



The Potential Influence of Vitamin A, C, and D and Zinc Supplements on the Severity of COVID-19 Symptoms and Clinical Outcomes: An Updated Review of Literature

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Abstract

Coronavirus disease-19 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 is an ongoing viral epidemic that originated in China in December 2019. To date, no specific treatment is available for COVID-19. However, several studies have reported the benefits of vitamins A, C, and D and zinc in critically ill patients and in those with various infections, including respiratory infections and sepsis. The objective of this review is to discuss the potential role of vitamin A, C, and D and zinc supplementation in enhancing immune response, and reducing the severity of symptoms, and mortality rate in patients with COVID-19. Several clinical studies have shown that different doses of vitamins A, C, and D and/or zinc supplements reduce the ventilator, length of intensive care unit stay, and mortality rate. Future randomized clinical trials are warranted to conclusively establish protocols for the optimal doses of vitamin A, C, and D, as well as zinc supplements for improved clinical outcomes in patients with COVID-19.



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Introduction

Coronavirus disease-19 (COVID-19) is an epidemic viral outbreak which began in China in December 2019.¹ Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus responsible of COVID-19, is a single stranded RNA from β -coronavirus cluster.¹⁻³ SARS-CoV-2 is a member of the *Coronaviridae* family which also

includes SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV); however, these organisms show slight differences in their protein structure.³ SARS-CoV-2, SARS-CoV and MERS-CoV cause acute respiratory infection.³ SARS-CoV and MERS-CoV causes Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS), respectively.³ Notably, all three

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varieties produce similar respiratory symptoms, such as fever, fatigue, cough, and dyspnea.^{1,3} Other non-respiratory symptoms include nausea, vomiting and diarrhea.^{3,4} Up to 34% and 10 % of patients with COVID-19 tend to develop diarrhea and nausea or vomiting, respectively.⁴ COVID-19 viral infection triggers the immune system and initiates an inflammatory response via T-cell activation and increased production of pro-inflammatory cytokines.³

According to the severity of the disease, the clinical features of COVID-19 can range from mild, to severe and critical disease.^{1, 2} Mild COVID-19 infection represents as mild pneumonia.^{1, 2} The severe disease manifests with dyspnea, low respiratory rate, and low blood oxygen saturation.^{1, 2} The critical COVID-19 represents as respiratory failure, septic shock, and/or multiple organ dysfunction.^{1, 2} Although, the majority of the cases (around 80%) had mild symptoms, approximately 26% of the cases with COVID-19 developed acute respiratory distress syndrome (ARDS) and required intensive care unit (ICU) care, which lead to increased mortality rate to around 3.4%.^{1, 2, 5} The severity of the disease and comorbidities are factors associated with ICU admission and increase the risk of mortality rate.^{5,7} Wang *et al.*, (2020) was one of the first reports presenting the clinical features of 138 hospitalized patients with COVID-19 in China.⁵ The study reported that age (>60 years old), presence of comorbidities such as cerebrovascular disease, cardiovascular disease, diabetes and hypertension are associated with ICU admission in patients with COVID-19.⁵ In addition, a meta-analysis study reported that the presence of cardiovascular disease is associated with increased the severity of COVID-19 symptoms and 11-fold increase the risk of mortality rate among COVID-19 cases.⁶

Nowadays, there are several COVID-19 vaccine trials; however, the development, approval, and production of an effective vaccine might require several months or even years. In addition, there is no specific treatment for COVID-19.^{1, 8} Several medications for COVID-19 patients are varied based on the presence and the severity symptoms including anti-inflammatory and antioxidants therapies.^{1, 3, 8} Strategies to improve immunity are particularly important in elderly patients and in patients with chronic diseases, such as cardiovascular disease, diabetes, and hypertension because they comprise

the high-risk group and tend to present with severe infection resulting in high mortality rates. Strong evidences showed that elderly and patients with chronic diseases are at risk of antioxidants, vitamin D and zinc deficiency.⁹⁻¹¹ It is important to correct the micronutrient status in this population to reduce the severity and the mortality rate in patients with COVID-19. A meta-analysis study reported the benefit of using multivitamins (including vitamin C, vitamin D and zinc) in critically ill patients to reduce the risk of mortality.¹²

There is not known evidence-based nutritional therapies for preventing, treating, reducing the severity or the mortality rate for patients with COVID-19. Thus, vitamin A, vitamin C, vitamin D and zinc supplements may have an additional influence on management of all clinical feature of COVID-19. The objective of this review was to discuss the possible influence of vitamin A, C, and D and zinc supplementations on enhancing immunity and reducing the severity of COVID-19 symptoms, and mortality rate in patients with COVID-19.

