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What is the role of supplementation with ascorbic acid, zinc, vitamin D, or *N*-acetylcysteine for prevention or treatment of COVID-19?

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ABSTRACT

Several agents intended to supplement dietary intake or endogenous molecules may have a theoretical role in preventing or treating COVID-19. Because of their potential to influence immune response, ascorbic acid (vitamin C), zinc, vitamin D, and *N*-acetylcysteine have been hypothesized to be useful for prevention or treatment of COVID-19. The authors outline the biologic plausibility, applicable clinical data, and potential role of each of these agents.

INTRODUCTION

As of yet, there is no high-quality evidence to support medication therapy for the prevention or treatment of patients with coronavirus disease 2019 (COVID-19). However, several agents intended to supplement dietary intake or endogenous molecules may have a theoretical role in preventing or treating the disease.

COVID-19 infection leads to upregulation of systemic inflammation as evidenced by elevated concentrations of pro-inflammatory cytokines interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF) alpha, as well as higher concentrations of the anti-inflammatory cytokine IL-10. Additionally, patients with COVID-19 likely have evidence of oxidative stress, which is characterized by production of reactive oxygen species and reactive nitrogen species, and a concomitant deficiency of antioxidants. Reactive oxygen species and reactive nitrogen species are known to damage cellular biochemical pathways by causing DNA strand breaks, lipid peroxidation, and antioxidant and antiprotease degradation.[1] There are multiple defense mechanisms against reactive oxygen species and nitrogen species, including enzymatic scavengers (superoxide dismutase, catalase, and glutathione peroxidase) and nonenzymatic molecules (glutathione and vitamins A, C, and E). It is the imbalance between production of reactive oxygen and nitrogen species and the antioxidant pool in the body that perpetuates further damage and, with a hyperinflammatory response, may contribute to severe manifestations of COVID-19. Because of their potential to influence immune response and reactive oxygen and nitrogen species, and because of their availability as over-the-counter medications, ascorbic acid (vitamin C), zinc, vitamin D, and *N*-acetylcysteine have been hypothesized to be useful for prevention or treatment of COVID-19. The biologic plausibility, applicable clinical data, and potential role of each of these agents are outlined below.

ASCORBIC ACID

Ascorbic acid is known to function as an antioxidant by savaging ROS, and a number of studies have suggested that vitamin C supplementation can impact the immune system. Moreover, in vitro and in vivo studies in avians have shown that vitamin C could be protective against avian coronavirus infection, and human trials have found that vitamin C may decrease susceptibility to viral respiratory infections and pneumonia.[2] High doses of ascorbic acid reduce the severity and duration of symptoms from the common cold, which is caused by rhinovirus.[3] Studies of vitamin C for the treatment of hospitalized and critically ill patients have shown mixed results on mortality, length of stay in the intensive care unit, and

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duration of mechanical ventilation.[4] However, high doses of intravenous vitamin C were generally safe. The impact of vitamin C for the treatment of patients with COVID-19 is unclear, and new clinical trials are under way in China and the United States.

ZINC

Zinc is known to be important for immune function and has a role in antibody and white blood cell production. Deficiency of zinc increases pro-inflammatory cytokine (IL-1, IL-6, and TNF alpha) concentrations and decreases the production of antibodies, while zinc supplementation has been shown to increase the ability of polymorphonuclear cells to fight infection.[2] Zinc has also been implicated in coronavirus biology, with increasing intracellular concentrations of zinc demonstrated to inhibit virus RNA polymerase activity and viral replication in an in vitro and cell culture model of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1).[5] In a meta-analysis evaluating studies comparing zinc supplementation and placebo, high-dose zinc reduced the duration but not the severity of symptoms of the common cold.[6] Overall adverse effects and specifically nausea were significantly more frequent with zinc (which may have been dose-dependent), and the effect of prophylactic zinc supplementation was inconclusive. Whether zinc supplementation can benefit patients with lower respiratory tract infections such as COVID-19 is unclear. Because of its role in immune function and potential to decrease coronavirus replication, zinc is currently being investigated for prophylaxis and treatment of patients with COVID-19.

