

REVIEW ARTICLE

The Effect of Micronutrients on COVID-19 Disease: A Review of Available Evidences

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ABSTRACT

Patients with coronavirus 2019 (COVID-19) are likely to experience a wide range of mild to severe symptoms that can lead to hospitalization or even death. Infection and poor nutrition are potentially interdependent. The immune response to infection is associated with increased demand for nutrients. Also, micronutrient supplementation can improve the body's defence against infections. This review of the literature was conducted to ascertain published studies on the relationship between micronutrients and the risk of COVID-19 or their effect on the recovery process of hospitalized COVID-19 patients. The findings from these papers show that patients who were deficient in vitamin D, vitamin C, selenium and zinc were likely to display more severe forms of COVID-19. Vitamin D seems to have the most significant impact when consumed in equal bolus before the development of COVID-19. Intravenous injection of vitamin C in COVID-19 patients admitted to the ICU at a dose of 24 gram in 24 hours was significantly associated with improved COVID-19. Selenium intake with vitamin D and zinc reported in COVID-19 patients with Hashimoto's thyroiditis infection positively affected the recovery process. More studies are required on group B vitamins due to their proven immune-boosting effect. Finally, there is a need to conduct clinical trials with higher power and subsequent meta-analysis studies in order to be able to make a definite statement about the effectiveness of micronutrients on the COVID-19 progression.

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Introduction

Coronavirus disease 2019, known as COVID-19, is caused by a new type of coronavirus. COVID-19 patients are likely to experience various symptoms leading to hospitalization or even death. Those COVID-19 patients with comorbid diseases, such as diabetes or hypertension, are more likely to display more severe symptoms (1). A healthy

lifestyle, proper dietary pattern, and physical activity could strengthen the immune system (2). Humans at any age may have a deficiency in one or more micronutrients. The immune response to an infection increases the demand for nutrients and may even exacerbate nutrition deficits (2). Micronutrient supplementation can improve the body's defence against infections (2, 3). A well-

balanced food and micronutrient intake can reduce inflammatory cytokines and the adverse effects of COVID-19 (4).

Dietary supplements enriched with vitamins and minerals are among the affordable and effective ways to boost the body's immune system (3). Vitamins are capable of improving innate and adaptive immunity. Some supplements can improve the efficiency of antiviral therapies (3, 4). Macronutrients, micronutrients, and intestinal fluoromic microbes can negatively affect the function of the immune system (4). There is evidence that nutrients, such as vitamins A, B6, C, E, B12, folate, copper, iron, zinc and selenium can strengthen the immune system (5). This paper reviewed some previously published studies to examine the relationship between micronutrient intake level and progression of COVID-19.

Vitamin C

Vitamin C, also demonstrated as L-ascorbic acid and ascorbate, is a water-soluble vitamin essential in producing catecholamines, cortisol, and vasopressin to scavenge oxygen free radicals directly (6). Vitamin C is accumulated in phagocytic cells, such as neutrophils, which play an essential role in fighting pathogens by enhancing chemotaxis, phagocytosis, and generating reactive oxygen species (ROS) (7). According to *in vitro* studies, vitamin C enhances human immune function by maturing T cells and producing immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies (8, 9). Vitamin C can reduce inflammation by decreasing the synthesis of tumour necrosis factor alpha (TNF- α), Interleukin 6 (IL-6), and Interleukin 1 beta (IL-1 β). Although the role of vitamin C in lymphocytes is not clearly recognized, regulating gene expression affects differentiation and proliferation, leading to increased proliferation of B and T lymphocytes (7).

Clinical trial studies have reported the positive effects of vitamin C on cold treatment. A meta-analysis reported that administering one dose of vitamin C could reduce the common symptoms of colds, such as chest pain, fever, chills, and shorten the disease duration (10). A review study reported that high doses of vitamin C improved septic shock and sepsis (11). While a large controlled clinical trial showed that one dose of intravenous vitamin C (50 mg) every 6 hours for 96 hours did not reduce inflammation and vascular injury markers in the acute respiratory distress syndrome (ARDS) patients with sepsis (12). A clinical trial study revealed that mixture of oral intake of vitamins E (400 IU daily) and C (1000 mg daily) did not significantly change clinical outcomes, length of stay, and mortality rate

in the non severe COVID-19 patients (13).

