Essential Immunonutrients in COVID-19: An Evidence-Based Review

Dr. Manish Maladkar[1], Dr. Ashok Yadav[2], Nehali Save[3]

Abstract

A 'well-fed' immune system is extremely important to ensure it performs the function of protecting against the viral offense. Various nutrients and minerals play a vital role in maintaining the integrity and function of the immune system. Among the various nutrients and minerals, vitamin C, vitamin D, and zinc stand out for having immune-modulatory functions which are demonstrated in a substantial body of evidence. In the ongoing pandemic of COVID-19, nutrients that can optimize the immune system to prevent or lower the risk of severe disease progression are very essential. Medical literature shows that deficiency of one or more of these nutrients may affect the immunity status of an individual and may predispose a person to an adverse prognosis of COVID-19. Therefore, adequate intake of vitamin C, D, and zinc may present as a promising tool in prehabilitation with immunonutrition for COVID-19 prevention and management. This review provides a comprehensive overview of the role of vitamin C, D, and zinc as an immunomodulatory agent in COVID-19 management.

Keywords: Vitamin C, vitamin D, zinc, immunity, immunonutrition, COVID-19

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Introduction

Currently, the world is struck by a global pandemic called Coronavirus Disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] This pandemic has become a global public health concern.[2] To this period, more than 50 million people are affected worldwide and more than 2 million have yielded to COVID-19. India at present stands at second position in the list of severely affected countries.[3]

The SARS-CoV-2 gains entry into the cells via the ACE 2 receptor in the lungs. Once inside the cells, it starts replicating and the viral load increases leading to the manifestation of COVID-19.[4] COVID-19 management currently constitutes the investigational drugs that are previously approved for another indication but are now repurposed to manage COVID-19.[5]

Amidst the global pandemic of COVID-19, utmost precautions ought to be taken to steer clear of SARS-CoV-2. Additionally, the strongest shield that will protect against SARS-CoV-2 is Immunity. An optimally working immune system will help build defense mechanisms against the virus and provide resistance to the infection as well.[6]

[1] President- Medical & Regulatory Affairs; [2] Assistant General Manager- Medical, Scientific Department; [3] Sr. Scientific Executive- Scientific Department, Aristo Pharmaceuticals Private Limited.

Corresponding Author: Dr. Manish Maladkar, President- Medical & Regulatory Affairs, Aristo Pharmaceuticals Private Limited. 23-A Shah Industrial Estate, Andheri, Mumbai, India. E-mail: scientific@aristopharma.co.in

The concept of a 'well-fed' immune system is widely recognized as one way of helping the immune system work effectively. An ideal immune system is a system that should be 'constantly alert and monitoring for signs of danger or invasion'. Therefore, nutritional sufficiency needs to be assured so that the immune system functions flawlessly.[7]

A review by Gombart AF *et al.* has identified that multiple micronutrients are essential to meet the complex requirements of the immune system. These micronutrients include vitamins A, B6, B12, folate, C, D, and E. Minerals like copper, iron, selenium, and zinc are essential as well. However, a huge body of evidence exists for the correlation of vitamin C, D and zinc for healthy functioning of the immune system.[8] Therefore, this review article focuses on the aforementioned nutrients with specific reference to their role in immunonutrition in COVID-19.

Immunonutrition with Vitamin C

Vitamin C is a vital nutrient required for numerous functions in the body. However, due to the loss of crucial enzyme in the biosynthetic pathway for vitamin C, it cannot be synthesized by humans.[9] Therefore, a regular and sufficient intake of vitamin C is essential to prevent hypovitaminosis C.[10] A diet supplying 100-200 mg/day of vitamin C is adequate at saturating plasma concentrations to healthy levels which ensures the vitamin C levels are sufficient for reducing the risk of chronic diseases.[11]

A serum concentration lower than 11.4 umol/L is defined as vitamin C deficiency. The prevalence of vitamin C deficiency varies across the world. It was found to be 7.1% in the United States and 73.9% in north India.[12]