Vitamin A

Vitamin A (or retinol) is a fat soluble vitamin. Vitamin A protects epithelium and mucosal integrity, and immune function, as well as regulates cellular and humoral immune responses.¹³ The average vitamin A intake in the United States is reported to be approximately 600 µg retinol activity equivalents/day.¹⁴ However, the Recommended Dietary Allowance (RDA) for vitamin A is 700 µg retinol activity equivalents/day for adult women and 900 µg retinol activity equivalents/day for adult men,¹⁵ which suggests that a considerable percentage of the American population might suffer from vitamin A deficiency, with consequently reduced immunity. It was suggested that vitamin A deficiency can be common across many countries, and indeed have been reported to reach up to 60-65 % of the population in developing countries.¹⁶

Vitamin A deficiency is known to be associated with numerous health conditions including increased rate of infection, and reduced immunity by reducing bacterial clearance from blood stream and increased macrophage mediated inflammation.^{17, 18} In addition, a study conducted in school age children found that vitamin A status was inversely associated with the gastrointestinal and respiratory morbidity rates.¹⁹

Another study conducted in critically ill adults with sepsis found that more than 50% of the patients had low beta carotene and retinol level.²⁰ A recent

study reported the influence of vitamin A deficiency on increased mortality rate in critically ill children with sepsis.²¹

Table 1: Randomized Controlled Trials to Assess the Association between Vitamin A and Clinical Outcomes

Population (Sample size of the study group)	Intervention and Duration	Health Related Outcome	Author Year
Healthy participants received anti-rabies vaccine (n=20)	Vitamin A (100,000 IU on the first day and 100,000 IU on the second day)	Vitamin A group had higher (2.1 times) IG anti-rabies titre	Siddiqui <i>et al.</i> ²³ 2001
Patients with sepsis (n=64)	Intramuscular vitamin A 100,000 IU over 7 days	Number of days on the ventilator and mortality rate: not significant	Lavanya <i>et al.</i> ²⁴ 2019

Vitamin A supplementation is beneficial in many health conditions.²²⁻²⁵ A recent study conducted in children found that two doses of vitamin A (20,000 IU) and D (2000 IU) supplementation has enhanced the immune response to influenza vaccine.²² Furthermore, vitamin A supplementation reduced the incidence of bronchopulmonary dysplasia and chronic lung disease in infants and children.²⁵ Limited Randomized Controlled Trials (RCT) have investigated the clinical outcomes of vitamin A supplementation in adults with infections, respiratory infection or sepsis (Table 1).^{23,24} Moreover, vitamin A supplementation (100,000 IU) has been shown to potentially improve the antibody response after administration of therabies vaccines.²³ However, Lavanya *et al.*, (2019) did not observe any association between 100,000 IU vitamin A supplementation for 7 days and the number of days on blood pressure agents, or the ventilator and mortality rate in adult patients with sepsis.²⁴ This result should be interpreted with caution, and could be attributed to the severity of the disease which might have required longer duration of the supplementation to find clinical outcomes in patients with sepsis.

In spite of the inconclusive results, it is still proposed that vitamin A may reduce the risk and the severity of COVID-19 infection.^{23,25} The vitamin A status in patients with COVID-19 is not known, the vitamin

A dose to prevent or treat COVID-19 also remains unclear. Therefore, it is recommended the correction any of hypovitaminosis of vitamin A to boost the immune system and meet the RDA of vitamin A for patients with COVID-19.²⁶

Vitamin C

Vitamin C is an essential water soluble vitamin that functions as an anti-oxidant in a variety of reactions and metabolic processes; it regulates the innate immunity of the lungs by increasing phagocytes and lymphocyte production, and decreasing virus replication.²⁷ It has a major role in protecting human body from free radicals and toxins.²⁷ Plasma vitamin C concentration was positively associated with markers of antioxidants and was negatively associated with markers of oxidative stress in critically ill patients.²⁸ Additionally, vitamin C diminished inflammatory responses in patients with sepsis syndrome.²⁷

Depending on age and gender, the RDA for vitamin C is between 75 and 90 mg/day.¹⁵ The average dietary intake of vitamin C in adults in the USA is between 100-140 mg/day.²⁹ Therefore, the majority of the healthy population (>70%) were able to meet the RDA for vitamin C by diet alone.²⁹ However, vitamin C deficiency (<11 µmol/L) is common in certain populations including smokers, elderly, post liver transplant, patients with anorexia, inflammatory

bowel disease, short bowel syndrome, or viral infections and critically ill patients.^{27, 29}

