Review article

Micronutrients- The crucial dietary elements in Covid-19 pandemic: A review

Sumit Kumar¹, Shailaja S. Moodithaya², Adithi K.³, Pratik Kumar Chatterjee⁴

¹Department of Physiology, KVG Medical College and Hospital, Sullia, Karnataka, India
²Department of Physiology, ³Department of Medicine, K.S Hegde Medical Academy, Nitte (Deemed to be University) Mangalore, India
⁴Department of Physiology, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, India

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Corresponding author: Shailaja S. Moodithaya. Email: Shailaja.moodithaya@nitte.edu.in

ABSTRACT

The mutation of the SARS-CoV-2 virus, which cause person-to-person transmission, is the pivotal reason for the pandemic outbreak in the year 2020. Infection symptoms include fever, dry cough, lethargy, severe pneumonia, respiratory distress syndrome, and death. COVID-19 induces a systemic inflammatory reaction that impairs the immune system, commonly known as cytokine release syndrome. Pro-inflammatory cytokines and chemokines are abundant in COVID-19 sufferers' bodies. COVID-19 has a disproportionate impact on the elderly, both directly and through several comorbidities associated with age. Nutrition is without hesitation, a crucial factor in maintaining good health. Some nutrients are essential for the immune system's health and function, exhibiting synergistic actions in critical immune response steps. Vitamin D, C, and Zinc stand out among these nutrients because they have immunomodulatory properties and help to maintain physical tissue barriers. Considering the viability of the virus, nutrients that boost the immunity henceforth the severity of viral infections declines with improved prognosis become important. As a result, the purpose of this review is to provide a complete outline of vitamins D, C, and zinc's involvement during the immune response towards infection, and to enlighten their commensal action of maintaining physical barriers including integument and mucous membrane. Appropriate vitamin D, C, and zinc consumption may represent a feasible pharmacological intervention during the COVID-19 pandemic due to the high surge in population interaction and the commencement of inflammation.

Keywords: COVID-19; vitamin D; vitamin C; infectious disease; virus.

INTRODUCTION

Coronavirus illness (COVID-19), caused by the SARS-CoV-2, is a universal public health hazard that poses a significant threat to global health care. In 2019, it was identified in a cluster of patients in Wuhan, China, who were suffering from pneumonia symptoms. It's linked to the viruses that cause severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Respiratory droplets, contact, and fomites are all ways for the virus to spread from person to person. COVID-19 symptoms include higher body temperature, dry cough, pneumonia, malaise, and respiratory distress syndrome, which can range from mild to severe. Around 80 percent of verified cases had mild or average symptoms, 13.8 percent had moderate symptoms, at the same time 6.1 percent had serious signs, with aged persons (60 ages) having the highest risk of acquiring serious illness (1). Some of the clinical presentations, such as asymptomatic illness, moderate upper respiratory infection, and bronchial pneumonia with respiratory failure all require hospital admission with either intensive or critical care unit (2).

The prevention strategies for COVID-19 such as, communal cleanliness, wearing facemasks and social distancing are the present options for reducing COVID-19. Nutritional supplementation may help COVID-19 patients, according to new evidence. Vitamin D, C, and Zinc in higher-than-recommended daily doses may help reduce SARS-CoV-2 virus load and hospitalization time (3).

Nutrition has a crucial role in maintaining homeostasis and the health of an organism, many organs, and biological systems, with immune function. In the recent COVID-19 disease, an individual's "nutritional status-immune response" dyad turns out to be even more important, for individual's response to the virus is the primary therapeutic/protective measure for the disorder in the absence of a broadly available, high-quality evidence-based vaccine or treatment (4). Inadequate nutrition is hypothesized to play an important role in the onset of viral illness by weakening the immune system, which raises infection rates as well as morbidity and mortality risks. Virus infections can raise micronutrient requirements, such as calcium, zinc, vitamin A, B, C, D. Micronutrients that have been linked to immune function can be added to the diet to promote immune response regulation and lower infection risk.