Pleiotropic Role of Vitamin C

Vitamin C exhibits multiple pleiotropic functions. Vitamin C is a potent anti-oxidant thereby promoting the oxidant scavenging activity and protecting against environmental oxidative stress. Vitamin C also supports immune function. It is involved in various cellular functions of the innate as well as the adaptive immune system. It also exhibits antimicrobial functions due to its property to enhance chemotaxis and phagocytosis. By the virtue of all the pleiotropic properties, vitamin C appears to be able to prevent and treat respiratory and systemic infections.[13]

Vitamin C deficiency may result in impaired immunity culminating in higher susceptibility to infections. Additionally, it also may significantly impact vitamin C levels due to increased inflammation and metabolic requirement. [13]

Proposed Role of Vitamin C in COVID-19

Multiple functions of vitamin C in COVID-19 are related to COVID-19-related sepsis and Acute Respiratory Distress Syndrome (ARDS).

- SARS-CoV-2 infection and depleted levels of antiviral cytokine interferon seem to be connected. Reduced interferon levels have been negatively associated with disease severity. In animal studies, vitamin C has been shown to enhance the levels of interferon α and β thus having a positive impact on viral infection pathology.[14]
- SARS-CoV-2 downregulates the expression of type-1 interferons which are the primary antiviral defense mechanism of the host. Vitamin C upregulates this crucial interferon and improves the pathology.[15]
- Another characteristic phenomenon of severe COVID-19 is the 'cytokine storm' which is a state of elevated inflammatory markers. Vitamin C due to its anti-inflammatory and anti-oxidant properties can potentially counteract this phenomenon.[14]
- Other complications of COVID-19 are coagulopathy and microthrombi formation which is observed in lung pathology and other pathologies. Early injection of vitamin C has been demonstrated to prevent the microthrombi formation and capillary plugging.[14]
- Vitamin C also demonstrates virucidal activity. Furthermore, due to its anti-oxidant effect, vitamin C reduces the reactive oxidative species (ROS) formation. It also reduces inflammation via attenuation of NF-κB activation.[15]

Table 1 mentions clinical evidence of injectable vitamin C as an adjunct therapy in pathologies related to COVID-19.

COVID-19 pneumonia and its progression to respiratory failure are found to be driven by immune hyperactivity in which various inflammatory markers play a crucial role. Vitamin C can effectively reduce the inflammatory markers in various inflammatory conditions. Therefore, vitamin C is clinically beneficial in COVID-19. Bearing in mind, the accumulating evidence on vitamin C supplementation, an oral dose (1-2 g/day) may be prophylactically used. In cases of severe COVID-19, a dosing regimen of > 2 g may be favourable. Results of the ongoing clinical trials are expected to provide more conclusive evidence.[20]

Table 1: Clinical evidence of vitamin C as an adjunct therapy in pathologies related to COVID-19

Sr. No.	Patients	Therapy	Results
1.	24 patients with severe sepsis [16]	Ascorbic acid (50 mg/kg/24h, n = 8), or Ascorbic acid (200 mg/kg/24h, n = 8), or Placebo in addition to standard of care.	Patients receiving ascorbic acid exhibited prompt reductions in SOFA scores while placebo patients exhibited no such reduction. ($p<0.01$) Ascorbic acid significantly reduced the pro-inflammatory biomarkers, C-reactive protein, and procalcitonin. ($p<0.05$)
2.	594 critically ill surgical patients [17]	Ascorbic acid 1 g every 8h for 28 days in addition to standard of care.	Significantly lower incidence of acute lung injury and multiple organ failure. (RR=0.43) Patients randomized to Ascorbic acid supplementation also had a shorter duration of mechanical ventilation and length of ICU stay.
3.	94 septic patients[18]	1.5 g every 6h for 4 days or until ICU discharge vs Placebo in addition to standard of care.	The hospital mortality was 8.5% (4 of 47) in the treatment group compared with 40.4% (19 of 47) in the control group. ($P < 0.001$)
4.	216 critically ill patients[19]	Vitamin C (500 mg/day)	There was a significantly reduced 28-day mortality after vitamin C intervention (45.7% in the antioxidant group and 67.5% in the regular-feeding group). $P < 0.05$

SOFA Score: Sequential Organ Failure Assessment, RR: Relative Risk, ICU: Intensive care unit.

