

COVID-19: A brief overview on the role of Vitamins specifically Vitamin C as immune modulators and in prevention and treatment of SARS-Cov-2 infections

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ABSTRACT

In December 2019 a pandemic of acute respiratory distress syndromes occurs in Wuhan, china, the early evidence suggests this may be due to exposure to local sea foods in china. The pathogen was isolated from Chinese patients and designated as severe acute respiratory syndrome corona virus 2 (SARS-COV-2). COVID-19 mainly affects lungs by producing respiratory predominant symptoms like fever, cough, flu and dyspnea. As SARS-Cov-2 firstly find a mechanism to escape the immune system of humans and animals followed by a huge release of cytokines named as cytokine storms and the hyper activation of the other immune system responses. To avoid these conditions in any type of viral infections such as in SARS-Cov-2 infections and influenza virus induce lung injury vitamin D is now is recently considered as proposed therapy. Vitamin C acts as strong antioxidant and help to scavenge all the damaged species that is why vitamin C is regarded helpful in SARS-Cov-2 and other viral infections. Many findings from different clinical studies show that vitamin C when administrated orally can reduce SAR-Cov-2 and other viral infection. Taking vitamin C intravenously has also profound effect on the reduction of viral infections. As health care workers and professional are risk community for COVID-19 so vitamin C should be included in prevention and treatment of COVID-19 in this community. As vitamin C is also a prooxidant so smaller pharmacological concentration of vitamin C milli-molar is beneficial. But in case of COVID-19 high intravenous dose of vitamin C would be the right choice.

Introduction

In December 2019 a pandemic of acute respiratory distress syndromes occurs in Wuhan, china, the early evidence suggests this may be due to exposure to local sea foods in china [1]. The pathogen was isolated from Chinese patients and designated as severe

acute respiratory syndrome corona virus 2 (SARS-COV-2). WHO announces this as global pandemic on March 11; 2020. COVID-19 mainly affects lungs by producing respiratory predominant symptoms like fever, cough, flu and dyspnea [2]. The virus primarily

attacks the angiotensin converting enzyme-2 receptor (Ace2) of the lung [3]. Corona virus are enveloped, positive stranded RNA virus, genome size ranges between 26kb to 32 kb, resembles a solar corona, have four sub families i.e. alpha, beta, gamma and delta Coronaviruses and was first described by Tyrell and Bynoe in 1996 [4-7]. Most accepted model at first was animal to human transmission from Wuhan sea food market but after sometimes person to person transmission model was the most acceptable mode of transmission i.e. by aerosol, air droplets and fecal oral transmission has also clarified [8-15].

As till now there is no specific pharmacological treatment against COVID-19 [16,17]. By advising people to adapt healthy lifestyle and to consume more healthy food would be more helpful to combat with this pandemic of COVID-19. People should strictly follow WHO recommendations regarding nutritional supplements [18-20]. Immune system has a major role in fighting against different types of infection but for proper immune cells functioning there is need of some supplements like vitamin C [21-23]. This vitamin has a major role in maintaining proper immune cell functions [24]. Lack of vitamin C makes one more susceptible to scurvy and pneumonia [25- 28]. Taking vitamin C less than or equal to 1g/day reduces the risk of mortality up to 35% from common colds [29]. Using early large dose of vitamin C intravenously can reduce risk of COVID-19 [30]. This review is an effort to highlight the immune modulatory function of vitamin especially vitamin C and role of these vitamins in prevention and treatment of COVID-19.

Etiology, Epidemiology and Mortality Rate of COVID-19

On the basis of previous reports, it was confirmed that SARS-Cov-2 has up to 96% genome resemblance with that of SARS Coronaviruses derived from bats [31]. Therefore, this virus is named as 2019 novel corona virus. The virus contains enveloped RNA and resembles solar corona [32]. The genome of coronavirus is enclosed in an envelope on the surface of that envelope there are spike protein which are four in number and these spikes help the virus for attachment to the human ACE2 receptor for entering into host cell [33,34]. At early time the transmission of the outbreak was attributed to sea animals but later on human to human transmission was also confirmed [35]. At the end of January WHO reported approximately 10,000 known cases. But at the middle of February about 13332 cases was reported [31]. Approximately 74,280 overall cases in china and 924 cases is reported in other countries by February 19, 2020 [36-38]. After some time, virus spreads in nearly 210 countries on April 26, 2020. And over all 2.4 million confirmed cases was reported in the month of April mainly on 26 to 30 April. 15 % mortality rate was observed in Algeria, 13.95% in Belgium, 13% in Italy and United Kingdom, and Netherland (11.35%). Lower mortality rate was found in countries Qatar 0.17%, Singapore 0.2%, United Arab Emirate 0.6%, and Australia 0.97%. The WHO keeps on updating and sharing these figures on daily basis and till April 28th it had issued ninety seven reports giving country wise details of number of cases [39] (Figure 1).

