Editorial

The Role of Vitamins and Antioxidants in the Prevention and/or Treatment of COVID-19

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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. 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.

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.

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 duration of mechanical ventilation[4]. However, high doses of intravenous vitamin C were generally safe.

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].

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].

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.

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 hyper-inflammatory 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 (including 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.

With the rapidity of hypothetical treatments' data being generated for COVID-19, clinical investigations up until this point have not provided efficacious treatments in eradicating the virus. While it is important to investigate treatments with the potential to reduce the severity and consequences of COVID-19, vitamins and supplements should be continued to be evaluated to provide the much-needed evidence for possible treatment modalities. These are particularly pertinent in the vulnerable elderly population, who represent a disproportionate burden of morbidity and mortality in these times. Roles of vitamins as important micronutrients in the immune system and their probable roles in the prevention/treatment of viral infections, including COVID-19 may be more effective on the immune system and emphasizes the importance of vitamins in the prevention of viral infections, including COVID-19, and sufficient vitamin intake is highly recommended to prevent viral infections like COVID-19. However, clinical trials based on the associations of diet and COVID-19 are lacking.

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