COVID-19 pandemic: Can boosting immune responses by maintaining adequate nutritional balance reduce viral insults?

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Abstract

The impact of nutrition on immunity is an intense area of research. Malnutrition is linked to a higher risk of microbial infections, while severe infections usually lead to a nutritional imbalance in affected patients. The nutritional status has an impact on the severity of the ongoing SARS-CoV-2 infection. Studies conducted on small numbers of patients have shown the benefits of maintaining optimal vitamin (B12 and D) and mineral (zinc and magnesium) balance in reducing the intensity of COVID-19. Although consuming a balanced diet with a healthy lifestyle is always desirable, the importance of such practice is even more meaningful during the COVID-19 pandemic. Keeping an optimal balance of vitamins and minerals through healthy dietary habits helps to maintain a robust immune system that is essential to combat invading microbial pathogens, including SARS-CoV-2.

Introduction

The COVID-19 pandemic is caused by the SARS-CoV-2 virus and has started to disrupt the food supply chain and affect nutritional insecurity in various parts of the world [1, 2]. COVID-19-related changes in food habits, and eating behaviors, with higher consumption of processed foods, have both short-term and long-term adverse health consequences [3]. Although the influence of nutritional status in the progression of SARS-CoV-2 infection is an evolving area [4], studies have reported the benefits of consuming adequate amounts of various micronutrients and vitamins in reducing the disease burden in various viral infections, ranging from H1N1 influenza virus to hepatitis C virus to herpes simplex virus [5, 6]. Maintaining adequate nutritional status may reduce the inflammatory events

to lessen the severity of virus-induced infections, including SARS-Cov-2-mediated infection, in order to improve the overall outcome of the diseases [7]. The vitamins and micronutrients, including vitamins B, C, and D, along with minerals like zinc, and magnesium, have immune-boosting effects [4, 7, 8]; maintaining an adequate balance of these nutrients could provide added resistance against the infections through enhancing immune responses to lessen the disease burdens [9]. Of clinical importance, the effectiveness of bovine coronavirus inactivated vaccines has shown to be markedly reduced in animal models with vitamin deficiency [10]. Various international agencies, including the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the Food and Agriculture Organization (FAO), have given specific nutritional guidelines to prevent and protect against the SARS-CoV-2 infection, available and regularly updated on their respective websites. Increased community awareness of these dietary recommendations and ensuring healthy eating behaviors to enhance overall nutritional status would likely be to provide an additional shield against the ongoing SARS-CoV-2 infection. The immune system involves various cells and (bio)chemicals that create a microenvironment to fight against the invading pathogens, including viruses and bacteria. Maintaining a healthy and functioning immune system is essential to prevent the flareup of infections. To enhance the immune system, keeping the optimal vitamin and mineral balance through dietary consumption is vital. In many viral insults, including the HIV infection, cellular components of the immune system are destroyed to compromise the protective immune responses. Of clinical importance, many of the identified risk factors for COVID-19 are related to impaired immunity [11]; for

instance, preexisting impaired immunity in obesity, asthma and other chronic lung diseases, liver diseases, diabetes, and the geriatric population are more likely to be infected by SARS-CoV-2 [12-14]. A detailed explanation of various immune-boosting nutrients is published elsewhere, and I will briefly discuss and reemphasize the role of vitamins (B12 and D) and minerals (zinc and magnesium) that might be relevant and useful to reduce the intensity of COVID-19.

COVID-19 and nutrients

Despite millions of people around the globe having been infected by SARS-CoV-2 with significant fatalities, yet, there is no specific treatment or vaccine available for COVID-19. With such uncertainty during this pandemic, minimizing the risk of infection by enhancing the immune system would be an essential deterrence. Both innate and adaptive immunity provide a necessary defense against invading pathogens. An adaptive immune system through creating an immunologic memory of past events could exert specific responses. The SARS-CoV-2 can invade the human body, mostly through nose, mouth, and eyes. Once the virus reaches to the lower respiratory tract by the inhalation, the spike-like proteins on the SARS-CoV-2 surface bind with the angiotensin-converting enzyme 2 (ACE2) protein; by using ACE2 as a cellular entry receptor, the SARS-CoV-2 gain entry to the epithelial cells of the respiratory tract and start replicating to increase viral loads [15]. The damaged cells elicit inflammatory responses that are translated into clinical signs and symptoms noted in COVID-19 patients [16].

