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COVID-19 pandemic: can maintaining optimal zinc balance enhance host resistance?

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Abstract

The novel coronavirus, COVID-19 is now officially declared as a pandemic by the World Health Organization (WHO), and most parts of the world are taking drastic measures to restrict human movements to contain the infection. Like millions of others around the world, I am wondering, is there anything that could be done, other than keeping high personal hygiene, and be vigilant of symptoms, to reduce the chances of infection, or at least to reduce the burden of the disease. So far, the National and International health agencies, including the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the WHO have provided clear guidelines for both preventive and treatment suggestions. In this opinion-based article, I want to discuss, why keeping the adequate micronutrient balance might enhance the host response and be protective of viral infections. A detailed in-depth discussion of various micronutrients

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is not the purpose of this article, I will mostly emphasize on the role of zinc in viral infection.

Key Words: Zinc, Antiviral, COVID-19, Pandemic, Host resistance

Zinc and antiviral responses

The novel coronavirus pandemic was termed as COVID-19 by the World Health Organization (WHO) in early February of 2020. The enormous physical, emotional, social and economic impact of the COVID-19 pandemic let the health professionals invest time, intellect and resources to develop meaningful therapeutic approaches to reduce the disease burden. Also, the need for identifying the factors to reduce the risk of COVID-19 infection that could be adopted by a large population at a low cost with minimal risk is a medical priority at this time of crisis. Zinc might be one of the micronutrients that could be consumed to reduce the intensity of COVID-19 infection and perhaps lessen the respiratory tract infection for its antiviral properties [1-3]. Zinc supplementation against rhinovirus infection, or "common cold" viruses including influenza virus has shown promising antiviral effects with reduced disease burden. It is important to mention that the amount of ionic zinc present at the oral and nasal mucosa (site of infection) positively correlated with the study outcome [1, 4]; a 42% reduction of 'cold duration' was estimated with a higher dose of ionic zinc [2, 5]. Of importance, COVID-19 also takes a similar route to get entry to the body, including the lungs. Whether the presence of a higher concentration of zinc at and around the site of infection would reduce the intensity of the COVID-19 infection, is an area that surely needs further clinical validation. However, in a pandemic situation, a courageous attempt to use zinc to reduce disease

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burden is worth trying. More importantly, consuming around 25-50 mg zinc per day is affordable, and less likely to induce human toxicity, as >200 to 400 mg per day of zinc consumption has shown to induce adverse effects, including nausea, vomiting, epigastric pain, lethargy, and fatigue [6, 7]. This opinion-based article, based on existing published information, will focus on possible benefits of maintaining adequate zinc balance to reduce COVID-19 associated disease load. Of clinical importance, severe acute respiratory syndrome (SARS) coronavirus replication has shown to be inhibited by zinc [8]. Zinc compound has also shown to reduce the in vitro replication potential of the influenza virus [9]. Zinc oxide nanoparticles demonstrated promising antiviral effects against H1N1 influenza virus infection [10]. In a similar line of study, zinc salt inhibited the replication of the respiratory syncytial virus [11]; the investigators have shown an 800-fold reduction in respiratory syncytial virus with 10μM concentration of zinc salt exposure [11]. Antiviral effects of zinc are also shown in the hepatitis C virus (HCV), where zinc salts reduced the HCV replication [12]. More importantly, zinc supplementation in HCV-infected patients reduced hepatitis, and enhanced the response to antiviral treatment [13-15]. Zinc supplementation significantly improved both cutaneous and genital warts that are induced by human papillomavirus (HPV) [16, 17]. Furthermore, in developing countries, zinc supplementation in children significantly reduced the prevalence of pneumonia [18, 19]. How zinc exerts its antiviral effects are not yet clear, it could inhibit viral binding to the mucosa, and subsequent replications. In vitro studies have shown that zinc could induce the generation of antiviral interferon (IFN)-α and IFN-γ to exert antiviral effects [20, 21]. In addition, zinc could also suppress inflammatory events.

