Nutritional Perspectives to Coronavirus Disease 2019 (COVID-19) Susceptibility and Severity: a review of the roles of vitamin D and C

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Abstract

Background: *Coronavirus disease 2019 (COVID-19) which was declared a global pandemic on March 11, 2020 is known to have affected more than 108 million people with more than 2 million deaths worldwide as at February 2021. The pathophysiology of disease severity is governed by a cytokine storm which could potentially be modulated by certain vitamins such as vitamins D and C with immunomodulatory and anti-inflammatory properties. The mechanisms underpinning the susceptibility to and severity of the disease when these nutrients that have shown anti-inflammatory properties are deficient is yet to be fully elucidated.*

Objectives: *The aim of this review was to explore the plausible mechanisms through which vitamin D and C can influence risk of SARS-CoV-2 infection and progression to severe symptomatic form of COVID-19.*

Method: *We performed a literature search to review the pathophysiology of COVID-19 as well as effects of supplemental vitamin D and C on risk of infection, disease progression and severity.*

Results: *Randomised control trials which administered high doses of vitamin D and C, have shown demonstrable beneficial effects in COVID-19 patients. Although there is no recommended dose of vitamin D and C for COVID-19, maintaining optimum plasma concentration of vitamin D (100-150 nmol/L) and vitamin C (60-80 µmol/L) may prove beneficial. Doses of 50-125µg/day of vitamin D3 and 2-3g/day of vitamin C have proven effective in maintaining this optimum plasma concentration in COVID-19.*

Conclusions: *Together these studies suggest that high dose supplementation of vitamin D and C to maintain optimum plasma concentration have shown better outcome, reduced risk of progression and fatality even in*

severe cases of COVID-19.

KEYWORDS: *COVID-19, SARS-CoV-2, Vitamin D, Vitamin C, cytokine storm.*

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It was first detected in Wuhan, China and reported to the World Health Organisation on December 31, 2019. It was declared a global pandemic on March 11, 2020 with more than 118,000 cases in 114 countries and over 4000 deaths.[1,2] SARS-CoV-2 has a higher infection rate per exposure compared to the earlier corona viruses – SARS-CoV and the Middle East Respiratory Syndrome-related coronavirus (MERS-CoV) with a higher infection rate compared to SARS-CoV in 2002-2003 (8,098) and MERS-CoV in 2012 (2,254), and the number of diagnosed cases and deaths continue to increase globally. [1] The most recent data on the epidemiology of COVID-19 can be found on: the WHO COVID-19 weekly epidemiological update and weekly operational update https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. As at February 16th, 2021, more than 108 million have been affected and it has claimed over two million three hundred lives globally (https://www.who.int/publications/m/item/weekly-epidemiological-update---16-february-2021).The disease is more devastating in the elderly with those 75 years and above having more than 200 times the average death rates [2,3] and individuals with comorbidities such as obesity, diabetes, cardiovascular, respiratory, renal, liver diseases, other immunosenescence or immunocompromising conditions, with about 2% case fatality rate.[5,6,7,8] Mortality rates of up to 20% have also been reported in certain groups.[5] In severe condition, the disease leads to death due to massive alveolar damage, progressive respiratory failure and multi-organ failure.[9,10,11]

Though the patho-mechanism of COVID-19 is beginning to be unravelled, the disease has shown wide range of clinical features with significant unpredictability of disease progression. However, progression to cytokine storm is usually indicative of severe or fatal outcome.[12,13] The exact mechanisms underpinning the susceptibility to and severity of the disease when certain nutrients that have shown anti-inflammatory properties such as Vitamin D and C are deficient, is yet to be fully elucidated. Hence, this review highlights plausible and explorable mechanisms through which deficiency of vitamin D and C can influence risk of infection and progression to severe symptomatic form of COVID-19.