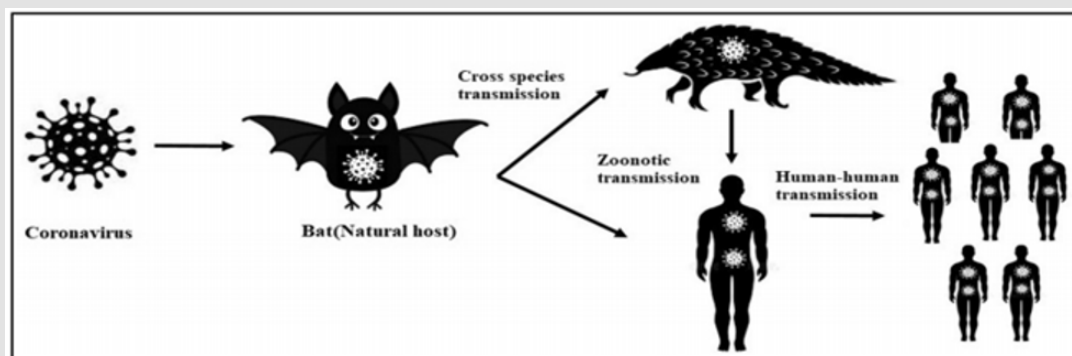


Figure 1: Shows the origin and transmission of SARS-Cov-2 [96].

Role of Vitamins as Adjuvant Therapy Against SARS-Cov-2 and Other Viral Infections

As SARS-Cov-2 firstly find a mechanism to escape the immune system of humans and animals followed by a huge release of cytokines named as cytokine storms and the hyper activation of the other immune system responses. As these are also common mechanisms in the acute respiratory syndrome and inflammatory response syndrome. To avoid these conditions in any type of viral infections such as in SARS-Cov-2 infections and influenza virus induce lung injury vitamin D is now is recently considered

as proposed therapy [39-41]. Vitamin D helps to reduce many complications associated with pneumonia and also reduces the cytokine storms in many of SARS-Cov-2 infections [42,43]. In case of HIV infections vitamin D is considered as supportive therapy in combination with many other antiviral drugs such protease inhibitors and many more [44]. Patients with ARDS can get recovered if he was pre-treated with vitamin D. vitamin D helps to modulate the rennin- angiotensin system which in turn regulate the normal expression of ACE2 receptor a common binding site for SARS-Cov-2.

The beneficial role of vitamin D get more clearer because of the presence of vitamin D receptor genes so if proper amount of the vitamin D is not present the body the receptor genes will make one more susceptible to viral and bacterial infections [45-48]. As COVID-19 is now declared as pandemic and the finding of effective therapy against this pandemic would take a lot of time, so the world is seeking to find an alternative to protect themselves from this pandemic. Vitamin C is also considered as one of the possible therapy for COVID-19 because vitamin C has a promising role in maintaining proper body functions and also helps in removing damaged ROS and protect cell from oxidative damage. Vitamin C is needed in larger amount for proper immune function. The beneficial role of vitamin C in SARS-Cov-2 and other viral infections is clear from the fact the level of vitamin C decreases during infection and body needs more of it to fight [49]. Table 1 shows the common complications associated with SARS-Cov-2 and other viral infections and role of vitamin D [39-48].

Table 1: Shows the common complications associated with SARS-Cov-2 and other viral infections and role of vitamin D.

Types of viral infection	Common complication associated	Role of vitamin D
SARS-Cov-2	Huge release of cytokines named as cytokine storms and the hyper activation of the other immune system responses, ARDS, IRS.	Vitamin D helps to reduce many complications associated with pneumonia and also reduces the cytokine storms in many of SARS-Cov-2 infections
influenza virus	Cytokine storms, lung injury	Vitamin D is now is considered as proposed therapy for lung injury caused by influenza virus
HIV infections	Cytokine storms and immune system dysfunction	vitamin D is considered as supportive therapy in combination with many other antiviral drugs such protease inhibitors