It is well-recognized that having adequate nutrition could enhance immunity and reduce the severity of infections [17, 18]. Several preliminary reports suggested the benefits of vitamins and minerals in reducing the severity of the SARS-CoV-2 infection [19, 20]. Although further controlled studies are needed to validate such claims, considering that specific vitamins and minerals have known immune-boosting effects, it might be prudent to keep them at optimal levels by consuming adequate amounts. As mentioned, maintaining optimal nutritional status through the consumption of an appropriate amount of vitamins B and D, along with minerals, like zinc and magnesium, could boost the immune responses to minimize the damages induced by the SARS-CoV-2 infection.

Vitamin D is a fat-soluble nutrient and believed to exert anti-inflammatory responses [21-23]. Like any other nutrients, its optimal level of vitamin D should be maintained, but whether its deficiency could make the progression of COVID-19 worse will need further study. Therefore, cautious approaches should be employed to promote vitamin D supplementation with the expectation of additional protection against COVID-19 [24]. Studies on 449 confirmed cases of COVID-19 showed that the investigators did not find any potential link between vitamin D concentrations and the risk of SARS-CoV-2 infection [24]. Some preliminary reports, however, suggest an association between low levels of vitamin D and disease severity of COVID-19 [25]. Of relevance, the Recommended Daily Allowance (RDA) for vitamin D is 600-800 International Units per day, as recommended by the Institute of Medicine's national guideline. It is, however,

important to mention that safe sunlight exposure, whenever possible, should be encouraged to maintain recommended levels of vitamin D [26].

Vitamin B12 is another immune-boosting nutrient and its adequate level should be maintained to achieve optimal immune responses (**Figure 1**) [27-30]. Inadequate vitamin B12 levels can impair the ability to generate antibodies in the body. Moreover, extreme inadequacy of vitamin B12 can lead to hyperhomocysteinemia to induce blood clot formations in the lungs and beyond [31-33]. Vitamin B12 is found in animal products, such as eggs, milk (Swiss cheese, yogurt), fish (salmon, clams, tuna), and meat (beef liver). Of note, elderly individuals are at high risk of vitamin B12 deficiency because of their inability to absorb vitamin B12 optimally from the consumed food. In a study conducted on elderly individuals with RT-PCR proved COVID-19 positivity, with a daily treatment of vitamin D3 (1000 IU), magnesium (150mg), and vitamin B12 (500mcg) for up to 14 days, showed a significantly reduced need for oxygen therapy compared to the non-treated patients, even after adjusting for age, gender, and other illnesses [34].

Maintaining optimal magnesium balance is also vital for the physiologic functions of skeletal muscles, heart, teeth, and bones. Importantly, magnesium is needed as a cofactor for the activation of vitamin D; from the storage or inactive form of vitamin D (25[OH]D) the bioavailability of magnesium is essential in order to convert it to an active form of vitamin D (1,25[OH]2D) [35, 36]. By consuming an optimal amount of magnesium, the risks of vitamin D deficiency might be lowered, and therefore could reduce the dependency on vitamin D supplements [37-40]. As mentioned, magnesium supplementation, along with vitamins has shown to exert beneficial effects on COVID-19

patients [34]; magnesium-associated benefits might be achieved: **1**) by potentiating the vitamin D activities, and **2**) by improving immune responses [38, 40-42]. Foods high in magnesium include nuts and beans, bananas, broccoli, brown rice, egg yolk, fish oil, green vegetables, mushrooms, pumpkin seeds, sesame seeds, sunflower seeds, chia seeds, basil seeds, sweet corn, tofu, and whole grains.

Maintaining the optimal level of zinc is essential for healthy immune functions, as well as for optimal skeletal features [43, 44]. It is also required for cellular functions, ranging from enzyme activation to cell signaling to energy metabolism [45]. Zinc is also needed for the adequate absorption of several vitamins. Zinc deficiency has shown to increase the risk of evolving infections and degenerative diseases [46-48]. High zinc-containing food includes lamb, beef, chicken, oyster, and lobster. Cereals and whole grains, black rice, black sesame, bread and noodles, legumes, nuts, seeds (sunflower), mushroom, and celery can also provide zinc. Existing reports suggest that zinc could exert antiviral effects: **1**) by reducing viral replication and **2**) by enhancing immune responses [5, 6]. The tolerable upper intake level for zinc is 40 mg/day (**Table 1**) and consuming an adequate amount of zinc is likely to exert protective effects against the SARS-CoV-2 infection. In a clinical study, when zinc sulfate was provided in combination with hydroxychloroquine and azithromycin, a better therapeutic response was noted among the COVID-19 patients, when compared with the COVID-19 patients who received hydroxychloroquine and azithromycin without the complement of zinc; of clinical importance, zinc sulfate addition resulted in a higher rate of hospital discharges with a reduced mortality of COVID-19 patients [19]. In an uncontrolled case series of laboratory-

confirmed COVID-19 patients, consumption of a high dose of zinc salt claimed to show symptomatic and objective improvements [20]. Ongoing clinical trials with zinc in various parts of the world would determine the exact role of zinc in the COVID-19 pandemic.