SARS-CoV-2 structure and genome replication

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA betacoronavirus of zoonotic origin (Fig. 1). [1,14,15] Its genome is organised in the order of 5′-replicase (ORF 1ab) - structural proteins [Spike-Envelope-Membrane-Nucleocapsid]−3′. The virus enters the host cell by binding to angiotensin-converting enzyme [2] (ACE2) receptor on the cell surface after priming of the spike glycoprotein by host transmembrane proteaseserine[2] (TMPRSS2). [1,6,16] The viral RNA which serves as both the genome and mRNA is then released into the cell cytoplasmand replication begins (Fig. 2). ACE2 is found on the cell membranes of cells in the lungs, heart, arteries, kidney, and gut.[17,18,19,20] The receptors are also found on hematopoietic cells, such as monocytes and macrophages;[21] on epithelial cells of seminiferous ducts of testis, adult Leydig cells, adrenal gland, prostate; [22] vascular endothelial cells, tongue, liver, and gall bladder.[1] This distribution may facilitate our understanding of the infection and migration of SARS-CoV-2 in the respiratory tract, blood, and digestive system. Details of viral RNA replication and expulsion of nascent viral particles are reviewed in Cascella *et al.*[2] and Guo *et al.*[1]

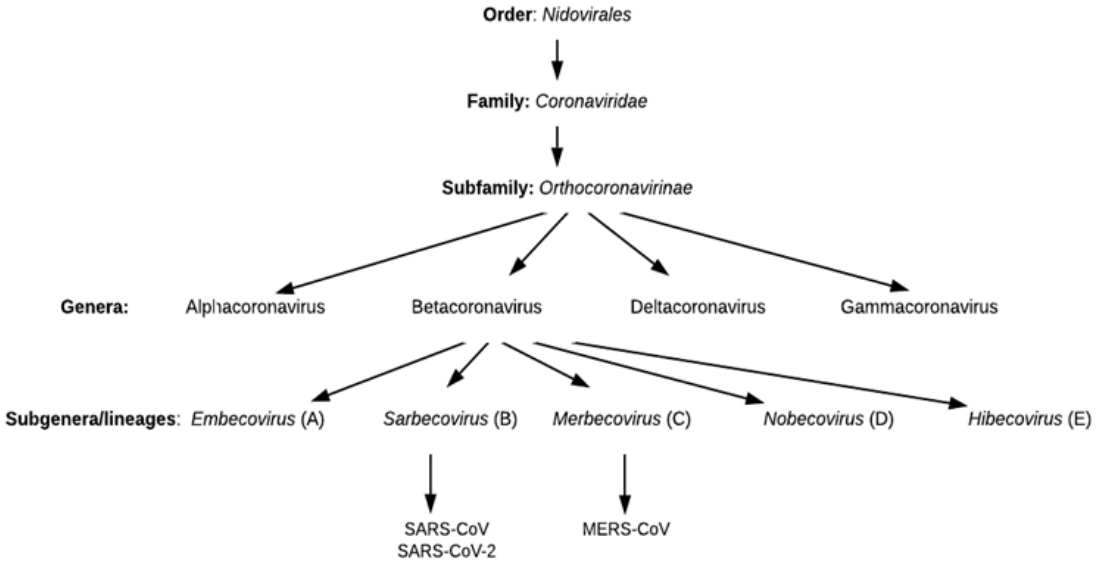

Figure 1. Taxonomic classification of SARS-CoV-2 (Severe acute respiratory syndrome-related coronavirus-2). The betacoronavirus genus is further subdivided into five lineages with the SARS-CoV and SARS-CoV-2 (which causes COVID-19) belonging to the B lineage. *MERS-CoV*, Middle East respiratory syndrome-related coronavirus. [23]

