Reply to LA Seale et al.

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Abstract:

We were very pleased that our finding of an association between coronavirus disease 2019 (COVID-19) outcome in China and selenium status (1) was endorsed by Seale and colleagues, based on their understanding of the likely mechanism by which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) interacts with the selenoprotein, cytosolic glutathione peroxidase (GPX1) (2).

Keywords: letter to the editor | COVID-19 | SARS-CoV-2 | selenoprotein

Article:

Dear Editor:

We were very pleased that our finding of an association between coronavirus disease 2019 (COVID-19) outcome in China and selenium status (1) was endorsed by Seale and colleagues, based on their understanding of the likely mechanism by which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) interacts with the selenoprotein, cytosolic glutathione peroxidase (GPX1) (2).

GPX1 is low in the hierarchy of selenoprotein expression, hence, it is among the first selenoproteins to be depleted in selenium deficiency (3). However, not only does selenium deficiency reduce the activity of GPX1 but it also significantly compromises the activity or concentration of other selenoproteins, including GPX4, thioredoxin reductase 1–3, and SELENOS, which have antioxidant or anti-inflammatory roles that are important in combatting viral infection (4). Infection with respiratory viruses, such as SARS-CoV-2, induces the production of reactive oxygen species and disturbs the host's redox balance, triggering pronounced inflammation and subsequent tissue damage (5). Moreover, excessive oxidative stress, in the absence of adequate GPX1, causes mutation of the viral genome, leading to the

emergence of more virulent strains (6). A variety of selenoproteins, in addition to GPX1, can counteract oxidative stress and inflammation, as provoked by SARS-CoV-2 (4).

The relative importance of GPX1 in the context of COVID-19 warrants further consideration. Platelet GPX1 activity, a more sensitive marker of selenium status than plasma GPX, was measured in a cohort of 119 healthy UK volunteers with a baseline selenium intake of 55 μg/d (7). GPX1 activity did not change significantly on supplementation of the volunteers with 50, 100, or 200 μg selenium/d, as selenium-yeast, over a period of 10 wk ($P = 0.16$), implying that an intake of 55 μg/d is sufficient to optimize GPX1 activity (7). We previously reported that the city of Enshi in Hubei province, with an intake of 550 μg/d, had a cure rate that was significantly higher than that of other Hubei cities (1). This implies the possible existence of a selenium-based mechanism or mechanisms for overcoming SARS-CoV-2 infection that are not solely based on optimization of selenoproteins and that may require a higher selenium intake, at least during the course of the infection.

On a separate issue, echoing our findings for China (1), Seale and colleagues also commented on the substantial regional differences observed in the severity of patient outcomes and case-fatality rates elsewhere (2). This being the case, they suggest "probing for selenium concentrations among both symptomatic and asymptomatic SARS-CoV-2–infected individuals." However, there is a problem in measuring selenium status by the usual methods of serum or plasma selenium in individuals who are already infected, as serum/plasma selenium concentration will fall as a result of the systemic inflammatory response (8). Erythrocyte selenium is not affected by inflammation and can be determined to give a reliable measure of selenium status (8). Alternatively, selenium can be measured in toenail clippings or hair, which will also not be affected by the inflammatory response, at least in the short term (9).

Despite the difficulties in the measurement of selenium status in infected individuals, it is possible to get some idea of their likely selenium status by their habitual location, as exposure to selenium from the diet is quite variable across the world (10). China exhibits the largest regional difference between maximum and minimum intake in any country; it may have been that fact that enabled us to see a significant difference between Chinese cities with respect to selenium status and cure rate (1). Of course, it is important to bear in mind that dietary-intake data are only estimations and are recognized to be of variable quality and accuracy and also that selenium supplementation is common, especially in the West (Figure 1).
Given those caveats, we are in agreement with Seale and colleagues in hoping that the link between selenoproteins, selenium species, and SARS-CoV-2 may be able to provide novel insights into mechanisms that will help us reduce the risk of infection and mortality from SARS-CoV-2 and other coronaviruses that may threaten us in the future. If appropriate, the efficacy of selenium species, which might include ebselen, should be explored in randomized controlled trials.

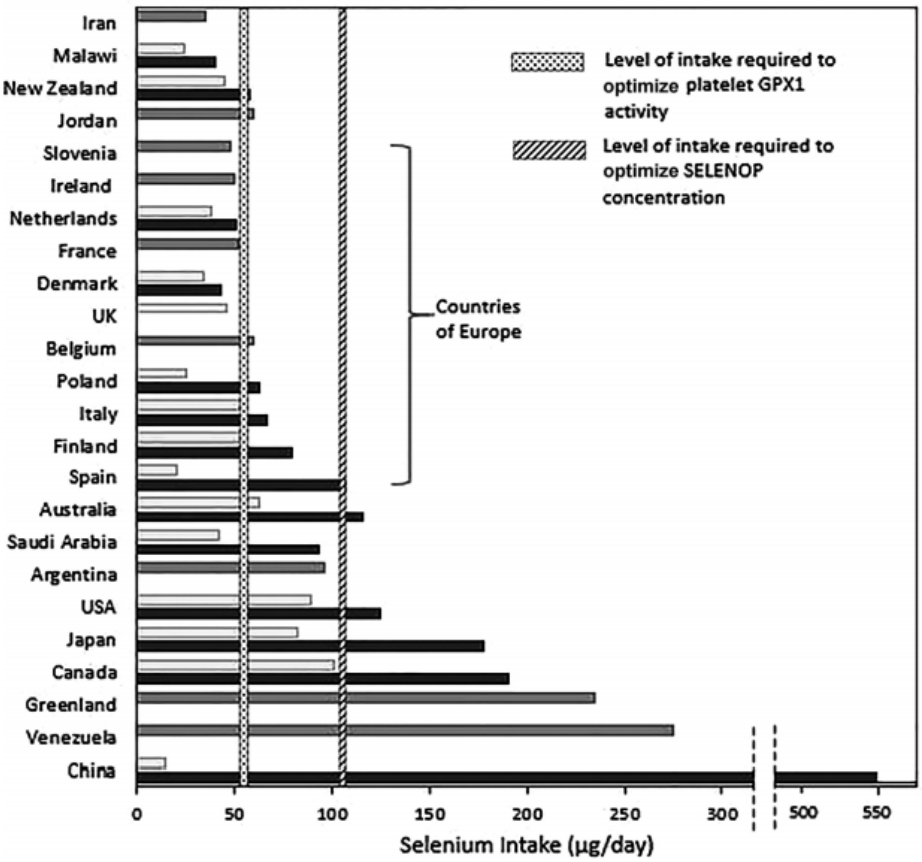

FIGURE 1. Selenium intake in different countries. The figure is based on data published since 2000, apart from the intake for Venezuela, which is pre-2000 but is included as the value is notably high. Where countries had >1 result, the highest values (dark grey) and the lowest values (pale grey) are shown. Where there was only 1 result or a median value, it is shown in medium grey. Dietary-intake data are recognized to be of variable quality and accuracy. Adapted from reference 10, with permission.

Notes

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