A previous study on the critical COVID-19 patients that were admitted to ICU illustrated that low levels of vitamin C was a codependent risk factor for mortality (14). Another study found that high dose intravenous injection of vitamin C (100 mg/kg/day) for seven days, decreased the occurrence and duration of systemic inflammatory response syndrome (SIRS) in the first week of admission in the moderate COVID-19 patients, also the level of c-reactive protein (CRP) and CD4 T lymphocytes (CD4) cells were lower in the patients who received high doses of vitamin C (15). A randomized open-label trial on the patients with severe COVID-19 showed that administration of 6 mg of vitamin C with typical medication treatment did not affect the oxygen saturation levels (Sp_o₂ level), the average ICU length of stay, and mortality rate (16).

Another study demonstrated that high doses of vitamin C (12 g every 12 hrs for seven days) improved the arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO₂/FiO₂) and reduced the level of IL-6 (17). A recent meta-analysis study showed that short-term vitamin C injections did not affect disease severity and mortality in COVID-19 patients (18). Although a systematic review study displayed that vitamin C, due to its antioxidant, anti-inflammatory, endothelial-restoring and immunomodulating properties, is a good treatment option to relieve fatigue and weakness after recovery from COVID-19 (19).

Vitamin D

Vitamin D deficiency is a widespread worldwide problem in which near 50% of people in the world have vitamin D deficiency (20). According to the European Classified Tissue Society Working Group, Vitamin D levels <30 nmol/l are considered vitamin D deficiency (21). Vitamin D deficiency has been displayed to increase the odds of severe COVID-19 by five times than patients without vitamin D deficiency (22). A controlled clinical trial study showed that one-shot high-dose of vitamin D (200,000 IU) had no effect on the duration of ventilation requirements, mortality rate and CRP levels in the COVID-19 patients (23). In a Quasi-Experimental study, researchers concluded that elderly who received regular bolus of vitamin D before infection with COVID-19 compared to subjects who received vitamin D immediately after COVID-19 infection or those who did not receive vitamin D at all had better survival rate (24).

Another quasi-experimental study reported that supplementation of vitamin D3 during the COVID-19 pandemic or before it was inversely linked with the

ordinary scale for clinical improvement (OSCI) scores and mortality in the elderly with COVID-19. In fact, survival was higher, and disease severity was lower among the elderly (25). One clinical trial study in the COVID-19 patients with vitamin D deficiency found that administration 60000 IU cholecalciferol for seven days compared with placebo significantly reduced fibrinogen marker levels but had no effect on CRP, ferritin, procalcitonin and D-dimer levels (26).

The Efficacy of vitamin D supplementation in the treatment of COVID-19 disease is also controversial in the meta-analysis studies. In one meta-analysis study, no relationship was found between vitamin D deficiency and COVID-19 outcomes; but this study suggested that calciferol supplementation may have a protective effect in COVID-19 patients that were admitted to the ICU (27). Also, the results of another meta-analysis study indicated that vitamin D supplementation reduced mortality risk, ICU admission rates and mechanical ventilation requirement (28). In contrast to the previous study, a meta-analysis study found no association between vitamin D supplementation, ICU admission, ventilator requirement, and risk of mortality (29).