Vitamin C as A Proposed Therapy for Prevention and Treatment of COVID-19

As acute respiratory distress syndrome, multi organs failure, cytokine storms, cellular injury are all the outcomes of SARS-Cov-2 and other viral infections. Vitamin C found to be helpful in these complications. Vitamin C acts as strong antioxidant and help to scavenge all the damaged species that is why vitamin C is regarded helpful in SARS-Cov-2 and other viral infections. Many findings from different clinical studies show that vitamin C when administrated orally can reduce SAR-Cov-2 and other viral infection. Taking vitamin C intravenously has also profound effect on the reduction of viral infections. There are two possible route of administration for vitamin C one is orally and other is intravenously studies have revealed that both administration routes of vitamin C has no side effects. As health care workers and professional are risk community

for COVID-19 so vitamin C should be included in prevention and treatment of COVID-19 in this community. As vitamin C is also a prooxidant so smaller pharmacological concentration of vitamin C milli-molar is beneficial. But in case of COVID-19 high intravenous dose of vitamin C would be the right choice [50-53] (Table 2).

Table 2: Shows list adverse responses of body against viral mechanism of infections and role of vitamin C in modulation of the responses.

Responses and complication	Role of vitamin C
acute respiratory distress syndrome	Vitamin C helps in regulation of ACE2 and modulation of rennin angiotensin system thus helps to restore proper lung function
cytokine storms and oxidative stress	prevention and management of oxidative stress and cytokine storms could be realized by large dose of antioxidants such as vitamin C
hyper activation of the other immune system responses	Immune system are group of cell which fight against infection but they also require proper vitamin C for proper function during infections
inflammatory response syndrome	Vitamin C helps to regulate inflammatory response so that immune cell may not damage.

Why Vitamin C as Therapy Against SARS-COV-2?

For reduction of ARDS, cytokine storms, neutrophils damage, oxidative stress, alveolar damage, acute respiratory failure, and mortality caused due to SARS-Cov-2 vitamin C is a proposed drug [54-57]. In a report of 29 patients with COVID-19 pneumonia, 27 (93%) showed increased hsCRP, a marker of inflammation and oxidative stress. Transcription factor, nuclear factor erythroid 2 (nfe2)-related factor 2 (nrf2), is a major regulator of antioxidant response element (ARE)-driven cytoprotective protein expression. Activation of Nrf2 signaling plays an essential role in preventing cells and tissues from injury induced by oxidative stress. Vitamin C is important part of cellular antioxidant system" [58,59]. Vitamin C is very effective in intensive care management [60]. Vitamin C is a suggested therapy in COVID-19 because it minimizes the effect of oxidative stress and cytokine and this promising role was also observed in 146 COVID-19 patients [61]. It has been reported that administrating high intravenous dose of 200mg/kg body weight can reduce clinical symptoms in viral infected [62]. And this reduction was also observed in patients infect with influenza virus [63,64]. Using antioxidants in nutrients decrease inflammatory response syndrome cause by SARS-Cov-2 [65]. Oral dosage vitamin C up to 6g per day can reduce the risk of many viral infections [66] and helps to improve health conditions [67]. In China upto 50 COVID-19 patients were treated using vitamin C by giving 10g to 20g dose per day [68]. For several decades high intravenous dosage of vitamin C is used in treating viral infection [69] (Table 3).

Table 3: Suggested doses of vitamin C for COVID-19 patients and health improvement related with dose.

Dose	Body weight	Improvement in patient health
high-dose intravenous vitamin C infusions of 200mg in 4 doses	Per kg body weight	Reduce the intensive care by 7.8% and decrease in mortality of COVID-19 patients
6 g daily orally	Compared with 200mg/kg	reduce viral infection risk
varied dose of 10 g and 20 g per day, given over a period of 8–10 h	Compared with 200mg per kg weight	Improve oxygenation index and many of COVID-19 patients are discharged by completing this dose.

Vitamin C Involvement in Immune Modulation and Proper Immune Function

Mainly vitamin C is accumulated in larger quantity by 50 to 100 folds in leukocytes which contribute to its normal functioning [70,71]. For normal immune cell function a person needs to take 100mg per day vitamin C [72,73]. As compared to immune cells another cell requires high vitamin C [70]. Neutrophils the first cell to travel at the site of infection accumulate vitamin C at 1mM concentration inside the cell [74,75]. Neutrophils can also take oxidized form of vitamin when it is needed in high concentration [76,77]. Dehydroascorbate known as DHA is oxidized form of vitamin C which is then converted to ascorbate the reduced form

to raise intracellular level of vitamin C up to 10Mm [77]. It is believed than milli molar concentration of vitamin C contributes to normal functioning of vitamin C [77]. vitamin C is very beneficial in scavenging activity of dead cell, normal neutrophils function, regeneration of vitamin E, activation of pro-inflammatory transcription factor nuclear factor κ B (NF κ B), modulation of signaling pathways, activation of signaling cascade, regulation of inflammatory mediators, phagocytosis, gene regulation and signaling pathways in T-cells, activation of κ B (NF κ B) in dendritic cells and neutrophils, increases neutrophils motility so that it may reach to the site of infection, vitamin c has also a promising role in immune modulation and proper immune functions [78-87] (Figure 2).

