EDITORIAL

Investigate Oral Zinc as a Prophylactic Treatment for Those at Risk for COVID-19

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THE NOVEL CORONAVIRUS DISEASE OF 2019 (COVID-19), which can cause a severe respiratory syndrome in humans, results from infection by the SARS-CoV-2 virus. A very recent report identified the interaction between the receptor-binding domain of the spike glycoprotein (S protein) of SARS-CoV-2 and the peptidase domain of angiotensin-converting enzyme 2 (ACE2) as critical for viral entry into host cells.[1] Because of the strong link between ACE2 and SARS-CoV-2 infection, inhibitors of ACE2 have been discussed as potential therapeutic agents against COVID-19.[2,3] We believe there already might be a safe, potential inhibitor of ACE2 function that could constrain the ability of SARS-CoV-2 to infect cells—and that is the trace mineral zinc. Given that zinc supplements are widely used, proven safe in moderate doses, and available without prescription, we propose that there is an urgent need to determine if zinc can be an effective prophylactic treatment against COVID-19.

SARS-CoV-2 is an enveloped, positive strand RNA virus that is about 80% identical to the SARS-CoV virus that was responsible for the severe acute respiratory syndrome (SARS) outbreak of 2002-2003. Research at that time identified interaction between the S protein of SARS-CoV and ACE2 as a mechanism of viral infection.[4] ACE2 is a type I integral membrane protein characterized by the HEXXH + E zinc-binding domain and is found on the surface of epithelial cells of the heart, lung, kidney, and intestine. ACE2 has also been found to be expressed in cells of the upper respiratory tract and in oral epithelial cells.[5,6] This could explain why the SARS-CoV-2 virus can be highly infectious and COVID-19 symptoms can include pneumonia and diarrhea. Despite being a zinc metallopeptidase, very little research has been done on the effect of exogenous zinc on ACE2 function. One report showed that zinc blocked the ability of ACE2 to metabolize substrate in a dose-dependent manner starting at concentrations as small as 10 μM,[7] indicating that zinc could possibly inhibit the interaction between SARS-CoV-2 S protein and ACE2.

Although limited, there are research findings concerning the antiviral effects of zinc.[8] It was first shown that zinc lozenges, which coat the oral cavity with zinc, were somewhat effective with short-term use at mitigating the duration of rhinovirus infections especially at doses greater than 75 mg zinc daily.[9,10] It has also been suggested zinc can limit influenza virus infections.[11,12] The antiviral effects of zinc against rhinoviruses and influenza are thought to be due to enhanced immune cell function,[8,11,12] although the ability of zinc to interfere with the binding of these viruses to cells remains a possibility. It has also been suggested that zinc can inhibit coronavirus replication by the inhibition of RNA synthesis.[13] Clearly, there is an urgent need to further study the antiviral mechanisms of zinc, particularly as they relate to coronaviruses. It should be noted that SARS-CoV-2, influenza, and rhinoviruses all use different cellular receptors, but the presence of ACE2 on the epithelium of the oral cavity and upper airway offers an excellent rationale for oral zinc therapy.

Based on the Age-Related Eye Disease Study (AREDS) and the AREDS 2 studies[14] many, primarily elderly, are already taking zinc-containing supplements in order to limit the progression of their age-related macular degeneration. Normal serum levels of zinc are around 12 μM, and the AREDS formula, which provides 80 mg of zinc daily, was able to increase serum zinc by 17% within 1 year.[15] It should be studied to determine if this increase in zinc can prevent or limit disease duration for those particularly vulnerable to COVID-19.

We realize the scientific and clinical evidence to fully support the use of an oral zinc supplement as a prophylactic agent remains incomplete. Given that a vaccine is at least a year away, any safe, natural compound with antiviral potential should be given serious consideration as a prophylactic agent. Double-blind, placebo-controlled studies will ultimately need to be done to prove the efficacy of zinc supplements against SARS-CoV-2. However, because of their availability, safety, and potential benefits, they merit strong consideration for immediate studies (analyzing

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possible differences in progression of respiratory disease patients between AREDS 2 users and abstainers) by health researchers at this time to identify a possible tool that can work against COVID-19. In view of the serious, life-threatening circumstances of this pandemic, we believe there is potential benefit in taking oral zinc for those at risk of developing COVID-19. Therefore, shorter open-label retrospective studies should be quickly completed.

Whether or not any benefit from oral zinc can be demonstrated, we warn users strongly against taking more zinc than provided by the AREDS 2 formula and developing a false sense of security by using oral zinc. Social distancing and meticulous hand hygiene remain of the utmost importance in limiting the spread of COVID-19 and should continue to be the primary strategy against the SARS-CoV-2 pandemic.

In summary, investigating oral zinc supplementation for the prevention of COVID-19 should commence immediately.

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In memory of our Chinese colleague Li Wenliang, MD (1986-2020).

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