conventional Therapy	500 participants of all ages with the indication of incubation, positive COVID 19 and interstitial pneumonia	In-hospital mortality	Italy
NCT03680274	Randomized, quadruple blinded, phase 3, parallel study	200 mg/kg/day and 16 doses of vitamin C intravenously	800 patients ≥ 18 years old; with COVID-19 in ICU. Treated with a continuous intravenous infusion of vasopressors	Decrease in death rate and dependency on mechanical ventilation	Canada
NCT04395768	Phase 2 interventional study	50 mg/kg vitamin C every 6 h day 1, 100 mg/kg/6 h for next 7 days	200 patients with a COVID-19 diagnosis	Symptom severity, length of hospital stay, ventilation requirement	Australia

Table 1: Clinical trials showing outcomes of Vitamin C supplementation in COVID-19 patients.

Vitamin-D

Role in immunity

Vitamin-D is a fat-soluble steroid hormone precursor generated when 7-dehydrocholesterol [7-DHC] is exposed to UVB light in the epidermis of the skin, where it is transposed to the circulating precursor cholecalciferol. Cholecalciferol is hydroxylated in the liver to generate 25-hydroxyVitamin-D, which is then converted to the

active hormone 1,25-hydroxyVitamin-D [1,25[OH]2D] in kidneys. Recently, the function of Vitamin-D in immune response has been reviewed concerning COVID 19 [14,29-31]. Antimicrobial peptides, which are part of the innate immune response, are vital in the initial line of defense against infections, including respiratory infections [32]. Vitamin-D also helps in the yielding of these antimicrobial peptides which are also known as cathelicidins macrophages in the epithelial cells of the airways [33]. A randomized controlled trial including the subjunction of Vitamin-D showed that levels of antimicrobial activity increased in airway surface liquid [34]. This fat-soluble vitamin also helps in reducing the production of pro-inflammatory T-helper type 1 [Th1] cytokines [12,14] which are responsible for the cytokine storm associated with more serious COVID-19 clinical outcomes like ARDS and multiple organ failure [14,35].

The decreased antiviral immune response in COVID-19 patients during insufficiency of Vitamin-D may be attributed to a reduced LL37 level, an antimicrobial peptide generated from cathelicidin [36] and also in Vitamin-D deficiency, the lungs lose epithelial integrity, become more sensitive to inflammatory processes and pathologies like asthma, chronic pneumonia, and cancer [37].

Role in incidence and severity of COVID

Deficiency of Vitamin-D has been suggested to increase the initiation and severity of COVID-19 infection. COVID-19 patients have been reported to have lesser Vitamin-D levels than controls, with mean plasma concentrations half of what controls have [38]. A meta-analysis of 25 randomized controlled studies showed supplementing Vitamin-D can reduce the risk of acute respiratory infection [39]. Supplementation of Vitamin-D and the consequent increase in serum Vitamin-D levels over 50 ng/ml [125 nmol/l] are assumed to decrease the numbers of cases related to a variety of viral illnesses, including COVID-19 [40,41].

Although the protective effect of Vitamin-D against the COVID-19 virus is associated with the stifling of cytokine response, there is also a possibility that prophylaxis of this vitamin [without over-dosing] probably reduces the asperity caused by COVID-19, especially where hypovitaminosis D is frequent [42]. Moreover, Marik., *et al*. [43] proposed that hypovitaminosis D may partly be related to the geographic variations in the reported case fatality rate of COVID-19, showing that supplementation with Vitamin-D can reduce the death rate of this pandemic.

Forty SARS-CoV-2 RNA positive individuals were randomized to intervention [n = 16] or control [n = 24] group and were administered with 60 000 IU of Vitamin-D3 [oral nano-liquid droplets] for daily up to 7 days and it was observed that 10 [62.5%] participants in the intervention group and 5 [20.8%] participants in the control arm [p < 0.018] became negative for SARS-CoV-2 RNA. Unlike other inflammatory indicators, fibrinogen levels reduced dramatically with cholecalciferol administration [44].

Metltzer., *et al*. [45] conducted a cohort study including 489 patients who had measured Vitamin-D level 1 yr before COVID-19 testing showed a statistically significant result that the possibility of testing positive for COVID 19 is 1.77 times greater in individuals having low Vitamin-D status than with those having sufficient Vitamin-D in their body.