Antioxidant and immunomodulatory properties are well-known properties of these nutrients (Table 1). Nutrient deficits in these areas can cause immune

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malfunction and higher vulnerability to pathological disease. Indeed, nutritional inadequacy of minerals and vitamins has been documented in higher-risk COVID-19 patients, such as the ageing, disease, and death. Due to immune-senescence, older people are more probable to be inadequate and have weakened immune system, putting them at a high risk of poor COVID-19 outcomes also stressing the significance of excellent nutrition. The importance of Zinc, vitamins D and C in immunity, as well as their status in SARS-CoV2 patients and their beneficial functions are explained.

Micronutrients and viral infections

The role of vitamin D3 in viral infections

Vitamin D is a fat-soluble steroid hormone. 10% of the vitamin D requirement is replenished through dietary animal sources (D3 or cholecalciferol) and non-animal supplements such as mushrooms. The remaining is resourced inside the gut (around 80-90%), following a process that initiates in the deep epidermis layers succeeding UV light contact and succeeded through several hydroxylation activities inside the liver and kidneys. Physiologically active molecule is 1,25 dihydroxy vitamin D, while the final metabolite is 1,25-dihydroxy vitamin D (1,25(OH)2-D or calcitriol) (6).

Skin pigment, age, and current sunscreen treatment may all diminish the body's ability to synthesize vitamin D (7). Pre cholecalciferol (pre vitamin D3) is converted to lumisterol (vitamin D1), an inactive form that sustains the equilibrium of vitamin D formation, after extended exposure to UV-B rays (8). In addition to its typical properties on bone metabolism and calcium homeostasis, cholecalciferol is involved in various significant roles in the body's immune system. Immune cells have receptors for vitamin D, which is linked to the of B and T lymphocytes differentiation that advances the anti-inflammatory roles by changing IL-10 levels which persuades monocyte also macrophage maturation and variation and it is linked to the creation of cytokines and chemokines through the nuclear factor kB (9). During viral infections, vitamin D's immunomodulating action is tough, and it appears to vary depending on the microorganism also the kind of resistant activity essential to reduce illness. The receptor for vitamin D is in the epithelial cells of the lungs as well as immune cells. When VDR is activated, it creates cathelicidins, peptides and defensins by antiviral activity (10).

Vitamin D may also aid to lower the intensity of inflammatory responses by reducing the production of cytokines (as a pro-inflammatory response) including TNF-a (Tumor Necrosis Factor) and IL-6 (interleukin) that play a huge role in the growth of cytokine-storm in ARDS (46). Data from almost five thousand cases of COVID-19 infection demonstrated a connection between hypo-vitaminosis D with the cytokine storm severity, as measured through increased C-reactive protein (CRP) levels in the blood (11).

Vitamin D and its receptor play a role to development of the proteins claudin, ZO1, and occludin at tight junctions (12). According to Fujita et al., claudin-12 and claudin-2 levels were less at the level of ileum, duodenum followed by jejunum and colon of vitamin D receptors in mice, limiting calcium intake by the small and large intestine (13). Furthermore, 1,25-dihydroxyvitamin D treatment increased the appearance of this two Claudins in the Caco-2 cells in an amount and time-dependent method, demonstrating that they are both vitamin D signaling targets. The authors speculate that claudin-12 and claudin-2 make paracellular Ca2+ channels in enterocytes and are also critically used for homeostasis of cations (13).

Table 1: Effects of micronutrients on the capacity of immune system to combat viral infections

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<th>Micronutrients</th>
<th>Immunomodulatory activity</th>
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| Vitamin D      | • Controlling protein production for adherens junctions, tight junctions (13), and gap junctions (14) improves the body's physical barriers.  
• Increasing antimicrobial peptide synthesis, such as defensins and cathelicidin (15).  
• Altering the actions of T helper (Th) cells to change the Th1 response to the Th2 response. (19)  
• Cytokine storms is prevented by reducing inflammatory cytokines (21) and nuclear factor B (NF-B) stimulation (22). |
| Vitamin C      | • Boosting antiviral cytokines like interferon (IFN) (24).  
• Increasing the production of free radicals reduce viral yield (25).  
• Reducing an overabundance of inflammatory responses (27).  
• Improving immune cell hyperactivation by changing energy metabolism. |
| Zinc           | • Enhances the activity of cytotoxic T cells and natural killer cells (NK cells) (CT cells). Increases B Cell receptor signalling, maturation, and antibody production.  
• Reduces B cell apoptosis and hyperactivation.  
• By regulating cytokines, balances the immune response and avoids hyper immunity. |
The metabolites calcitriol and calcidiol improved blockade role in human corneal epithelial cells, along with increased production of occluding proteins. Human colon cancer cell lines provide more evidence of vitamin D's role in adherence and tight junctions integrity.

