Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

The differential roles of zinc in immune responses and their potential implications in antiviral immunity against SARS-CoV-2

Dear Editor,

In their recent recommendations for the nutritional management of individuals with SARS-CoV-2 infection, Barrazoni and colleagues emphasized that "While it is important to prevent and treat micronutrient deficiencies, there is no established evidence that routine, empirical use of supraphysiologic or supratherapeutic amount of micronutrients may prevent or improve clinical outcomes of COVID-19" [1]. We would like to support this notion with observations made by our and other groups on the multifacetted role of zinc in immune responses.

The multifunctional essential trace element zinc has long been considered a potential antiviral agent during infections, either through direct antiviral activity that can be enhanced by ionophores such as chloroquine, or by enhancing virus-specific immune responses [2–4]. Zinc deficiency is accompanied by higher infection rates with different viruses, including common cold viruses, HSV, HCV, and HIV [3]. Therapeutic zinc supplementation was shown to compensate for zinc deficiencies and to lower infection rates [2]. However, mechanistic studies demonstrating the antiviral activity of zinc *in vitro,* including effects on viral enzyme activity [2], are frequently based on the use of zinc concentrations that significantly exceed those observed under physiological conditions [3].

Based on these observations, the controlled supplementation of zinc to reach a balanced zinc homeostasis has been proposed as a possible component in the prevention and healing approach for viral infections, including SARS-CoV-2 [4].

However, there are several caveats to be considered in the treatment of patients with zinc supplementation. Zinc functions as an essential trace element for immunity as well as many pathogens; therefore, zinc can affect immune responses and infections in multiple ways. It should be noted that some patients suffering from SARS-CoV-2 infection/COVID-19 disease may show a decrease in total leukocyte counts. Furthermore, reports indicate that lymphocytopenia is present in the majority of patients. Importantly, zinc supplementation has the potential to suppress immune responses and should only be administered in a controlled manner. We and others reported a possible mechanism underlying this observation by showing that high concentrations of zinc aspartate inhibit human and mouse T cell activation and T cell function *in vitro* [5,6]. This effect can be used therapeutically to treat autoimmune disease *in vivo*. The therapeutic application of zinc aspartate intraperitoneally or orally is capable of strongly diminishing the severity of clinical signs of experimental autoimmune encephalomyelitis (EAE), a T cell-mediated autoimmune disease of the central nervous system [6]. Of note, this work was done using physiological concentrations achieved by oral application of an approved zinc therapeutic.

While zinc administration in conditions of zinc deficiency is well supported, the potential effects of zinc homeostasis and therapeutic supplementation in viral infections like COVID-19 need to be carefully considered and should be further investigated in controlled clinical trials.

Conflict of interest

The authors declare no competing interests.

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