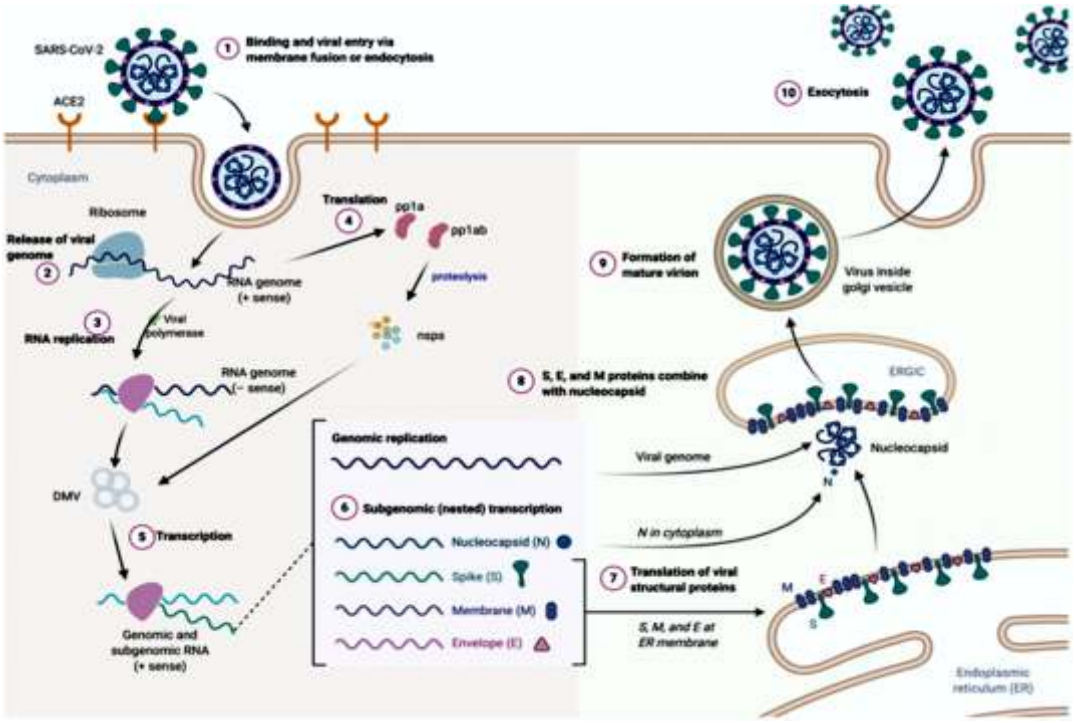

Figure 2. SARS-CoV-2 viral entry and replication.

The virus enters the host cell by binding to angiotensin converting enzyme[2] (ACE2) receptors on the surface of the cell via the spike (S)-protein[24,25] and is endocytosed. Alternatively, it can fuse directly with the host cell membrane. The lipid membrane and protein envelop are then degraded by lysosomal enzymes in the endosome. The viral RNA is then released into the cell cytoplasm where it serves as both the genome and viral mRNA. The genomic RNA encodes *ORF1a*, while *ORF1ab* is translated by a ribosomal frameshifting. The genomic *ORF1a* and *ORF1ab* are translated into replicasepolyproteins (pp1a and pp1ab), which undergo proteolytic cleavage by *ORF1a*-encoded proteases -

chymotrypsin-like protease (3CLpro) and papain-like proteases (PLpro) – to produce RNA-dependent RNA polymerase (RdRp, viral polymerase) and 15 other non-structural proteins (nsps) required for RNA synthesis. The nsps form the replication/transcription complex (RTC, viral factories) in double membrane vesicles (DMV) using rough endoplasmic reticulum (rER)-derived membranes. Viral replication and transcription occurs in the DMV using the RTC viral factories. [26] Simultaneously, viral RNA genome is transcribed in to subgenomic RNAs (sgRNA) by the RTC. The sgRNA is translated into structural proteins (S, E, M, N) in the cell's ER. Next, the structural proteins are assembled and budded in the ER-Golgi intermediate compartment (ERGIC) to form nascent viral particles with nucleocapsid and viral envelope. The final step is the expulsion of the nascent viral particles by fusion of the smooth-walled vesicles with the cell membrane (exocytosis).[1] Adapted from Benjamin Goldman-Israelow as *created in Biorender.com*

Pathophysiology of SARS-CoV-2 infection

The incubation period for SARS-CoV-2 infection ranges from 3-7 days and up to 14 days.[1,27] SARS-CoV-2 primarily infects the epithelial cells of the respiratory tract and causes pneumonia through a complex pro-inflammatory mechanism.[2] In severe cases, the infection produces a "cytokine storm" or cytokine release syndrome (CRS), which is essentially an excessive host immunological response characterised by rapid increase in inflammatory cytokines, and more importantly determines progression of the disease from mild to severe, and then to critical (Fig. 3).[1]High levels of inflammatory cytokines including IL-1β, IL-2, IL-6, IL-7, IL-12, IFN-γ, Interferon gamma-induced protein 10 (CXCL10), and monocyte chemoattractant protein-1 (MCP-1), MCP-2, GCSF, macrophage inflammatory protein 1-α (MIP-1α), TNF-α, IL-4 and IL-10 have been detected in blood samples of critically ill SARS [28,29] and COVID-19 patients.[1,9] This cytokine profile resembles that of secondary haemophagocyticlymphohistiocytosis (sHLH). COVID-19-associated mortality might be due to virally-driven sHLH-like hyperinflammatory response.[21,30] SARS-CoV-2 infection and associated CRS also upregulates the expression of ACE2, which could further promote viral infection and transmission. [31]

