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Micronutrients and Infection with COVID-19: A Critical Mini-Review

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ABSTRACT

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been the cause of a global pandemic. Given the impact of nutritional status upon immune function, it is crucial to understand the relationship between micronutrient intake and severity of the disease. This mini-review aimed to summarize the known associations between specific micronutrients (vitamin A, D, E, C and zinc, selenium and magnesium) and the health of coronavirus-infected patients. Low serum levels of these micronutrients are associated with the incidence and severity of SARS-CoV-2. However, further studies are needed to evaluate the outcomes of supplementation with these nutrients.

Keywords: Covid-19, Diet, Micronutrient, Vitamin, Mineral

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Introduction

The coronavirus disease 2019 (COVID-19) has been the cause of a global pandemic. From December 2019, strict restrictions and quarantine have been imposed around the world, but prevalence of the disease and mortality remained high [1]. Patients with COVID-19 exhibit varying clinical manifestations, ranging from asymptomatic or mild symptoms, to serious complications which may,



potentially lead to death [2]. Advanced age, obesity, diabetes mellitus, existing respiratory system disease, hypertension, and cardiovascular disease are associated with a poor prognosis [3].

Epidemiological studies are in progress to investigate the relationship between dietary micronutrients, nutrient, foods, or food patterns and COVID-19 [4, 5]. In this mini-review, we have summarized the potential associations or effects of micronutrients and COVID-19 as deficiencies have been shown to reduce immune function, and therefore potentially increase susceptibility to COVID-19 and subsequent secondary infection [6]. Vitamins such as A, D, E and C and minerals like zinc, selenium and magnesium have received particular attention in previous studies. Therefore we focused on these micronutrients in this mini-review [7].

Vitamin A

Vitamin A is present in two forms in the diet: carotenoids as a precursor form predominantly found in vegetables such as carrots, squashes, pumpkin, spinach and broccoli; or an active form called retinol which is consumed through animal sources, such as egg, turkey and fortified foods [8]. Vitamin A has been proposed to enhance immune response against influenza and measles viruses [9]. Vitamin A deficiency commonly accompanies protein malnutrition; therefore, both protein and vitamin A supplementation are recommended to treat these deficiencies. Cough, fever and greater total respiratory resistance were reported to be associated with vitamin A deficiency in patients who were infected with respiratory tract diseases with manifestations similar to COVID-19 [10].

Vitamin D

The fat-soluble vitamin D, is primarily synthesized in the skin during exposure to UV light, it is then hydroxylated by liver and kidneys to produce the active form of vitamin D, calcitriol (1, 25-dihydroxy-vitamin D₃) [11]. Beyond its effects on

musculoskeletal, cardiovascular, endocrine and nervous systems, vitamin D has been shown to confer immunoprotection [12]. Vitamin D is an anti-inflammatory and anti-microbial regulator, which assists with the maintenance of the immune system by suppressing the transcription of inflammatory cytokines [13]. Previous studies have shown that cytokine release syndrome (known as cytokine storm) is an important cause of death among patients with COVID-19 [14]. The association between vitamin D deficiency, cytokine storm, and high mortality in COVID-19 infected patients have been highlighted by several studies [15, 16]. For example, a cross-sectional study investigating relationship between COVID-19 and vitamin D status in 37 Asia pacific countries has shown a negative association between mean vitamin D levels and rate of morbidity; however, the association between vitamin D levels and mortality was not significant [17]. Furthermore, a study of 137 coronavirus-infected patients with vitamin D deficiency, revealed an inverse association between serum vitamin D levels and in-hospital mortality [18]. A systematic review study suggests that vitamin D supplementation has protective effects against overall acute respiratory tract infection and that vitamin D supplementation was most beneficial in those patients who were vitamin D deficient [19]. In summary, coronavirus-infected patients with vitamin D deficiency are more likely to get worse than patients without vitamin D deficiency. More investigations on advantages and disadvantages of vitamin D supplementation are needed.

Vitamin C

Vitamin C is a well-known antioxidant and immune-protective nutrient which can be obtained mostly from plant sources like citrus fruits, tomatoes and peppers [20]. Previous studies suggest that vitamin C can improve immunity through its effective role on T-cells maturation [21]. Some evidence indicates that vitamin C might also have antiviral effects [22, 23] and can help the body

against respiratory infections [24]. For example, an observational investigation suggested that food source intake of vitamin C may reduce the risk of upper respiratory tract infections among women, and a combination of vitamin C and vitamin E supplementation may lower the risk of upper respiratory tract infections among men [25]. These results led researchers to consider the impact of vitamin C deficiency and intake upon the prevalence and progression of COVID-19. Physiological stress like infection may lead to a decrease in serum vitamin C levels as it occurs in coronavirus-infected patients [26]. Based on previous studies, the most protective effects of vitamin C administration were observed in patients with decreased levels of vitamin C [27]. Further evidence also suggests that high-doses of vitamin C (100 mg/kg/day) in COVID-19 infected patients with vitamin C deficiency may be beneficial [28]. A review investigating COVID-19 and vitamin C supplementation, could not confirm a significant protective effect of vitamin C against the disease, but suggests that high dose administration of vitamin C in those who are critically ill, especially those with decreased levels of vitamin C, may be beneficial [29]. However, a clinical trial on 30 patients with COVID-19 did not find any significant difference in a case group treated by high doses of vitamin C (6 g/day) and the control group [30]. Another investigation regarding patients with severe COVID-19 infection in China failed to demonstrate any reduction in 28-day mortality rates after high-dose vitamin C administration; however, a potential positive effect on oxygenation was highlighted [31]. Given the conflicting findings in the literature, further clinical trials are required to clarify the effects of high-dose vitamin C administration in patients infected with COVID-19.