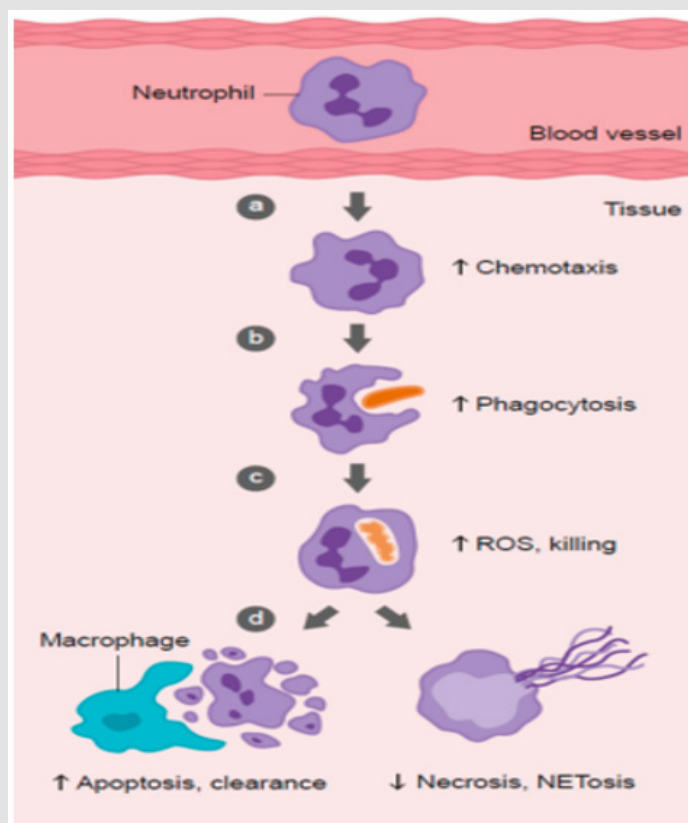


Figure 2: Highlights the role of vitamin C in immune cell function vitamin C is involved in following different function

- Shows enhance neutrophils migration in response to chemo attractants (chemo taxis),
- Enhance engulfment (phagocytosis) of microbes, and
- Stimulate reactive oxygen species (ROS) generation and killing of microbes.
- Vitamin C supports caspase-dependent apoptosis, enhancing uptake and clearance by macrophages, and inhibits necrosis, including NETosis, thus supporting resolution of the inflammatory response and tissue damage" [87].

Vitamin C Deficiency and Onsets of Infections

Scurvy one of the outcomes of vitamin C deficiency makes one susceptible to respiratory infection [88]. Pulmonary infections are also associated with low vitamin C level [89]. And many of the lung infections can be cleared by using intravenous vitamin C [90]. Decrease in intracellular concentration of vitamin C is observed in common colds [91-96]. Patients admitted with respiratory complication shows improvement by administration of vitamin C [89].

Conclusion

Vitamins especially vitamin C has a lot of positive impacts on immune system functions. Vitamin C is also a strong antioxidant helps in scavenging of oxidative species, normal neutrophil function, regeneration of vitamin E, activation of pro-inflammatory transcription factor nuclear factor κ B (NF κ B), modulation of signaling pathways, activation of signaling cascade, regulation of inflammatory mediators, phagocytosis, gene regulation and signaling pathways in T-cells, activation of κ B (NF κ B) in dendritic cells and neutrophils, increases neutrophil motility so that it may reach to the site of infection, vitamin C has also a promising role in immune modulation and proper immune functions. As health care workers and professional are risk community for COVID-19 so vitamin C should be included in prevention and treatment of COVID-19 in this community. As vitamin C is also a prooxidant so smaller pharmacological concentration of vitamin C milli-molar is beneficial. But in case of COVID-19 high intravenous dose of vitamin C would be the right choice. More ever vitamin C should be used as preventive therapy against COVID-19 and other viral infections.

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