Immunonutrition with Vitamin D

Vitamin D, a steroid hormone is produced endogenously in the skin when exposed to ultraviolet radiation. It is also made available from exogenous food sources or dietary supplements. Currently, vitamin D insufficiency is a public health concern worldwide that affects over a billion people at different life stages.[21]

Vitamin D insufficiency may compromise respiratory immune function, increasing the risk of COVID-19 severity and mortality.[22] Protective effects of vitamin D have been well demonstrated in subjects at risk of chronic diseases like cardiovascular diseases, respiratory tract infections, diabetes mellitus, hypertension, cancer, etc. Emerging data has suggested that vitamin D supplementation to increase the serum vitamin D levels above 50 ng/ml (125 nmol/l) may have constructive effects in reducing the incidence and severity of several viral diseases, including COVID-19.[23]

Pleiotropic Benefits of Vitamin D

The classical functions of vitamin D include the regulation of calcium-phosphorus homeostasis and bone metabolism. It is well known that vitamin D insufficiency can increase bone turnover, reduce bone density, and is associated with high fracture risk. Accumulating evidence documents the pleiotropic benefits of vitamin D other than its role in skeletal health.[24]

The interaction of vitamin D with the immune system is one of the well-known pleiotropic benefits. Vitamin D also exhibits anti-inflammatory properties. It is involved in the differentiation of active CD4+ T cells, and enhancement of the inhibitory function of T-cells.[25]

Active vitamin D exhibits negative feedback on the Renin-Angiotensin System. The Renin-Angiotensin System is involved in regulating blood pressure, electrolyte levels, and blood volume status. Studies have shown that low active vitamin D serum levels may culminate into high blood pressure or diseases related to high plasma renin activity.[26]

Various *in-vitro*, as well as *in-vivo* studies, have demonstrated the effectiveness of vitamin D in preventing the destruction of pancreatic beta-cells and thereby reducing the incidence of diabetes mellitus.[27]

Proposed Role of Vitamin D in COVID-19

Vitamin D receptors are widely present on many immune cells like macrophages, dendritic cells, T cells, and B cells. Therefore, vitamin D in its active form plays a critical role in regulating the innate and adaptive immune system. These aspects of the immune system contribute to defense against COVID-19.[28]

COVID-19 pathophysiology involves a typical innate response that comprises of reduced type-1 IFN production and increased levels of inflammatory cytokine IL-6 and many others. Vitamin D is shown to exhibit suppressive effects on the production of IL-6 thus help in modulating the immune responses in COVID-19.[29]

COVID-19 is also characterised by cytokine storm which results due to the increased generation of pro-inflammatory markers. Vitamin D by enhancing cellular immunity is known to reduce the cytokine storm.[30] Vitamin D is also known to reduce the production of

pro-inflammatory Th1 cytokines, such as TNF-α and IFN-γ. Administration of vitamin D has been found to decrease the expression of pro-inflammatory cytokines and increase the expression of anti-inflammatory cytokines by its action on macrophages.[31]

Vitamin D supplementation enhances the expression of genes of glutathione reductase- cysteine ligase modifier unit involved in the anti-oxidation process. Due to the increased glutathione production, usage of ascorbic acid as an anti-oxidant is spared. Ascorbic acid is then utilized in the anti-microbial activities targeted against COVID-19.[32]

Previous studies supporting the beneficial effects of vitamin D supplementation in a variety of infectious diseases and other chronic diseases with underlying inflammatory issues are summarized in Table 2.

A study by Rastogi *et al*. has reported that daily 60,000 IU of vitamin D for 7 days was effective in conferring protective effects in treating COVID-19. A large amount of patients suffering from vitamin D deficiency and COVID-19 turned SARS-CoV-2 negative on the above high-dose vitamin D supplementation.[36]

Table 2: Clinical evidence of oral vitamin D as an adjunct therapy in pathologies related to COVID-19 and in COVID-19 management