The virus can spread through the respiratory mucosa and infect other cells thereby stimulating systemic immune response, CRS and decreased immune cell (especially T lymphocytes) count.[32] Though lymphocytes do not express ACE2 receptors, lymphocytopenia - reduced $CD4^+$, cytotoxic $CD8^+$ T [7] and natural killer cells, is a common feature of COVID-19, but B cells are not significantly affected. Lymphocytopenia is associated with the severity and mortality of the disease,[7,10] although its cause is still unknown as the virus do not infect lymphocytes.[1,7] However, SARS-CoV-2's ability to act as a super-antigen activating large numbers of T cells leading to apoptosis could be an underlying mechanism. However, the mechanisms underpinning the combination of CRS and lymphocytopenia are still speculative and requires further investigation. [1] IL-6 is central to the cytokine-driven hyperinflammatory syndrome associated with COVID-19 (Fig. 3).[2,21] IL-6 is a pleiotropic cytokine that regulates immune and inflammatory responses. It is a B cell stimulating factor that promotes the production of IgG.[33,34] It modulates a broad spectrum of cellular activities through classic and trans-signalling pathways. Both pathways activate gp130 by binding to membrane-bound (mIL-6R) or soluble (sIL-6R) receptors respectively. Activation of classical pathway results in pleiotropic effects on both the innate and acquired immune systems, which facilitates CRS (Fig. 3).[21] Activated gp130 initiates signal transduction via JAK/STAT3 and SHP2/Gab/MAPK pathways.[33] In cells such as endothelial cells that do not express mIL-6R, IL-6/sIL-6R–JAK/STAT3 signalling results in a systemic "cytokine storm" characterised by release of vascular endothelial growth factor (VEGF), MCP-1, IL-8, more IL-6, and low expression of E-cadherin on endothelial cells.[35] Elevated VEGF and

decreased E-cadherin expression aid vascular permeability and leakage, which are implicated in the pathogenesis of hypotension and pulmonary dysfunction in acute respiratory distress syndrome (ARDS).[21] Given the association of CRS and sHLH-like hypercytokinaemia with COVID-19, inhibition of the IL-6 pathway may be of therapeutic benefit for severe COVID-19. [21,30]