Zinc

Zinc is one of the crucial micronutrients that significantly helps to regulate the immune system. Zinc deficiency is directly associated with increased levels of inflammatory mediators (3). Zinc supplementation has been reported to be associated with reduced oxidative stress and the duration of the common cold (3). The results regarding the effects of zinc on the improvement of respiratory diseases are contradictory. Some studies have reported significant and positive effects of zinc on reducing respiratory infections (30-32), while several other studies have indicated no positive impacts of zinc supplements on the risk of respiratory infections and the process of recovery and death (33, 34). Since zinc inhibits RNA-dependent RNA polymerase *in vitro*, this micronutrient is likely to be effective in inhibiting COVID-19 infection (35). One study reported that patients with COVID-19 had lower serum zinc levels than healthy individuals, also zinc deficiency was linked with more extended hospitalization and elevated mortality risk (36).

A retrospective observational study showed that supplementation of zinc sulfate reduced mortality and length of hospitalization in the COVID-19 patients who did not require ICU. Also, this study demonstrated that zinc supplementation had no therapeutic effects in the patients who were admitted to ICU (37). One study showed that zinc levels below 50 µg/dL was associated with higher mortality and

longer time to achieve stability in the COVID-19 patients (38). Another study showed that zinc intake might shorten the median duration of gustatory and olfactory function recovery in these patients (39). A clinical trial study revealed that supplementation of zinc (50 mg) alone or in combination with vitamin C (800 mg) did not significantly change the course of symptoms compared to the standard treatment in the COVID-19 patients (40). Also, in another clinical trial study, zinc supplementation did not increase the efficiency of hydroxychloroquine (41). Eventually, a meta-analysis study demonstrated that zinc supplementation did not decrease ICU admission and mechanical ventilation requirement, but had a significant impact on the discharge and mortality rate of COVID-19 patients (42).

Selenium

Selenium is one of the essential micronutrients in human health. Human and animal studies have shown that selenium levels is one of the main determinants of the host response to viral infections (41). Selenium is involved in modulating immune responses and homeostasis by participating in selenoproteins and enzymes (42). An investigation showed that COVID-19 survivors had significantly higher serum selenium levels than those who died from COVID-19 (43). A cross-sectional study found that selenium concentrations in the first trimester were negatively related to week of gestation, D-dimer factor, and IL-6 in pregnant women. Also, serum selenium levels were positively associated with neutrophil and lymphocyte count and also hemoglobin and hematocrit status in the second trimester. In the third trimester, maternal selenium level was directly associated with monocyte counts and indirectly associated with CRP level (44).

A study on COVID-19 patients with Hashimoto's thyroiditis found that patients with Hashimoto's thyroiditis who consumed zinc, vitamin D, and selenium supplements had milder symptoms after developing COVID-19 (45). One study indicated that increased serum levels of selenium and zinc were associated with decreased serum levels of CRP in patients with COVID-19 (46). On the other hand, another study reported that supplementation with zinc, selenium, copper or vitamin K₁ had no beneficial effect on the COVID-19 related outcomes (47).

Group B Vitamins and Minerals

Group B vitamins play a key and vital role in cell function, energy metabolism, and the immune system. For example, thiamine, as a carbonic anhydrase isoenzyme inhibitor, can increase blood oxygen levels, riboflavin, along with ultraviolet

Table 1: Studies associating micronutrients and COVID-19.