Sr. No.	No. of patients	Therapy	Results
1	Meta-analysis of 11 placebo-controlled studies of 5660 patients [33]	The average vitamin D dose was 1600 IU/day and the dosing interval varied between 24 hours and 3 months.	Vitamin D supplementation showed a protective effect against respiratory tract infections. (p=0.01)
2	Meta-analysis of 5 placebo-controlled studies of 1868 patients of all age groups [34]	400 IU/day to 2000 IU/day. In one clinical trial single parenteral dose of vitamin D was given (100000 IU). Duration- 3-6 months with one study giving vitamin D supplements for 3 years.	Events of respiratory tract infections (like influenza, pneumonia, the common cold) were significantly lower in the vitamin D group as compared to the control group. (p=0.001)
3	Meta-analysis of 25 randomised controlled trials (total of 11321 participants, aged 0 to 95 years) [35]	25 mcg (1000 IU) to 3 mg (120000 IU)/day and dose interval varied between daily, weekly, and monthly.	Vitamin D supplementation reduced the risk of acute respiratory tract infection among all participants. (p<0.001)
4	40 SARS-CoV-2 RNA positive individuals [36]	Daily 60,000 IU of cholecalciferol (oral nano-liquid droplets) + standard of care for 7 days vs placebo.	10(62.5%) participants in the intervention group and 5 (20.8%) participants in the control arm (p<0.018) became SARS-CoV-2 RNA negative. Fibrinogen levels significantly decreased with cholecalciferol supplementation (intergroup difference 0.70 ng/ml). P=0.007

IU: International units

Immunonutrition with Zinc

Zinc is one of the most important trace elements abundantly distributed in the body. Important functions of zinc comprise of catalysing enzymatic activity of over more than 300 enzymes, contributing to the protein structure and regulating gene expression.[37]

According to the International Zinc Association, 2 billion people are zinc deficient worldwide and about 8,00,000 people are at risk of death due to conditions linked with zinc deficiency. In India, a population of approximately 30% is at risk of zinc deficiency.[38]

Adequate zinc intake within a range of 10-15 mg/day is important to maintain the plasma zinc concentration in a normal range of 84–159 mcg/dl.[39] Adequate zinc intake is critical for the healthy functioning of the body.

Pleiotropic Role of Zinc

Zinc plays a pivotal role in many essential functions in the body. Zinc is involved in physical growth and development. It plays a critical part in cell division, DNA synthesis, RNA transcription, activation and prevention of apoptosis.[40]

Apart from this, zinc also plays an important role in the development, integrity, and functioning of the immune system. Zinc is essential for the normal development and function of various immune cells like neutrophils, NK cells, macrophages, T cells, and B cells.[41] The production as well as the potency of several cytokines which are the messengers involved in immune system functioning is also perturbed by zinc deficiency.[42] Additionally, zinc also exhibits anti-oxidant properties and membrane stabilizing properties. These properties of zinc are instrumental in the prevention of free radical-induced injury during inflammatory processes.[41]

Proposed Role of Zinc in COVID-19 [43]

The proposed protective mech-

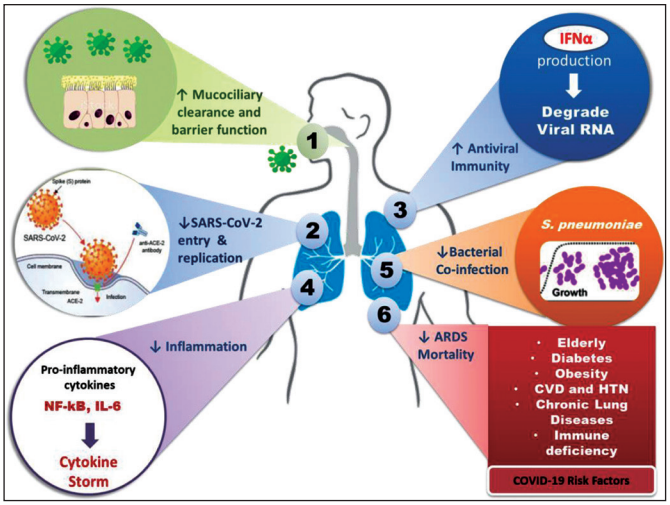

Figure 1: Protective mechanisms of zinc in COVID-19

anisms of zinc in COVID-19 have been illustrated in figure 1.

