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SHORT COMMUNICATION:

ZINC SUPPLEMENTATION FOR TREATMENT OF SARS-COV-2 INFECTIONS

Short Running Title: Zinc for SARS-CoV-2 infections

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ABSTRACT:

The COVID-19 pandemic disproportionately affects older people, who have a higher risk of severe infections and mortality. Zinc is a readily available supplement that is gaining interest as potential treatment for SARS-CoV-2 infections. Zinc deficiency is associated with susceptibility to infections. People with COVID-19 infections have a reduced level of serum zinc compared to controls. Zinc supplementation has been shown to be helpful for people with respiratory tract infections through multiple mechanisms including improving viral clearance. A study on community zinc supplementation found a lower rate of symptomatic COVID-19 infections compared to control. The use of zinc in critically unwell COVID-19 patients was associated with reduced 30-day mortality. A study of COVID-19 infected inpatients showed that zinc reduced the rate of needing intensive care, while outpatient treatment may reduce symptom duration by three days. Given the higher rate of adverse outcomes in older people, zinc supplementation should be further evaluated and considered for treatment of SARS-CoV-2 infections.

Keywords: COVID-19, immunity, older people, zinc

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Zinc supplementation for treatment of SARS-CoV-2 infections:

As of late 2019, the world faced an unprecedented coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Older people are a vulnerable group and are disproportionately affected by COVID-19 infections. Approximately half of the older patients affected by COVID-19

infections have severe infections, one in five become critically unwell and a one in ten die [2]. Trials are ongoing to evaluate the efficacy of specific treatment, ranging from antimalarials, such as chloroquine, and antivirals such as lopinavir/ritonavir and remdesivir to reduce the rate of these adverse outcomes [3].

Zinc supplementation is gaining interest as potential therapy for individuals with SARS-CoV-

2 infections due the pre-existing evidence of its role in the development and function of the immune system against viral infections [3-5]. Zinc is inexpensive, readily available globally, can be administered orally and has minimal side effects [5]. Individuals with suboptimal zinc levels were found to have an associated higher risk of infections, autoimmune disorders and cancer [5]. Prolonged zinc deficiency may contribute to an imbalance in the immune system, with a higher susceptibility to infections with severe zinc deficiency [3].

A cohort study identified a significant reduction in circulating serum zinc in COVID-19 patients compared to healthy controls [6]. Serum zinc levels were also associated with disease severity, with severe COVID-19 infections having lower serum zinc levels [6]. In Asian populations, there were no significant correlations observed between zinc deficiency and COVID-19 deaths; however, there was a significant positive correlation between zinc deficiency prevalence and COVID-19 cases per million population in Asian countries [7]. While the exact role of zinc in SARS-CoV-2 transmissibility is unclear, it is hypothesised to be related to its antiviral properties of inhibiting RNA synthesis, topoisomerase and viral replication [4].

Administering zinc supplements in individuals with respiratory tract infection has been shown to reduce symptom severity, frequency and

duration of the infection [5]. Zinc supplementation has also been proposed by research and clinical groups to manage patients with SARS-CoV-2 infections [8]. This is because zinc may play a role in improving mucocilliary clearance of virus particles, supporting integrity of the respiratory epithelia, reducing viral replication, conserving antiviral immunity, reducing hyperinflammation risk, facilitating anti-oxidative effects and thus minimising lung damage and secondary infections [5].

A prospective single-blinded study conducted in 2020 during the peak of the COVID-19 pandemic evaluated the effects of oral zinc supplementation in a community with circulating SARS-CoV-2 [8]. Participants were treated with daily doses of 10 mg, 25 mg, or 50 mg zinc picolinate. Although there were no differences in the COVID-19 symptomology of participants between the three treatment groups, individuals administered zinc picolinate were less likely to develop symptomatic COVID-19 infections compared to the control group [8]. These findings suggest that zinc supplementation even at 10mg daily doses may be beneficial in alleviating severity of COVID-19 infections in the community.

A 2021 retrospective study observed an association between the use of zinc sulphate as adjunctive therapy with significantly lower 30-day mortality in critically ill patients with COVID-19 infections [9]. Survival benefits were also

observed in these patients after they were prescribed zinc supplements within 30 days of their hospital stay [9]. A 2022 prospective randomised double-blind placebo-controlled multicentre trial reviewed the efficacy of zinc supplementation in COVID-19 inpatients and outpatients [10]. In addition to standard supportive care, patients were given 25 mg elemental zinc twice daily for 15 days or placebo and were evaluated over a 30-day period [10]. There was a significant decrease in the risk of Intensive Care Unit (ICU) admission within 30 days, and a shorter duration of COVID-19 symptoms in the inpatient group treated with zinc supplementation compared to placebo. For the outpatients, zinc supplementation reduced the duration of COVID-19 symptoms by approximately 3 days. These studies support zinc supplementation to treat patients with COVID-19 infections who seek medical treatment in outpatient and inpatient settings, including critically unwell patients.

The optimal formulation and administration route of zinc for COVID-19 infections requires further evaluation. For instance, the cellular uptake of zinc can be improved when combined with a zinc ionophore such as hydroxychloroquine [11]. In a 2020 retrospective observational study of COVID-19 inpatients not requiring ICU care, treatment with zinc sulphate combined with hydroxychloroquine and azithromycin was associated with reduced mortality or transition towards palliative care [11]. However, whether

the addition of zinc ionophore is superior than that of zinc alone has yet to be determined.

In summary, there are several studies demonstrating the benefits of zinc in the management of SARS-CoV-2 infections in multiple settings, ranging from community supplementation during a pandemic, outpatients, inpatients and critically ill patients. This may be a useful therapeutic approach to consider for older people, who are at a higher risk of severe infections and mortality. Further research is required to elucidate the role of zinc in SARS-COV-2 infections and the optimal dose, formulation and preferred route of administration.

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