Animal and human studies have reported the association between vitamin C deficiency and respiratory viral infection, pneumonia, ARDS, sepsis and mortality rates.^{27, 30-34} In an animal study, vitamin C deficiency was associated with the immune response to influenza virus and induced lung pathology.³⁰ In addition, rats with vitamin C deficiency were

more susceptible to sepsis.³¹ A study has conducted in ICU patients found that one third of critically ill patients had vitamin C deficiency.³³ Patients with septic shock had lower vitamin C compared to non-septic patients. Further more, critically ill patients with hypovitaminosis (vitamin C levels < 23 μmol/L) were significantly lower in C-Reactive Protein level than critically ill patients without hypovitaminosis (vitamin C levels > 23 μmol/L).

Table 2: Randomized Controlled Trials to Assess the Association between Vitamin C and Clinical Outcomes

Population (Sample size of the study group)	Intervention and Duration	Health Related Outcome	Author Year
Patients with septic abdominal surgery (n=10)	450 mg/day of vitamin C was divided into 3 equal doses for 6 days	Vitamin C reduced neutrophil apoptosis (antiapoptotic effect) on peripheral blood neutrophils, (caspase-3 and PARP levels)	Ferrón-Celma, <i>et al.</i> ⁴¹ 2009
Patients with severe sepsis in the ICU (n=16)	Low: (50 mg/kg/24 h) High (200 mg/kg/24 h) IV vitamin C was divided into 4 doses and administered over 30 min q 6 hours for 96 hours	Patients receiving vitamin C had lower SOFA scores than the placebo Vitamin C reduced the pro-inflammatory biomarkers (C-reactive protein and procalcitonin).	Fowler <i>et al.</i> ⁴² 2014
Patients with septic shock who need a vasopressor medication (n=28)	25 mg/kg IV ascorbic acid every 6 hours for 72 hours	Length of ICU stay: not significant 28-day mortality was significantly lower in the vitamin C group (14.3%) than the placebo (64.3%) The dose and the duration of norepinephrine and duration of ventilator was lower in vitamin C group than the placebo group	Zabet <i>et al.</i> ³⁹ 2016
Patients with sepsis and ARDS present for less than 24 hours (n=84)	IV vitamin C 50 mg/kg in dextrose 5% in water every 6 hours for 4 days	SOFA scores or alter markers of inflammation: not significant At day 28, mortality rate was 46% in the placebo group vs 30% in the vitamin C group The number of ICU-free days was 10.7 in the vitamin C group vs 7.7 in the placebo group	Fowler <i>et al.</i> ⁴⁰ 2019

Abbreviation: ARDS: acute respiratory distress syndrome, ICU; Intensive care unit, IV; Intravenous, SOFA; Sequential Organ Failure Assessment.

Several clinical studies and RCTs have reported the effect of vitamin C supplementation on different clinical outcomes in critically ill patients (Table 2).³⁵⁻³⁸ Studies have shown that vitamin C was associated with reduced mortality rates, shorter duration of ventilator use, shorter days in ICU stay, lower Sequential Organ Failure Assessment (SOFA) scores, and lower levels of biomarkers of infection and inflammation.³⁹⁻⁴² Mortality rate declined from 46-64% in placebo group to 14-46% in patients with sepsis and vitamin C supplement.^{39, 40} However, the aforementioned RCTs did not report consistent results with regard to the prevention and/or the therapeutic dose of vitamin C,³⁹⁻⁴² and different treatment protocols were proposed, and using varying intravenous dose of vitamin C doses in patients with sepsis (12000 mg/ day, 6000 mg/ day, and < 6000 mg/ day).³⁸ A recent study found that 6000 mg/day intravenous vitamin C (1500 mg every 6 hours) was adequate to correct hypovitaminosis C (11-23 $\mu\text{mol/L}$) in patients with septic shock.⁴³ Therefore, it is reasonable to conclude that correction of vitamin C deficiency in patients with COVID-19. Oral supplement or IV dose of vitamin C (50-200 mg/kg/day) seemed to have positive health outcomes in severe and critical conditions of COVID-19.^{39, 40} However, optimal vitamin C doses should be determined based on different variables including age, vitamin C status, and the severity of the disease.