Conclusion

An appropriate balance of vitamins, micronutrients, and minerals, including vitamin B12, vitamin D, zinc, and magnesium, is essential for maintaining good health, and nutritional dysregulations lead to various diseases [5, 6, 27-30, 37-40, 49-57]. To reduce the global COVID-19 burden, enhancing immunity by maintaining functional nutritional status is desirable, and more importantly, such enhancement is achievable by consuming a balanced diet. A healthy diet with an active lifestyle can boost the immune responses to better combat the SARS-CoV-2 infection. The simple preventive measures, such as frequent washing of hands with soap or alcohol-based sanitizer, maintaining social distancing, using the mask in public places, along with boosting the immunity through consuming balanced diet are likely to reduce the transmission of the SARS-CoV-2 infection significantly. As explained, optimal levels of vitamins (B12 and D) and minerals (zinc and magnesium) could be a factor in reducing the intensity of the SARS-CoV-2 infection in COVID-19 patients. It is important to note that for the nutritional safety net, Recommended Daily Allowance (RDA) and tolerable upper intake level (UL) should be considered (**Table 1**) while consuming vitamins and minerals to avoid unnecessary toxicity. The results of the ongoing clinical trials will illuminate the necessity of any specific nutrients in COVID-19 patients.

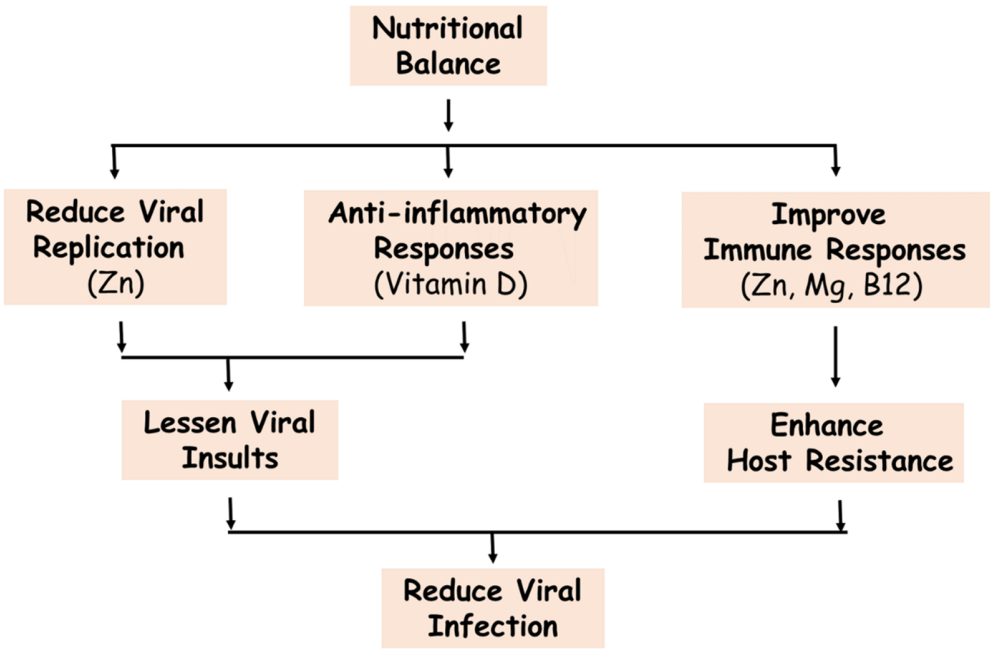
Table 1:

Tolerable upper intake level (UL) for adults, set by the Food and Nutrition Board (FNB)

- Magnesium: 350 mg/day
- Zinc: 40 mg/day
- Vitamin D: 50 μg/day
- Vitamin B12: no UL for vitamin B12 because of its low potential for toxicity

Figure 1:

Schematic illustration of possible cellular and molecular events, ranging from anti-inflammatory responses to reduce viral replication to enhance host resistance that can be elicited and mediated by various nutrients, to exert cumulative effects of reducing viral infection. Modified from earlier publication [5]. (**Zn**: Zinc, **Mg**: Magnesium, **B12**: Vitamin B12)



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