Yisek., *et al*. [46] reviewed nine studies out of which seven [77.8%] showed that COVID-19 infection, prognosis, and mortality were correlated with the status of Vitamin-D and the majority of the studies found that blood Vitamin-D levels can predict the likelihood of contracting COVID-19, the rigorousness of COVID-19, and COVID-19 death. Therefore, maintaining enough amounts of Vitamin-D by supplementation or natural ways, such as skin exposure to sunlight, is advised for the general public to overcome the epidemic. Whereas more recent trials of respiratory infection prevention in children and adults have reported both a beneficial [47-49] and no effect [50-53] of Vitamin-D supplementation. A recent big experiment [n = 5110] in New Zealand reported that a bolus dosage of Vitamin-D was inefficient on the risk of acute respiratory infection [54]. The outcome of another large trial in 25,871 men [≥50 y] and women [≥55 y] of Vitamin-D and/or omega-3 fatty acids found zero effect on mortality [55,56]. Due to this controversial data, clinical studies are needed to define better cut-offs for Vitamin-D level and, finally, which dosage is the best.

Zinc

Zinc is a trace element that is essential for growth and development. It is the second most dominant trace metal in the human body after iron, and it is also a major factor for protein structure and function [57]. The mineral is also helpful against the COVID 19 due to the immunomodulatory and antiviral activities of this mineral and its ionophores candidates [58,59].

Role in immunity

Zinc is indispensable for sustaining the integrity of the immune system [60] due to its vital role in maintaining, developing, and activating the cells during innate and adaptive immune responses. It also helps in the maintenance of the wholeness of epithelial barriers, which are necessary for organism defense and pathogen entry prevention [61-63]. It can modulate the development and activity of T cells, hence reducing the cytokine storm, characterized by high levels of proinflammatory cytokines and chemokines that lead to systemic immune response impairment, resulting in ARDS or multiple organ failure [64-66]. The synthesis, replication, and transcription complex of coronaviruses have all been reported to be inhibited by zinc [67]. It can also directly get involved in viral multiplication and protein synthesis, giving antiviral benefits and therapeutic effects [66]. Natural killer [NK] cells and cytolytic T cells, both of which are important in the elimination of viruses, bacteria, and tumor cells, are both affected by zinc deficiency [68,69].

Antiviral role

Zinc's direct antiviral activity is another vital role, making it necessary for the immunological response to viral infection. When the intracellular concentration of zinc increased, it can decrease the replication of a variety of RNA viruses [57,67,70,71] and also intervene with the proteolytic processing of polyproteins of the virus [72]. Furthermore, this mineral also increases the interferon [IFN] cytokine signaling as opposed to RNA viruses [73-75] and prevents the action of angiotensin-converting enzyme 2 [ACE2], which has a crucial role in the entry of SARS-CoV-2 to the host cells [76,77]. It can also directly intervene with viral multiplication and protein synthesis hence gives antiviral benefits and therapeutic effects [66].

Role in symptoms related to COVID

Zinc aids in the protection of the physical barriers of the skin and mucous membranes against pathogen invasion [63] and it may also play a key role in decreasing the possibility of contamination by SARS-CoV-2.

A meta-analysis that compared the supplementation of zinc and placebo showed that mega doses of zinc can reduce the length of the common cold [78]. In a randomized double-blind study, 48 volunteers with colds have received zinc supplementation that is zinc acetate lozenges [80mg of elemental Zn/day] or placebo within 24h after the onset of symptoms. A study showed that the administration of zinc is significantly related to the decrease in cold symptoms in comparison to placebo [79]. Various clinical studies have reported a favorable effect of zinc on various cold symptoms, such as fever, cough, sore throat, muscle pain, and nasal congestion, and reduction of these symptoms by up to 54% [79-81], which may also occur after SARS-CoV2 infection.

Incidence of diarrhea in COVID-19 cases 2 to 50% [82,83]. In some cases, if diarrhea presents, it can worsen the disease condition [84,85] and also decrease the zinc level due to malabsorption and dehydration [86]. Supplementing zinc has shown a positive effect in the therapy of acute diarrhea which is probably the result of viral infection [87]. In preschool children it was found that supplementing zinc amino acid chelate, compared to placebo and zinc sulfate, is a good source of zinc as it had a more positive impact in lowering the occurrence of diarrhea and acute respiratory infections as well as in lowering the incidence of side effects [88]. Through its function over the intestinal barrier [89] and by multiple mechanisms which act straightly on pathogens involving a decrease in the expression of virulence factors [90], zinc reduces the possible occurrence of diarrhea. The intervention of zinc is also related to a 41% diminution in the ratio of the number of occurrences of childhood pneumonia [91] which is a lower respiratory tract infection. These effects have been possible due to restraining of viral uncoating, binding, and replication which may be pertinent to COVID-19 [92].