Vitamin D

Vitamin D, a fat-soluble vitamin, is a steroid derived from cholesterol in the body following exposure to sunlight. Food sources of vitamin D are very limited including fatty fish, liver, egg yolk and vitamin D-fortified foods such as milk, some orange juices and margarine.⁴⁴ Studies performed across different countries have reported that the average vitamin D intake exclusively from dietary sources was not exceed 300 IU/day, which is less than the Estimated Average Requirement (EAR).⁴⁴⁻⁴⁶ Due to limited dietary availability of vitamin D and lack of exposure to sunlight, vitamin D deficiency is very common worldwide.⁴⁶

Vitamin D has multiple roles in innate and adaptive immune system.⁴⁷ It reduces B cell proliferation, blocks B-cell differentiation and immunoglobulin secretion and suppresses T cell proliferation leading to increased macrophages activity.⁴⁷⁻⁵¹

Notably, the cytokine storm in patients with COVID-19 is associated with poor clinical outcomes, and increased mortality. Furthermore, vitamin D deficiency is known to be associated with increase the risk of respiratory infection such as influenza, ARDS and mortality rate.^{52, 53} A study that investigated 2135 adult patients with hospital-acquired infections found that vitamin D deficiency (<25 nmol/mL) was associated with an increase in the hospital acquired blood stream infection.⁵⁴ Moreover, the severity of respiratory infection and ARDS in COVID-19 patients was observed in countries which lie at 30 degree latitude south and 50 degree latitude north due to insufficient sunlight.⁵⁵ Vitamin D supplementation was associated with positive clinical outcomes, including reduced the risk of acute respiratory infection, mortality rate, length of hospitalization, reduce pro-inflammatory cytokines in elderly and critically ill patients (Table 3).⁵⁶⁻⁵⁹ Several animal studies have shown that varying doses of vitamin D supplements improved lung maturation and reduced airway inflammation.^{60, 61} Two meta- analyses have reported that daily or weekly oral vitamin D supplementation (average 2000– 4000 IU/day) was associated with reduced the risk of respiratory tract infections.^{62, 63} A double blind randomized controlled trial study reported that enteral vitamin D supplementation (50,000 IU or 100,000 IU daily for five days) in mechanically ventilated adults in ICU care was associated with a shorter hospital stay and lower rates of germ positive bacteria infections with no adverse event related to high dose of vitamin D.⁵⁷

It has been shown that dietary sources alone cannot meet the RDA of vitamin D, and vitamin D supplementation is essential to enhance immunity.⁴⁴⁻⁴⁶ Up to 2000 IU of vitamin D supplement is adequate for patients with comorbidities to prevent any vitamin D deficiency.⁶⁶ For patients with vitamin D deficiency and COVID-19, vitamin D dose between 25,000- 50,000 IU/week (or 40,000 IU/month) was suggested.^{26, 66} Indeed, for severe and critical COVID-19 cases, very high vitamin D dose was thought to contribute to different health outcomes such as hospital stay and mortality rate.⁵⁷

Zinc

Zinc is an abundantly distributed trace element in the human body.⁶⁷ Zinc has a major role in a various metabolic processes, and stabilizes cell

membrane.^{67, 68} Zinc homeostasis is a crucial process for cell maturation, differentiation and progression.^{67, 68} Zinc also plays an important role in innate and adaptive immunity,^{67, 68} and it controls the pro-inflammatory production (cytokines) and

macrophages activity.⁶⁸ Moreover, serum zinc and vitamin A levels are related; zinc affects the transportation and the oxidation of vitamin A via the action of zinc-dependent retinal dehydrogenase enzyme.⁶⁹

Table 3: Randomized Controlled Trials to Assess the Association between Vitamin D and Clinical Outcomes

Population (Sample size of the study group)	Intervention and Duration	Health Related Outcome	Author Year
Medical and surgical critically ill adults with vitamin D deficiency (≤ 20 ng/mL)(n=492)	Oral or nasogastric tube of vitamin D3=540 000 IU (onedose) followed by maintenance doses of 90 000 IU/month for 5 months	Lower hospital mortality in severe vitamin D deficiency <12 ng/mL Hospital stay/ hospital mortality/6-month mortality: not significant	Amrein <i>et al.</i> ^{64, 65} 2014
Critically ill patients with severe sepsis or septic shock (n=67)	1)A single dose of IV calcitriol (800 IU/ day) Duration of the study: 24 h	Vitamin D group had higher expression of cathelicidin and IL-10 mRNA than the placebo group	Leaf <i>et al.</i> ⁵⁶ 2014
Mechanically ventilated ICU patients (n=31)	Low dose: 50,000 IU/day vitamin D3 enterally for 5 days (total=250,000 IU) High dose:100,000 IU vitamin D3/ day enterally for 5 days (total= 500,000 IU)	Vitamin D groups (low dose group (25 \pm 14 days); high dose group(18 \pm 11 days)) had significantly lower in hospital length than the placebo group (36 \pm 19 days)	Han <i>et al.</i> ⁵⁷ 2016
Elderly Participants(n=107)	High dose group= 30000-4000 IU/day (100,000 IU /month) for 12 months Standard dose group= 400-IU/dayz	Acute respiratory infection was lower in high dose group (31%)han standard dose group (46%)	Ginde <i>et al.</i> ⁵⁸ 2017
Elderly participants with vitamin D deficiency receiving influenza vaccine (n=38)	Vitamin D (100,000 IU/ 15 days) for 3 months	Vitamin D group had higher TGF β levels without improved antibody response than the placebo group Vitamin D group had lower TNF α and IL-6 than the placebo group	Goncalves-Mendes <i>et al.</i> ⁵⁹ 2019