Calcitriol treatment elevated the appearance of various proteins from such junctions including vinculin, E-cadherin, ZO1, ZO2, and occludin, resulting in reduced permeability of membrane as evaluated by the resistance of transepithelial electrical (14). The transmembrane protein E-cadherin is required for sustaining the polarized epithelial cell phenotype in addition to cell adhesion. Loss of E-cadherin expression, which occurs frequently throughout the conversion of adenoma to carcinoma as a result, significant epithelial morphological alterations occur, as well as the acquisition of invasive potential (15). Following colon cancer treatment, vitamin D-producing cells restored the structure of the injured tissue by increasing the appearance of adherens and tight junction proteins.

**Role of vitamin C in viral infections**

Vitamin C (ascorbic acid) is a water-soluble antioxidant vitamin which supports the immune system's epithelial barrier against pathogen entry as well as the cellular functioning of the adaptive and innate immunity (16). Vitamin C acts as an antioxidant, preventing injury toward biological molecules (carbohydrates, nucleic acids, lipids, and proteins) caused by oxidants produced by regular metabolism as well as pollutants and poisons (17). Moreover, the present vitamin is a composition for several enzymes entangled in the maintenance of collagen structure (18), hormonal biosynthesis like vasopressin, norepinephrine and catecholamines (19).

Vitamin C levels can be affected by environmental factors such as air pollution and disorders like type 2 diabetes. Vitamin C deficiency is more common in the elderly, who are more likely to suffer from chronic or acute illnesses, with age associated to decreasing vitamin C levels (20). Low levels of vitamin C (17 mol/L) were associated to death in an older British population (21).

Respiratory distress syndrome, subsequent infection, and sepsis have been linked to COVID-19. Sepsis and septic shock can be helped with an intravenous (iv) therapy of high-dose vitamin C (22). After comparing to control group, an infusion of vitamin C (50 mg/kg B.W) each 6 hours for 96 hours suggestively reduced death also enhanced the quantity of ICU-free days in patients with sepsis and respiratory distress (23). When comparing with control group, intravenous (iv) vitamin C, thiamine, and hydrocortisone for seven months suggestively reduced hospital death rate in sepsis patients. Another example, a 74 years’ old lady with COVID-19, caused respiratory distress syndrome and septic shock. After receiving treatment with a higher dose of vitamin C, that patient recovered quickly (11 g/day for 10 days) (23). Vitamin C has antiviral effects. The investigations suggested that higher dose vitamin C treatment is helpful in contrast to the common cold (24). After comparing with control group, vitamin C supplement with a high dose treatment (Initially, 1000 mg of vitamin C every six hours. Then, three times daily for three days) reduced cold and flu signs in patients (24).

Lower vitamin C levels and older age seemed to be collegial risk factors for the death rate, signifying that the serum vitamin C has a role in the importance of age as a prediction of mortality (25). Patients with respiratory distress syndrome, a high dose vitamin C is linked to several positive outcomes, including reduced swelling and damage of organs, lower pathogen infection, in addition improved immune system protection (26). Liquids and proteins permeate the alveoli in ARDS, causing pulmonary oedema. Higher permeability to body fluids, erythrocytes and neutrophils is caused by tight junction breakdown in the endothelium of lungs, ensuing in an oversupply of this components in alveolar space. During acute lung damage, neutrophils in the extravascular and intravascular areas are typically linked with platelets, producing aggregates that cause inflammatory processes because of their inflammatory thrombogenic activity.

Parenteral infusions of vitamin C (200 mg/kg) improves alveolar fluid elimination, improved alveolar epithelial barrier’s structural function suppresses the pro-inflammatory response in mice with septic infection and pulmonary dysfunction, dropping the effects of septic infection in acute pulmonary dysfunction (27). These outcomes were found through normalizing the component of intercellular junction protein and preventing ascorbic acid-induced cytoskeleton rearrangements.