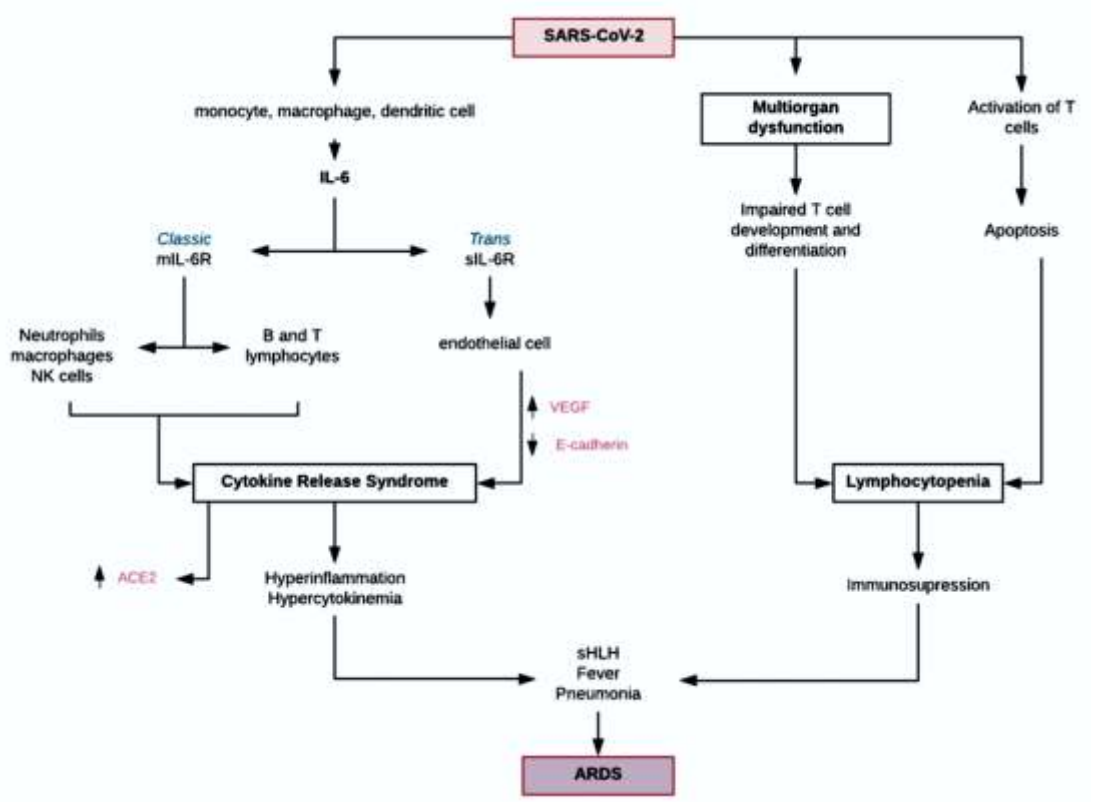

Figure 3. Pathogenesis of SARS-CoV-2 infection and acute respiratory distress syndrome (ARDS). ARDS associated with severe COVID-19 and death is characterised by an IL-6-mediated cytokine release syndrome ("cytokine storm") that leads to hyperinflammation; and lymphocytopenia mediated by multiorgan failure and T cell apoptosis. Multiorgan failure can also arise due to the cytokine storm, which can also trigger increased expression of ACE2. *ACE2,* angiotensin converting enzyme – 2; *mIL-R*, membrane bound interleukin-6 receptor; *sHLH*, secondary haemophagocyticlymphohistiocytosis; *sIL-6R*, soluble interleukin-6 receptor; *VEGF*, vascular endothelial growth factor;

Role of Vitamin D in ameliorating COVID-19

Apart from its established role of maintaining calcium homeostasis and bone health,[36] vitamin D and its metabolite modulate many of the same pathways dysregulated during SARS-COV2 infection including innate and adaptive immune response [37] as well as RAS pathway.[38] Thus, vitamin D and its metabolite may prevent and lower the risk of severe SARS-COV2 infection.

Studies have shown increased risk and severity of respiratory tract infections, particularly COVID-19 infection for individuals whose vitamin D serum/plasma concentration were below 75 nmol/L compared to individuals whose vitamin D concentration were ≥ 75 nmol/L .[39,40,41]In a retrospective study, 27 SARS-CoV-2 positive male patients aged 74 years exhibited significantly lower plasma 25-hydroxyvitamin D (25(OH)D) (median value = 27.8 nmol/L) compared to 80 SARS-CoV-2 negative patients (median = 61.5 nmol/L) (male = 48.8%; median age = 73 years, *P*=0.004)." 42 Similarly, a meta-analysis of

seven retrospective studies reported an average serum vitamin D concentration of 22.9 nmol/L in 1,368 patients with COVID-19. [43]
It has been suggested that maintaining a serum 25(OH)D concentration ≥ 95 nmol/L should significantly reduce the incidence of acute viral respiratory tract infections, including influenza.[44] This may suggest a need for supplementation with vitamin D so as to raise concentrations to ≥ 100-150 nmol/L would be beneficial in improving COVID-19 disease outcome. A cross-sectional analysis of a COVID-19 database of 235 adult patients conducted in Iran reported that vitamin D sufficient (25(OH)D ≥ 75 nmol/L) patients had significantly lower serum CRP and higher lymphocyte percentage in the blood compared to vitamin D insufficient patients. Vitamin D sufficiency was also associated with reduced clinical severity, lower risk of unconsciousness and hypoxia as well as reduced inpatient mortality.[40]