Vitamin E

Vitamin E available as tocopherols and tocotrienols is a fat-soluble vitamin, which is naturally present in foods such as vegetable oils and

nuts [32]. Vitamin E has antioxidant capabilities, which rely on other cellular antioxidant components such as vitamin C [33]. The antioxidant potential of vitamin E protects polyunsaturated fatty acids (PUFAs) against free radicals. Vitamin E supplementation enhances human immunity by increasing lymphocyte proliferation and interleukin 2 (IL-2) production, and reducing interleukin 6 (IL-6) production [34]. Several animal and human studies have demonstrated inverse associations between respiratory disorders (like pneumonia, influenza, and asthma) and vitamin E status due to its immunoregulatory features [35]. Despite this, the efficacy of vitamin E supplementation regarding respiratory tract infections is not fully known. One study designed to investigate the effect of 200 IU/day vitamin E supplementation in an elderly population did not find any significant relationship; however, a lower incidence of the common cold among those who received the supplementation was revealed [36]. A previous cohort study indicated an inverse relationship between dietary intake of vitamin E among women and incidence of upper respiratory tract infection [37]. However, other evidence has demonstrated harmful effects of vitamin E supplementation in elderly individuals with respiratory tract problems [38]. More recently, a randomized control trial has commenced to evaluate the effect of daily intake of multivitamins, including vitamins E, A, D, C and B, upon patients with COVID-19 [39]. More robust studies are needed to fully elucidate the relationship between vitamin E status and the progression of COVID-19.

Zinc

Zinc is an essential trace mineral, which plays a crucial role in several activities in the body including gene expression, protein synthesis, enzymatic reactions and immune function. Zinc is widely found in plant and animal food sources. It can also be obtained by supplementation [40]. Although severe zinc deficiency is not common, mild zinc deficiency

is prevalent especially among vegetarians and elderly individuals [41]. An observational study showed that low serum zinc levels in elderly might make them susceptible to pneumonia. Also, zinc deficient individuals may respond better to supplementation [42] and previous studies have shown that zinc deficiency leads to immune dysfunction that may worsen inflammation or infection status [43]. Zinc is potentially an antiviral agent that plays role in influenza and COVID-19 inhibition [44, 45]. A meta-analysis has shown a positive effect of zinc supplementation for the treatment of the common cold [46]. Furthermore, an investigation on the efficacy of zinc treatment on 28 outpatients with COVID-19, demonstrated an improvement in all participants [47]. Moreover, another clinical study on serum zinc levels in 249 COVID-19 patients revealed a strong correlation between low serum zinc levels (<50 µg/dl) and the intensity of disease and mortality rate due to immune system dysfunction. This suggests that serum zinc levels may be a predictive factor of COVID-19 outcomes [48]. In some COVID-19 infected patients, it is necessary to use mechanical ventilation and low levels of serum zinc has been shown to decrease the tolerance of the lung against mechanical ventilation damage [49]. Given the importance of zinc status in immune function, more studies should investigate the effect of zinc supplementation on COVID-19 patients.

Selenium

Selenium is a vital compound which has antioxidant and enzyme activities [50]. Selenium is necessary for maintaining the function of immune system [51]. Based on previous studies, individuals who were deficient in selenium were more prone to infections and inflammation and respond better to dietary selenium intake as well as supplementation [52]. Low levels of plasma selenium are associated with an elevated level of oxidative stress and higher susceptibility to viral infections [53, 54]. Due to important role of selenium in immune function,

some studies have suggested a relationship between selenium status and coronavirus disease. An investigation in China, demonstrated a positive correlation between patients who recovered from COVID-19 and selenium status [55]. This finding was also corroborated by a recent cross-sectional study in Germany, which highlighted a strong relationship between selenium deficiency and the mortality rate of patients infected with COVID-19 [56]. As few studies have examined the relationship between selenium status and COVID-19, more investigations are suggested in this regard.

Magnesium

Magnesium is an essential trace element, which is functionally related to vitamin D. Vitamin D activation, is dependent on magnesium, via regulating the blood transportation of vitamin D. Magnesium deficiency may lead to a reduction in calcitriol (active form of vitamin D) levels [57, 58]. Poor diet, chronic disease and stress are some causes of magnesium deficiency. Magnesium deficiency can result in inflammation and damaged immune function. It can also lead to an increase in oxidative stress [59, 60]. One study demonstrated a remarkable reduction in NK (natural killer) and CD8+ (cytotoxic) T cells (which are crucial for combating viral infections) in coronavirus-infected patients with magnesium deficiency; that may cause cytokine storm in the lungs and consequently worsen the progression of COVID-19 [61]. Magnesium supplementation (in the form of L-threonate) increases intracellular magnesium levels and help the NK and CD8+ T cells restoration [62]. A recent study on older patients infected with COVID-19, interestingly demonstrated a decrease in the oxygen and intensive care support requirement in patients who were treated by a combination of magnesium, vitamin D and vitamin B12 [63]. Since magnesium and vitamin D deficiency worsen the inflammation status, a previous study has suggested to consider magnesium

and vitamin D co-supplementation as a helpful approach during COVID-19 pandemic [64]. Although the vital role of magnesium in health maintenance is well known, further studies are needed to ensure the effect of magnesium supplementation on COVID-19 patients.

Conclusion

Several studies have highlighted the negative effects of COVID-19 on numerous aspects of human life including health status. This review suggests that low serum levels of certain micronutrients may be associated with the incidence and severity of the disease. Consumption of rich sources of these nutrients may be helpful for preventing and treating patients infected with COVID-19 and may facilitate their recovery. Despite this, further studies are needed to evaluate the outcomes of supplementation with these nutrients.

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Authors' contributions

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Conflict of Interest

The authors declare that there is no potential conflict of interests in this review.

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