In COVID-19 patients, vitamin C may also help to manage the cytokine storm, which is categorized by higher level of proinflammatory interleukins (IL-6), which increases the chances of respiratory failure and the need for mechanical ventilation (28). A study involving 12 patients, pre-treatment with vitamin C can decrease the quantity of interleukins produced through the Vasoconstrictor Endothelin-1 (ET-1), decreasing vascular-dysfunction and higher ET-1 expression has been related to ARDS, pulmonary hypertension, pneumonia, interstitial lung fibrosis (29).

Despite the boundaries, COVID-19 patients can be treated with vitamin C supplements to recover this illness, as this vitamin is involved in the growth, preservation, and appearance of the immune system.
response, all of which influence the severity and risk of viral infections like SARS-CoV 2.

The role of zinc in viral infections

Zinc is crucial for intestinal barrier homeostasis and integrity. Zinc therapy reduced intestinal permeability in a rat colitis model due to its act on tight junctions (30). Intracellularly reduction of zinc increases the intestinal barrier permeability in human intestinal cancer cells and mice colons since tight junctions remained disrupted through an important decline in protein levels of claudin-3 and occluding (31).

Zinc supplement, restores the homeostasis of intestinal barrier, lowering the permeability of tight junction. Claudins, the proteins that make up tight junctions, regulate the magnitude and control of particles that passes via paracellular space. Claudins are split into two groups depending on its functions: pore-forming (claudin-2 and 15) and these cover the membrane (claudin-1, -3, -4, -5, -6, -8, -12, -18, and -19) (32).

Claudin-7 and claudin-2 protein levels were dramatically decreased after the zinc therapy, according to the findings (33). The decreasing of these proteins and addition of zinc supplement effects the higher epithelial barrier resilience and that is related by lower electrolytic permeability. In spite, the improved flux of mannitol, that shows greater non-electrolyte permeability, suggests zinc adjusts the junctional complex finely, operating differently depending on the kind of electrolyte (33).

In Caco-2 cells, zinc deficiency not only altered the tight junction’s structure, affected adherens junctions, causing B-catenin and E-cadherin but also proteins to delocalize. Increased permeability and, as a result, neutrophils infiltration in the paracellular space resulted from the intestinal epithelium’s malfunction, triggering inflammation (34).

In zinc deficient epithelial cells of the lung, cytokines are promoted cell death via apoptosis and barriers dysfunction, through B-catenin and E-cadherin proteolysis (35). Zinc supplementation restores adherens junction degradation and that is beneficial in sustaining barrier function and cellular integrity (35). The authors hypothesized that based on their observation’s mobilization of zinc to epithelial cells during the early stages of an inflammatory response in the lung is an important response that boosts immune activity while also protecting other cells from inflammation-induced damage (35). Similarly, neutrophil infiltration suppressed in zinc-treated Caco-2 cells, showing that restoring zinc levels reverse the epithelial barrier integrity and stopped the inflammation (36).

CONCLUSION

Antioxidant, immunomodulatory, and antibacterial properties of several minerals and vitamins may aid the immune system against SARS-CoV 2 virus. Vitamin supplementation emerges as a significant option for boosting immunity and delaying the emergence of serious conditions in the nonappearance of broadly accessible medication or else immunization for COVID-19. These microelements include vitamins D, C, and zinc.

The importance of micronutrients like vitamin D, vitamin C, and zinc in the immune system was investigated in this review considering these microelements have most indications used for immunological sustenance. The literature shows that zinc, vitamin D and C are essential components of the immune system and have collective roles in numerous phases of the defenses, including the preservation of physiological barriers with their functions, which build the adaptive and innate systems. As a result, a lack of or inadequacy of these essential nutrients, which cooperate in adherens and tight junction proteins can weaken mucosal epithelial cell’s ability to function, perhaps rendering them extra vulnerable to pathogens like SARS-CoV-2.

Several research show that vitamin D, vitamin C, and zinc intake can help to prevent viral respiratory infections. As a result, in the state of the COVID-19 pandemic, appurtenance by these microelements may be considered a broadly accessible, harmless, and cost-friendly measure that can be suitable in managing the higher order for these nutrients in the event of virus interaction and beginning of immune responses, also in reducing the chance of serious viral infection growth and prognosis. Further clinical trials would provide additional information on their effects on COVID-19 patients.

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CONFLICT OF INTEREST

Authors have no conflicts of interest to declare.

REFERENCES