Randomised controlled trials that have evaluated the effect of vitamin D and its metabolite on COVID-19 patients have shown promising results.[45,46] An RCT conducted in Spain which administered high oral dose of 1064 µg calcifediol or 25-hydroxyvitamin D3, a main metabolite of vitamin D (0.532mg on day one of admission, and 266 µg on day 3 and 7, and then weekly until discharge from intensive care unit (ICU)) among 76 hospitalised COVID-19 patients observed significant reduction for ICU treatment among patients compared to control.[45] Another study that administered oral 1500 µg of vitamin D_3 daily for a week to 40 asymptomatic SARS-CoV-2 RNA positive vitamin D deficient (25(OH)D < 50nmol/L) individuals found treatment helped to achieve SARS-CoV-2 RNA negativity by the 14th day in 63% (greater proportion) of the patients. The treated group also showed significant decrease in fibrinogen (inflammatory marker that contributes to higher risk of thrombotic events in COVID-19) in patients achieving 25 (OH)D status >125 nmol/L as compared to vitamin-D deficient individuals.[46]

In contrast, there have been reports of no beneficial effects of vitamin D_3 administration on clinically relevant outcomes and hospital stay in COVID-19 hospitalised patients. An RCT of 240 hospitalised COVID -19 patients conducted in Brazil which administered a single oral dose of 200 000 IU (5,000µg) of vitamin D_3 did not show any significant clinically relevant effects and a reduction in hospital length of stay compared to the placebo group.[47] It is important to note that the small sample size in this trial could have had inadequate power to exclude small, but clinically significant differences between the groups. In addition, the percentage of patients with vitamin D deficiency randomised in this study was considerably lower than those reported in other cohorts,[48] possibly due to differences in geographic locations. Therefore, caution should be applied while generalizing these findings to patients from other geographical regions.

Potential mechanisms by which Vitamin D ameliorates COVID-19

Vitamin D mediates its biological effects by binding to a nuclear receptor – vitamin D receptor (VDR) which renders cells responsive to vitamin D. Respiratory epithelial cells of the bronchi and immune cells including activated Cd4+, CD8+ T cells, B cells, neutrophils, monocytes, macrophages, and dendritic cells all express the VDR.[49] This indicates vitamin D ability to play a vital role in proliferation and immunomodulation of cells, affecting several immune pathways enhancing the protective properties of the mucous membranes of the body and inhibiting excessive inflammation.[50]
Vitamin D_3 stimulates immunoglobulin and complement-mediated phagocytosis by inducing the maturation of monocytes to macrophages Additionally, it maintains self-tolerance by suppressing a hyperactive adaptive immune system51and has been shown to attenuate viral replication of influenza A[52] and rotavirus.[53]These suggest that the dysregulated innate immune response and its associated cytokine storm induced by viral and other microbial infections observed in SARS-CoV-2 could be reduced by vitamin D.9
Injury to lung epithelial cells as observed in

SARS-CoV and MERS-CoV results in increased release of T helper 1 (T_h1), pro-inflammatory cytokines.[29,54] Pathogen-associated molecular patterns on infectious microbes bind to and activate specific toll like receptors (TLRs) present on immune cells and induce the NF-κB signal transduction pathway, which upregulates expression of pro-inflammatory cytokines. NF-κB is inactivated by inhibitor of nuclear factor kappa B (IκB protein).[55] During viral infection of the respiratory epithelium, vitamin D upregulatesIκBα, which decreases NF-κB signalling by binding to NF-κB subunits so as to decrease release of multiple pro-inflammatory cytokines.[56]

Vitamin D also regulates the adaptive immune system by suppressing T_h1 cytokines such as interleukin (IL)-2, IFN-γ, and TNF-α and inducing anti-inflammatory T_h2 cytokines including IL-3, IL-4, IL-5, and IL-10 resulting in the suppression of inflammation[37] Vitamin D supplementation also enhances the expression of genes related to antioxidation (glutathione reductase and glutamate–cysteine ligase modifier subunit) that may lead to a decrease in oxidative stress. [57]

Vitamin D and metabolites balance the dysregulation of RAS which leads to acute lung injury by modulating the expression of the RAS including ACE2 in lung tissue.[38] Vitamin D have been shown to significantly attenuate lung damage caused by lipopolysaccharides by down regulating renin and angiotensin 11 and upregulating ACE2 expression in rat lung tissues.[38] Low plasma vitamin D concentrations are associated with increased renin synthesis resulting in increased angiotensin II production which in turn leads to increased inflammation, fibrosis and vascular permeability as seen in COVID-19.[58] The administration of vitamin D upto sufficient concentrations may improve lung function whilst suppressing inflammation and fibrosis.