1. Zinc increases mucociliary clearance and the epithelial barrier function. Zinc helps in maintaining the cilia beating frequency which ensures proper mucociliary clearance. This prevents the entry of the virus into the lungs. Zinc helps in maintaining the tight junctions that bind the epithelial cells together. The tight binding forms a strong epithelial barrier which helps to prevent the entry of the virus into the lungs.
2. Zinc decreases the viral load. Zinc stops the entry of the virus into healthy cells. It also reduces the activity of the ACE2 receptors which is important for the entry of the virus into healthy cells. Zinc inhibits the replication process and thus decreases the viral load.
3. Zinc acts as an anti-inflammatory agent and helps protect against lung inflammation. It modulates the regulatory T-cell functions, limits excessive inflammatory response, and prevents cytokine storm (a condition where excessive pro-inflammatory cytokines are produced).
4. Zinc inhibits bacterial co-infection. All the above processes make the body immunodeficient and more susceptible to other infections. One of the common infections in such patients is the one caused by *Streptococcus pneumoniae*. Zinc is known to inhibit *S. pneumonia* due to its anti-bacterial and immunity booster activity.
5. Zinc is beneficial in patients with COVID-19 risk factors.

Table 3 mentions the clinical evidence of oral zinc as an adjunct therapy in viral infections and COVID-19 management.

The doses used in registered clinical trials for patients with COVID-19 vary between studies, with a maximum dose of 50 mg of elemental zinc twice daily. [48]

Numerous ongoing clinical trials are investigating the effects of vitamin C, vitamin D, and zinc in COVID-19 patients. As per the clinical trials database (www.clinicaltrials.gov), a total of 13, 5, and 6 trials are currently recruiting patients for investigating effects of vitamin C, vitamin D, and zinc respectively in COVID-19. As per the clinical trials registry

Table 3: Clinical evidence of oral zinc as an adjunct therapy in pathologies related to COVID-19 and in COVID-19 management.

Sr. No.	No. of patients	Therapy	Results
1	50 healthy elderly patients (aged >55 y) [44]	Zinc (45 mg/d) or placebo for 12 months.	After zinc supplementation, the incidence of infections was significantly lower. Generation of cytokines and oxidative stress markers was significantly lower in zinc-taking patients.
2	2121 patients ranging from 1 to 65 years of age, included in a meta-analysis of 17 RCTs [45]	Zinc 10 mg- 50 mg. The duration of treatment was different in all trials (range 3–14 days or until symptoms resolution).	Zinc reduced the duration of cold symptoms in adults (MD −2.63 days, 95% CI −3.69 to −1.58).
3	932, confirmed COVID-19 hospitalized patients [46]	HCQ + Azithromycin + Zinc (50 mg twice daily) vs. HCQ + Azithromycin for 5 days.	Zinc sulphate increased the frequency of patients being discharged home (77.1 vs. 68.3, p=0.003), decreased the need for ventilation (8 vs. 16.5, p=0.01), admission to the ICU (9.2 vs. 15.7, p=0.004), and mortality or transfer to hospice for patients who were never admitted to the ICU (13.1 vs. 22.8, p<0.0001).
4	3,473 adult hospitalized COVID-19 patients[47]	HCQ + Zinc (50 mg once or twice daily) vs. no HCQ + Zinc.	HCQ + Zinc was associated with a 24% reduced risk of in-hospital mortality (p=0.023). More patients who received HCQ + Zinc were discharged home (72% vs. 67%, p=0.003).

HCQ: Hydroxychloroquine, MD: Mean Duration, CI: Confidence Interval

of India (www.ctri.nic.in), 3, 5, and 2 trials are enlisted which are investigating the role of vitamin C, vitamin D, and zinc respectively (as one of the interventions) in COVID-19.

Conclusion

A considerable amount of medical literature demonstrated that vitamin C, vitamin D, and zinc are essential for the efficient functioning of the immune system. Therefore, the deficiency or insufficiency of these key nutrients can make an individual more susceptible to COVID-19. In the current scenario, more emphasis is given on prevention and prehabilitation with immunonutrition. The supplementation of these key nutrients due to their easy availability, safety, and low cost can prove helpful in coping with the ongoing pandemic. The supplementation can lower the risk of severe progression and prognosis of COVID-19. Results of the ongoing clinical trials can shed some more light on their efficacy in COVID-19 patients.

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