Abbreviation: ICU; Intensive care unit, IV; Intravenous

The RDA of zinc in adults is between 8–11 mg/day.¹⁵ Zinc deficiency was estimated to be around 20% worldwide, and specifically observed in elderly and vegetarian individuals.⁶⁷ It has been reported that zinc deficiency is associated with inflammation and mortality due to sepsis.⁶⁸ Zinc deficiency has been associated with increase susceptibility to infectious diseases.^{70, 71}

Zinc deficiency was observed in 9% of critically ill patients with tube feeding.⁷⁰ Strong evidence in children have shown that zinc supplementation (10-20 mg/day) was positively associated with the duration of pneumonia, the respiratory rate, and oxygen saturation.⁷² Notably, zinc supplementation is known to reduce the incidence of respiratory infections in children, and a dose of 20 mg/day was associated with an improved in respiratory rate and oxygen saturation levels in Mexican children with pneumonia.^{72, 73} One RCT study in adults was found that zinc supplementation (150-400 mg) enhances the immune response.⁷⁴ Additional RCTs are warranted to conclusively establish the doses and duration of zinc supplementation that would be effective across different population groups with acute diseases, such as in critically ill patients in the ICU and in those with sepsis and/or ARDS. Currently, no specific recommendations for zinc supplementation to treat or reduce the severity of COVID-19. A recent report suggested that 30-50 mg of zinc may help to control COVID-19.⁷⁵

Vitamin A, C, and D and Zinc Supplementation in Patients with Coronavirus Disease-19

The majority of the nutritional guidelines were focused on energy and protein intake innutrition support for critically ill patients with limited information about the vitamins and minerals recommendation. ESPEN recommended to supply adequate amount of vitamins and minerals to patients with COVID-19 to prevent or treat any vitamins and/or minerals deficiencies.⁷⁶ A study reported from Italy highlighted the importance of vitamin A, C, and D and zinc supplementation in improved immunity in patients with COVID-19.²⁶ Vitamin D supplements and multivitamins and minerals were administered to all hospitalized patients with COVID-19 as a part of the treatment protocol implemented in Italy. This protocol

includes intravenous administration of multivitamin and multimineral supplements that meets the RDA of those vitamins and minerals. For patients with vitamin D deficiency, cholecalciferol was supplied at dose of 50,000IU/week (vitamin D < 20 nmol/mL) or 25,000IU (vitamin D = 20-30 nmol/mL). To our knowledge, no published study or clinical trial has investigated the contribution of vitamin A, C, and D and/or zinc supplementation for the treatment or prevention of COVID-19. However, ESPEN recommended to establish protocol(s) regarding the micronutrients supplements to prevent or reduce the risk of clinical outcomes and complications in patients with COVID-19.⁷⁶ Several ongoing RCTs have investigated the efficacy of vitamin D, C, E and other nutrients to treat the severity and the complications of COVID-19.

Conclusion

In conclusion, vitamin A, C, and D and zinc appear to have an immense influence on enhancing immunity. Indeed, supplementation with vitamin A, C, and D and zinc have been shown to be associated with positive clinical outcomes in patients with pneumonia, respiratory infection and sepsis, which strongly suggested that vitamin A, C, and D and/or zinc might help to enhance immunity, improve the severity of COVID-19 symptoms, reduce the length of ICU stay, and reduce the mortality rate in patients with COVID-19. However, further clinical trials are necessary to investigate the role of vitamins A, C, and D, and zinc as preventive and therapeutic agents in patients with COVID-19 and to establish the optimal doses of these supplements that need to be included in the treatment protocols for COVID-19.

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Conflict of Interest

The author declares no conflict of interest.

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