The potential role of zinc, magnesium and selenium against COVID-19: a pragmatic review

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\textbf{ABSTRACT}

\textbf{INTRODUCTION}: Several studies have analyzed the role of antioxidant minerals as positive modulators of the immune system in facing viral infections. We discuss their possible protective role in Sars-Cov 2 infection selecting minerals for which literature provides most evidences, such as zinc (Zn), magnesium (Mg), and selenium (Se).

\textbf{DISCUSSION}: All these minerals have a role in modulating antiviral and antibacterial immunity and to regulate the inflammatory response. Their deficiency is associated with a higher prevalence of respiratory tract infections and endothelial dysfunction. These features are related to COVID-19 pathophysiology.

\textbf{CONCLUSIONS}: It seems that an optimal micronutrient status in terms of Zn, Mg and Se, is able to effectively strengthen the immune system during the COVID-19 infection. Anyway, further studies are necessary.

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Several studies have analyzed the role of antioxidant minerals as positive modulators of the immune system in facing viral infections (Iddir et al. 2020). Specifically, zinc, magnesium and selenium are required as cofactors for a variety of enzymes involved in antioxidant reactions and have been implicated in boosting the immune system (Iddir et al. 2020). In light of the proved role of antioxidant minerals as boosters of the immune system (Iddir et al. 2020), we discuss their possible protective role in Sars-Cov 2 infection through a non-systematic review including the most relevant studies on the potential link between “micronutrients and covid-19”, present on databases including PubMed and MEDLINE, from inception to 1 August 2020. Search
terms included “zinc”, “magnesium”, “selenium”, “immune system” and “COVID-19”. Analyzing critically the scientific literature and focusing the attention on the articles that deepen the supportive role of these minerals in facing viral infections, such as COVID-19, a total of 8 articles were selected. Findings are summarized narratively below for each study and in Table 1.

**Zinc**

Zn is known to modulate antiviral and antibacterial immunity and to regulate the inflammatory response. Zn deficiency is associated with a higher prevalence of respiratory tract infections in both children and adults and with increased complications rate. Several in-vitro experiments confirmed a possible antiviral activity of Zn against COVID-19. In particular, Zn ionophore inhibits SARS-coronavirus RNA polymerase activity (Skalny et al. 2020). In vitro studies demonstrated increased antioxidant activity in respiratory epithelium and improved mucociliary activity both stimulated by Zn, the latter being typically reduced in COVID-19. All these experimental findings suggest a possible protective effect of Zn supplementation against COVID-19 (Skalny et al. 2020). A small observational study, however, has recently demonstrated the lack of a causal relationship between Zn and the survival of hospitalized COVID-19 patients, but the authors underline the limits of this kind of study, suggesting to use a prospective trial to establish the real utility of Zn (Yao et al. 2021).

**Magnesium**

Mg plays a role both in innate and adaptive immune systems, it is involved in balancing the inflammatory state and in maintaining adequate endothelial

| Author/Year | Type of article | Mineral | Outcome |
|-------------|-----------------|---------|---------|
| Iddir, 2020 | Review          | Micronutrients | Micronutrients as boosters of the immune system |
| Skalny, 2020 | Review          | Zinc     | Protective role against respiratory infections |
| Yao, 2020   | Observational study | Zinc     | No causal relationship on COVID-19 patients survival |
| Iotti, 2020 | Research study  | Magnesium| Deficiency may lead to more severe COVID-19 disease |
| Wallace, 2020 | Review       | Magnesium| Possible connection between low Mg levels and incidence of Sars-Cov 2 |
| Kieliszczek, 2020 | Research article | Selenium | Antiviral activity of selenium |
| Zhang, 2020 | Population-based retrospective study | Selenium | Association between COVID-19 cure rate and basal selenium status |
| Moghaddam, 2020 | Cross-sectional study | Selenium | Lower Selenium levels in COVID-19 non survivors compared to survivors |

Table 1. Characteristics of the included studies about the link between micronutrients and COVID-19.
function. The pro-inflammatory state created by low Mg levels increases the endothelial thrombogenicity, promotes platelet aggregation and diminishes endothelial fibrinolytic activity, leading to endothelial dysfunction (Iotti et al. 2020). Low Mg levels are also associated with chronic low-grade inflammation, correlating both with serum C reactive protein and IL-6 levels. Mg deficiency in Covid patients could exacerbate virus-induced inflammation and endothelial dysfunction. At present, there are no data about Mg homeostasis in COVID-19 infection, being Mg not routinely evaluated. An interesting survey was recently conducted comparing official data of current COVID-19 outbreak and available data on Mg intake (using the map of water hardness in USA), suggesting a possible connection between low Mg levels and incidence of Sars-Cov 2 (Wallace 2020).

**Selenium**

The immune system relies on a set of specific Se-proteins to perform its normal activity. Se possesses oxidant capacity determining an important antiviral activity. A recent study has shown an association between the cure rate from COVID19 and the basal Se status in different areas. Results could however be questionable due to possible confounders such as age and comorbidities (Zhang et al. 2020). Another recent study has analyzed Se levels in COVID-19 patients, discovering an overall deficiency in COVID-19 patients compared to healthy European adults. Se deficiency was found to be more severe in samples obtained from non-survivors as compared to COVID-19 survivors (Moghaddam et al. 2020). These studies could suggest that Se should be relevant in preventing infection and in modifying the disease course *per se*.

**Conclusion**

It is quite clear that further studies could better explain the role of Zn, Mg, Se in modulating the immune response against COVID-19. However, we already have results suggesting that an optimal micronutrient status in terms of Zn, Mg and Se is able to effectively strengthen the immune system during the COVID-19 infection.

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