Author/year	Study design	Sample size	Participants	Type of Micronutrient and dosage or variable type	Outcomes
Atousa Hakamifard <i>et al.</i> , (13)	Randomized controlled clinical trial	N=72	Hospitalized non-severe COVID-19 patients	Oral vitamin C 1000 mg daily plus oral vitamin E 400 IU daily	The combination of these two vitamins with the prescribed doses did not change the clinical results, length of stay and mortality of both groups
Cristian Arvinte <i>et al.</i> , (14)	Pilot cohort Study	N=21	Critically ill COVID-19 patients	Serum levels of vitamin C and vitamin D levels in COVID-19 patients	Serum levels of vitamin C and vitamin D were low in most patients with COVID-19
Bing Zhao <i>et al.</i> , (15)	A Retrospective propensity matched before-after study	N=110	Patients with moderate COVID-19	Intravenous injection of vitamin C (100 mg/kg/day, for 7 days)	SIRS ,CRP levels and CD4 + T cells were lower in the group who received high doses of vitamin C
Saeidreza Jamali Moghadam Siahkali <i>et al.</i> , (16)	Randomized open-label clinical trial	N=60	Severe COVID-19 patients	High-dose intravenous vitamin C (6 g daily)	High-dose intravenous vitamin C did not affect spo ₂ levels, length of ICU stay, and mortality
Jing Zhang <i>et al.</i> , (17)	Randomized, controlled, clinical trial	N=56	Critically ill COVID-19 patients	High-dose vitamin C (12 g every 12 h. for 7 days) or placebo	Improved the (PaO ₂ /FiO ₂) and reduced the level of IL-6 and no effect on invasive mechanical ventilation-free days (during 28 days)
Guangyu Ao <i>et al.</i> , (18)	Systematic Review	Nine clinical studies with 720 participants	Post Viral Fatigue with Focus on Long COVID-19	Therapeutic use of IV vitamin C>1g	A significant reduction in fatigue scores in the vitamin C group compared with the control group
Claudia Vollbracht <i>et al.</i> , (19)	Systematic review and meta-analysis	Seven studies	COVID-19 patients	Administration of intravenous vitamin C or placebo	Does not reduce the risk of severity and mortality in patients with Covid-19 compared to the placebo group
Joseph Katz D.M.D <i>et al.</i> , (22)	Cross-sectional	N=987849	Patient's registry platform at the University of Florida Health Center	Vitamin D deficiency and COVID-19	Vitamin D deficiency increases risk for COVID-19
Igor H Murai <i>et al.</i> , (23)	Randomized Clinical Trial	N=240	Hospitalized patients with COVID-19	Single oral dose of 200,000 IU of vitamin D3 or placebo	Did not affect the duration of mechanical ventilation and mortality and CRP levels

Gaëlle Annweiler <i>et al.</i> , (24)	The GERIA-COVID Quasi-Experimental Study	N=77	Elderly with COVID-19	Vitamin D bolus regularly before infection with COVID-19 or received vitamin D immediately after COVID-19 infection or those who never received vitamin D	Vitamin D bolus regularly before infection with COVID-19 showed a better survival rate
Ashu Rastogi <i>et al.</i> , (26)	Randomized, placebo-controlled, study	N=40	No symptoms or mild symptoms COVID-19 patients with vitamin D deficiency	Receiving daily 60,000 IU of cholecalciferol for 7 days or placebo	The level of fibrinogen marker significantly decreased, while no significant difference was observed in levels of CRP, ferritin, procalcitonin and D-dimer
Timotius Ivan Hariyanto <i>et al.</i> , (28)	Systematic review, meta-analysis and meta-regression study	11 studies with 22,265	COVID-19 patients	Vitamin D supplementation	Reduction in intensive care unit admission rate, mechanical ventilation requirement and mortality
Dimple Rawat <i>et al.</i> , (29)	Systematic review and meta-analysis	5 studies (3 RCTs and 2 Quasi-experimental) n=467	COVID-19 patients	Vitamin D supplementation	Does not reduce mortality, ICU admission rates and needs for mechanical ventilation
Marina Vogel-González <i>et al.</i> , (38)	Observational cohort study	N=249	COVID-19 patients	Serum zinc levels	Zinc levels below 50 µg/dL were associated with higher mortality and longer time to achieve stability
Aida A. Abdelmaksoud <i>et al.</i> , (39)	Clinical Trial	N=134	COVID-19 patients	Zinc sulfate 220 mg equivocal to 50 mg elemental zinc twice daily	Zinc intake might shorten the median duration of gustatory and olfactory function recovery
Suma Thomas <i>et al.</i> , (40)	Randomized clinical trial	N=214	Ambulatory patients With COVID-19 infection	Zinc supplementation (50 mg) or vitamin C supplementation (800 mg) or a combination of both	Did not significantly change the course of symptoms compared to the standard treatment
Sherief Abd-Elsalam <i>et al.</i> , (41)	Randomized, multicenter trial	N=191	COVID-19 patients	Only hydroxychloroquine (HCQ) or both HCQ and zinc	Zinc supplementation failed to increase the efficiency of hydroxychloroquine
Park, Hye Won <i>et al.</i> , (42)	Systematic review and meta-analysis	4 studies	COVID-19 patients	Zinc supplement	Does not reduce admission to the ICU and the needs for mechanical ventilation, but has a significant impact on the discharge rate and mortality of COVID-19 patients