Vitamin D supplementation studies support the hypothesis that higher concentrations is associated with a lower risk and severity of SARS-CoV-2 infection.[45,46] However, there are no standard recommendations regarding the dose and the desired optimal concentration required to protect people from respiratory tract infections but it is observed that the degree of protection generally increases when the concentration reaches its optimal range of 100-150 nmol/L . To achieve this optimal concentration, an individual must take between 50-125 µg / day of the vitamin .[59] These effects of vitamin D on the immune response and RAS pathway modulation indicates its benefit in lowering the risk of SARS-CoV-2 infection.The anti-inflammatory roles of vitamin D especially against SARS-CoV-2 and other similar acute respiratory tract infections requires further investigations. The differences in the prevalence of COVID-19 and severity of the disease in temperate versus tropical regions could also have investigable components of vitamin D's anti-inflammatory actions.

Role of Vitamin C in ameliorating COVID 19

This essential water soluble nutrient has been proposed to prevent and ameliorate COVID-19.[60] Vitamin C has important immunomodulatory, anti-inflammatory, antioxidant, antithrombotic and anti-viral properties which impact the innate and adaptive immune function particularly immune cell proliferation and differentiation.[61, 62, 63] Vitamin C concentration in humans decline rapidly under conditions of physiological stress including infection. Vitamin C deficiency, defined as a plasma concentration of vitamin C ≤ 11 µmol/L has been reported in COVID-19 patients.[64,65] Sub-groups who are at higher risk of severe COVID-19 such as older patients and those with co-morbidities of diabetes, hypertension, COPD have been shown to have lower serum vitamin C concentration.[66] The study of 21 critically ill COVID-19 patients admitted to ICU in the US found a mean concentration of 22 µmol/L, thus a majority had hypovitaminosis C. Mean concentration for 11 survivors was 29 µmol/L compared to 15 µmol/L for the 10 non-survivors; out of which half had concentration ≤11 µmol/L.[64] Another ICU study of 18 COVID-19 patients meeting acute respiratory distress syndrome (ARDS) criteria found that 17 had undetectable concentration of vitamin C (i.e., <9 µmol/L) and one patient had a low vitamin C (14 µmol/L).[65]

A possible explanation for this low vitamin C concentration is increased metabolic consumption.[65] Suggesting a need for vitamin C supplementation.

The first RCT to test the effect of high dose intravenous vitamin C (24 g per day for 7 days), in 56 critically ill COVID-19 patients in ICU found IL-6 concentration to be significantly lower in the treatment group compared to placebo after 7 days of treatment. Treatment also improved oxygenation in patients.[68] Similarly, a recent meta-analysis from 8 vitamin C trials of a total of 685 patients reported that vitamin C shortened the duration of mechanical ventilation in critically ill patients.[69] Overall, these studies suggest vitamin C ameliorates COVID-19.

There is a connection between SARS-CoV-2 infection and depleted concentration of the antiviral cytokine interferon,[70] and a negative association between interferon concentration and disease severity.[71] Of note, vitamin C has been shown to increase interferon concentration in animal models of viral infection.[72]

By contrast, vitamin C administration has also proven ineffective in shortening the duration of mechanical ventilation in critically ill COVID-19 patients as observed by Hemillä et al.[69] The RCT performed in 56 critical COVID-19 patients living in China showed that high-dose intravenous vitamin C (HDIVC) (24 g/day for 7 days) failed to improve invasive mechanical ventilation-free days but may provide a potential signal of benefit in oxygenation and IL-6 for critically ill patients with COVID-19 in ICU.[68] Of note, this pilot trial did not attain the predefined sample size, and the introduction of vitamin C occurred more than 10 days after the first symptom, which may affect the efficacy of HDIVC.[68]

Postulated mechanisms for vitamin C amelioration of COVID-19

In complications of COVID-19 lung pathology such as coagulopathy and microthrombi formation,[73] timely injection of vitamin C has been shown to prevent microthrombi formation and capillary plugging,[74] and a case series has shown decreased D-dimer concentration in COVID-19 patients who were administered intravenous vitamin C.[75] Neutrophil-derived oxidative stress is believed to induce tissue damage in COVID-19,[76] and intervention studies show that the administration of vitamin C and other antioxidants to patients with septic shock and ARDS stabilized oxidative stress markers and improved cardiovascular parameters and survival.[77]