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Zinc and immune responses

Micronutrients, in general, play an important role in maintaining adequate immune activity, and impairment of micronutrient balance adversely affects the immune system to increase the susceptibility to various bacterial and viral microorganisms. Studies have shown how a wide range of vitamins and micronutrients influence the functionality of various immune cells [22, 23]. Zinc is an important dietary trace mineral that can influence the functions of the immune cells [22, 24]; it also acts in the activation and inactivation of over 300 enzymes and coenzymes that are involved in vital cellular functions, including energy metabolism, DNA synthesis, RNA transcription, etc. [22, 24]. Of relevance, zinc is the main structural component of around 750 zinc-finger transcription factors [25-27], and incorporated into about 10% of all human proteins [28]. Meat and seafood, including lamb, beef, chicken, oyster, and lobster are good sources of zinc; for better absorption of zinc, these should be eaten together with vegetables [29]. In addition, black rice, black sesame, soy foods, mushroom, celery, legumes, lentils, nuts, sunflower seeds, and almonds are also good sources of zinc [30].

Earlier studies have shown that zinc deficiency can hinder host-defense systems [31] to increase the susceptibility to various viral and bacterial infections [23]. The human genetic disorders related to zinc malabsorption are commonly associated with severe fungal, viral, or bacterial infections, along with immune system dysregulation [32]. Acrodermatitis enteropathica is a rare genetic disorder with decreased zinc absorption causing low plasma zinc concentrations; patients suffering from acrodermatitis enteropathica experienced fewer infections when treated with a high dose of zinc

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supplementation [33, 34]. Studies conducted in vitro, have shown that low concentrations of zinc can induce apoptotic cell death of mouse CD4+CD8+ thymocytes, [35], while, a higher concentration of zinc can block such apoptosis [36]. Zinc deficiency not only reduced lymphocyte counts but also impaired T and B lymphocyte functions; when murine T and B lymphocytes were challenged with mitogens, markedly reduced proliferative activities were noted in zinc-deficient mice, as compared to controls [37, 38]. In a similar line of observation, zinc supplementation resulted in a higher proportion of CD4+CD3+ cells in peripheral blood, with enhanced T-cell-mediated immunity in supplement-treated children [39].

In vivo experimental studies have shown that zinc deficiency could compromise B-cell development [40] with low IgG production [41], leading to an increased rate of infection, and higher mortality [42]. Maternal zinc deficiency in animal studies also resulted in reduced antibody production in the offspring [43]. Of clinical importance, such impaired antibody-mediated responses could be restored by zinc supplementation [43]. Moreover, studies have shown that in inadequate zinc microenvironment, macrophages have lower the phagocytic ability against the parasites, and zinc treatment could restore the phagocytic ability of the macrophages [39]. Higher intracellular zinc concentration has shown to increase monocyte resistance to apoptosis via suppressing the activation of caspase 3 [44].

Conclusion

Of concern, clinical zinc inadequacy is more common in elderly individuals [31], and the global prevalence of zinc deficiency is estimated to be around 20% [45, 46]. Elderly

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individuals are commonly infected by the COVID-19 [47, 48], and whether impaired zinc balance is causing these individuals to be more vulnerable to infection is an area that needs further clinical studies. However, existing evidence shows that zinc could exert antiviral effects: **1**) by suppressing viral replication and **2**) by boosting immune responses. As mentioned, zinc possesses antiviral properties and may provide inexpensive and effective adjunct therapy for some viral species, that can induce a wide range of infections, including respiratory tract infections [3]. Consumption of 45mg elemental zinc per day for all year has markedly reduced the incidence of infection in elderly individuals, ranging from 55 years to 87 years [49]. In vitro studies have shown the potent antiviral effects of free zinc, which are validated in human trials with high free zinc contenting creams, lozenges, and supplements. Whether gargling with zinc-containing fluid would reduce viral load in oral and pharyngeal areas will need clinical evaluation. Of relevance, in Asian countries, including Japan, gargling is recommended and commonly practiced for influenza virus infection [50, 51]. In a randomized trial conducted on upper respiratory tract illness, a 36% reduction of infection was documented in patients who gargled with water, as compared with a non-gargling control group [52].

In conclusion, maintaining adequate zinc balance is important to protect from microorganisms, including viral infections. Summarizing the available information, consuming up to 50 mg of zinc per day might provide an additional shield against the COVID-19 pandemic, possibly by increasing the host resistance to viral infection to minimize the burden of the disease. As mentioned, the potential beneficial role of zinc in

COVID-19 infection needs further clinical validation, however, in this pandemic situation, using zinc to reduce disease burden would be a well-intentioned trial.

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