VITAMIN D

Vitamin D is found in foods such as dairy products, cereals, and oily fish, and is converted to its biologically active form 25-hydroxyvitamin D in the skin through the effect of ultraviolet B radiation on 7-dehydrocholesterol. In vitro, vitamin D has immunomodulatory effects (including inhibition of antigen-presenting cells), antiproliferative effects on T cells, modulating expression and secretion of type 1 interferon, and inhibition of proinflammatory cytokine expression (IL-6 and TNF alpha).[7]

Deficiency of vitamin D is common, with studies showing approximately 40% of the US population to be vitamin D deficient, especially during the winter season. Factors such as older age, corticosteroid use, and darker skin are associated with lower concentrations of 25-hydroxyvitamin D, putting these patient populations at higher risk for vitamin D deficiency. Vitamin D deficiency has been associated with a higher incidence of acute respiratory infections, with a hypothesized link between the seasonality of influenza and vitamin D deficiency. Intriguingly, vitamin D deficiency in calves was associated with an increased susceptibility to infection with bovine coronavirus,[2] which may have implications for COVID-19 infection in humans.

A number of randomized trials have evaluated the effect of vitamin D supplementation for the prevention of acute respiratory infections. In a meta-analysis, vitamin D supplementation decreased the incidence of acute respiratory infection.[8] In subgroup analyses, the protective effect of vitamin D was greater in patients with baseline serum 25-hydroxyvitamin D concentrations < 25 nmol/L (vs ≥ 25 nmol/L) and isolated to those receiving daily dosing (vs bolus dosing).[8] In light of these data, a recent article recommended that patients at risk for COVID-19 consider starting daily vitamin D supplementation to raise serum 25-hydroxyvitamin D concentrations in order to reduce the risk for infection.[7] While this strategy is unlikely to cause harm, it has not been specifically evaluated for prevention of COVID-19 infection and should be further studied before it is recommended to patients.

N-ACETYLCYSTEINE

Glutathione is an endogenous antioxidant that is frequently depleted in patients with oxidative stress or systemic inflammation, including those with chronic obstructive pulmonary disease and acute respiratory distress syndrome. After systemic administration, *N*-acetylcysteine is rapidly converted to cysteine, which is a precursor to glutathione, leading to significant increases in plasma and alveolar glutathione concentrations. Furthermore, *N*-acetylcysteine itself is a direct scavenger of ROS, leading to antioxidant effects. Administration in vitro and in vivo leads to anti-inflammatory effects (eg, decreased IL-6 and TNF alpha concentrations) and antioxidant effects in a number of pulmonary diseases, including viral pneumonia and acute respiratory distress syndrome.[9]

N-acetylcysteine also has activity as a mucolytic due to its ability to disrupt disulfide cross-bridges in the glycoprotein matrix of respiratory mucus. However, these effects have not consistently translated to clinical outcome benefits in patients with hyperinflammatory diseases,[10] and *N*-acetylcysteine is not routinely used as an anti-inflammatory or antioxidant in clinical practice. Because patients with COVID-19 have evidence of systemic inflammation (includ-

ing possible cytokine release syndrome), often have their course complicated by acute respiratory distress syndrome, and may have respiratory mucus buildup limiting adequate airflow (such as endotracheal tube obstruction due to mucus), systemic or aerosolized *N*-acetylcysteine (or both) may be beneficial in this specific patient population.

There does not seem to be a role for *N*-acetylcysteine supplementation to prevent COVID-19. However, through the varied mechanisms described, *N*-acetylcysteine administration may improve outcomes in patients with established COVID-19 and should be further studied.

SUMMARY AND RECOMMENDATIONS

Ascorbic acid, zinc, vitamin D, and *N*-acetylcysteine have biologic plausibility for the prevention and treatment of COVID-19 and are candidates for clinical trials evaluating patients with these indications. Although there is likely little risk for patients taking labeled over-the-counter doses of these supplements, clinical evidence does not currently support routine use of any of these agents for the prevention or treatment of COVID-19. Unless a patient has a confirmed or suspected micronutrient deficiency, additional research is needed before providing doses of these agents higher than the recommended daily intake established by the US Department of Agriculture.

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