Importantly, and with specific reference to the critical phase of COVID-19, vitamin C contributes to the downregulation of cytokines, protecting the endothelium from oxidant injury and has an essential role in tissue repair.[78] Vitamin C reduces reactive oxidative species and inflammation observed in COVID-19 via attenuation of NF-κB activation.[79]

In rat ARDS model, vitamin C significantly increased superoxide dismutase, catalase and glutathione and decreases serum TNFα and IL-1β concentrations.[83]The protective effects of vitamin C may be attributed to its epigenetic regulation of various genes, i.e., upregulation of antioxidant proteins and downregulation of proinflammatory cytokines.[80] While SARS-CoV-2 downregulates the expression of type-1 interferons (the host's primary anti-viral defence mechanism),[70] vitamin C upregulates these key host defence proteins.[80]

Based on the identification of ACE2 as the receptor for SARS-CoV-2 entry, there is a hypothesis that the increased risk of severe COVID-19 is a function of upregulated ACE2, as is found in the co-morbidities of diabetes, cardiovascular disease and hypertension.[82] It is noteworthy that, in human arterial endothelial cells, vitamin C abolished ACE2 upregulation induced by IL-7.[83] Furthermore, vitamin C improves lung epithelial barrier function in an animal model of sepsis.[84]

To exert antioxidant protection and prevent scurvy, the European Union recommended average daily intake (90 mg for men and 80 mg for women) of vitamin C in order to maintain a normal serum/plasma concentration of 50 μmol/L.[85] but may be inadequate following viral exposure as seen in COVID-19. Pharmacokinetic studies in healthy volunteers support a 200 mg daily dose to produce a

plasma concentration of circa 70 to 90 µmol/L.[86] Complete plasma saturation occurs between 1 g daily and 3 g every four hours, being the highest tolerated oral dose, giving a predicted peak plasma concentration of circa 220 µmol/L. The same dose given intravenously raise plasma vitamin C concentration approximately ten-fold. Higher intakes of vitamin C are likely to be needed during viral infections with 2–3 g/day required to maintain normal plasma levels between 60 and 80 µmol/L. Vitamin C has been shown to act synergistically with vitamin D as well as zinc.[87]

Concluding remarks

SARS-CoV-2 primarily infects the epithelial cells of the respiratory tract and causes pneumonia through a complex pro-inflammatory mechanism. In severe cases, the infection produces a "cytokine storm" or CRS, which is essentially an excessive host immunological response characterised by rapid increase in inflammatory cytokines, and more importantly determines progression of the disease from mild to severe, and then to critical.

Vitamin D and C have shown beneficial effects in modulating the excessive immune responses seen in severe cases of COVID-19 as well as reducing the risk of disease progression even though a few RCT studies have not seen any significant benefits.

Vitamin D_3 is of benefit in preventing and lowering the risk of SARS-CoV-2 infection by modulating the RAS pathway. Vitamin D supplementation studies support the hypothesis that higher vitamin Dconcentrations is associated with a lower risk and severity of SARS-CoV-2 infection and the degree of protection against respiratory tract infection increases with increasing concentration of vitamin D_3 up to an optimal range of 100-150 nmol/L. Doses of 50-125µg of vitamin D_3 is necessary to achieve this optimal plasma concentration.

Vitamin C on the other hand, ameliorates COVID-19 by reducing inflammation and reactive oxidative species through attenuation of NF-κB activation and provides protection against tissue injury by downregulation of proinflammatory cytokines with a concomitant upregulation of antioxidant proteins. COVID-19 causeshypovitaminosis C that may result from metabolic consumption and very low plasma concentration (≤11 µmol/L) were seen in patients with fatal outcome. To maintain normal plasma concentration of 60-80 µmol/L, doses up to 2-3g/day would be necessary in SARS-CoV-2 infections. Combination of high doses of both vitamins in the treatment of SARS-CoV-2 infections is likely to provide even better outcome because of their synergistic actions.

Conflict of interest

None.

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Author contribution

FR and EA: Conceptualisation, literature search, Writing – Original draft preparation, Reviewing and Editing. TA: literature search, Writing – Original draft preparation, Reviewing and Editing. EO: Writing – Reviewing and Editing. ALL: Final approval for submission.

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