There has been a suggestion that supplementing zinc possibly has a positive role in increasing the efficiency of other therapies currently under study such as hydroxychloroquine [65]. Clinical symptomatic improvements have also been seen in 4 patients who have been treated with mega-doses of zinc [93].

Role in severity of COVID

Various clinical studies have reported a favorable effect of zinc on various cold symptoms, such as fever, cough, sore throat, muscle pain, and nasal congestion, and reduction of these symptoms by up to 54% [80,81], which may also occur after SARS-CoV2 infection. In a randomized double-blind study, 48 volunteers with colds have received zinc supplementation that is zinc acetate lozenges [80mg of elemental Zn/day] or placebo within 24h after the onset of symptoms. A study showed that the administration of zinc is sig-

nificantly related to the decrease in cold symptoms in comparison to placebo [79]. In comparison to the placebo, zinc administration was related to a significant reduction in the total severity score of all symptoms [$p < 0.002$] [79].

In a clinical study a case report series of four patients with COVID-19showed that treatment with high doses of oral zinc that is up to 207 mg/day was probably connected with reinforced oxygenation and quick resolution of a dyspneic condition after 1 day of administration with no adverse effects [93].

A systematic review done by James., *et al*. [94] showed that in univariate analysis, the administration of zinc sulfate leads to the increased frequency of discharge of patients, and lower need for ventilation, admission to the ICU, and death. After the adjustment of the time at which zinc sulfate was added to the protocol, a rapid frequency of discharge and a decrease in mortality or transfer to hospice remained significant. This data render initial *in vivo* evidence suggesting the role of zinc sulfate in the therapeutic management of COVID-19. Conversely, a prospective study with 242 patients did not find any significant correlation between zinc administration and reduced COVID-19-related mortality so the authors highlighted the requirement of randomized clinical trials to investigate the potential of zinc in COVID-19 therapy [95]. Various studies have also shown that apart from micronutrient supplementation, a home cooked balanced and healthy diet is also essential to boost the immunity [96].

Conclusion

While there is no presence of widely available treatment for COVID-19, micronutrient supplementation appears to be a crucial step in improving the immunity of the human body and preventing the onset of severe symptoms related to COVID-19. Vitamins like A, B, C, D, and E and minerals like selenium, magnesium, and zinc, are among these micronutrients.

The role of zinc, vitamin-C, and Vitamin-D in immunity was investigated in this review as these vitamins and minerals have the most evidence for immunological support. In this case, the various findings show that zinc and vitamins C and D are essential components of the body's immune function and exhibit interactive role at multiple steps of the host defenses, including the sustainment of the integrity of natural barriers as well as the functional efficacy of cells which represent the indigenous and adaptive systems. Hence, the deficiency or insufficiency of these essential nutrients, acting in synergy in tight and adherence junction proteins, can lead to impairment of mucosal epithelial cells which make them more susceptible for entry of pathogen, such as SARS-CoV-2.

These three micronutrients play an immune-modulatory role and in general, the medical literature shows that the subjection of the above-mentioned micronutrients can palliate viral respiratory infections, lower the continuance and rigorousness of symptoms, reduce the rate of hospitalization, need for an ICU or ventilator, length of stay in ICU and increase the frequency of discharge from hospital. Therefore, in the context of this pandemic of COVID-19, these nutrients supplementation probably qualified as a cosmopolitan, secure and inexpensive measure that can be used to deal with the enhanced necessitate for the micronutrients in case of viral contact and onset of the immune responses, as well as to decrease the risk of severe viral infection progression and prognosis. More information on their effect on COVID-19 patients will be provided by an ongoing clinical trial. Although likely, the little risk for patients taking labeled over-the-counter doses of these supplements, so further research is required before providing very high doses of these agents as there is limited evidence that mega-dose micronutrient supplements will either prevent disease or speed up treatment, thus instead of relying on high dose supplementation, the focus should be on measures to promote a balanced diet and minimize the infective burden, until we get more concrete evidence from clinical trials.

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