Arash Moghaddam <i>et al.</i> , (43)	Cross-sectional study	N=166	COVID-19 patients	Serum selenium levels	Survivors had significantly higher serum selenium levels than those who died from COVID-19
Zelija Velija Asimi <i>et al.</i> , (45)	Cohort observational study	N=356	Hashimoto's patients who had COVID-19 infection	Selenium, zinc, and vitamin D supplementation	Patients with Hashimoto's thyroiditis who consumed zinc, vitamin D, and selenium supplements had milder symptoms after developing COVID-19
Chuen Wen Tan <i>et al.</i> , (49)	Cohort observational study	N=43	Patients ≥ 50 y of age with COVID-19	1000 IU/d oral vitamin D ₃ , 150 mg/d oral magnesium, and 500 mcg/d oral vitamin B ₁₂	Supplementation in older COVID-19 patients was associated with less required oxygen support and intensive care support

SIRS: systemic inflammatory response syndrome, CRP: C-reactive protein, CD4+T: CD4 T lymphocytes, IU: International unit, PaO₂/FiO₂: Arterial oxygen partial pressure to fractional inspired oxygen ratio. IV: Intravenous, ICU: Intensive care unit, IL-6: interleukin 6

light, has been able to help destroy the MERS-COV virus. Niacin has also been shown to reduce neutrophil infiltration and has anti-inflammatory properties in patients with lung injury. Vitamin B6 plays a key role in upregulating IL-10. Folic acid has been shown to reduce the fourin enzyme responsible for bacterial and viral infections. Vitamin B12 may reduce the symptoms of colitis by reducing oxidative stress, improving the circulatory system, and acting as an anti-inflammatory and analgesic micronutrient (48). One observational cohort study found that elderly COVID-19 patients who received supplements including 1000 IU oral vitamin D₃, 150 mg magnesium and 500 mcg vitamin B12 needed less oxygen and intensive care support than those who did not receive any supplements (49). Minerals such as iron, copper, zinc, and manganese regulate function of immune system and inflammatory responses (35). Serum iron levels were significantly associated with the severity of COVID-19 and could predict the progression of the disease from mild to severe and the state of inflammation (50). Increased ferritin/transferrin ratio was associated with more extended ICU stay and increased requirement of mechanical ventilation (50). Also hepcidin levels, regardless of ferritin concentration, can predict the severity of COVID-19 (51). One study suggested that due to the antiviral properties of copper, this element may be effective in treating COVID-19 (52). But another study showed that serum copper levels were higher in COVID-19 patients. The same study noted that the serum levels of iron, calcium, selenium, and zinc were associated with the severity of COVID-19, and inversely related to fever, lung damage and CRP (53) (Table 1).

Conclusion

The present study reviewed published studies on the relationship between micronutrients and the risk of COVID-19. According to the results of these studies; deficiency of vitamin D, vitamin C, selenium and zinc were shown to be associated with worse outcomes and severity of COVID-19. The effectiveness of intravenous injection of vitamin C in COVID-19 patients in the ICU varied in different doses. Vitamin D seems to have the most significant impact when consumed before development of COVID-19. More studies are required on group B vitamins due to their proven immune-boosting effect. Finally, there is a need to conduct clinical trials with higher power and subsequent meta-analysis studies in order to be able to make a definite statement about the effectiveness of micronutrients on the COVID-19 progression and treatment.

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Conflict of Interest

None declared.

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