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# The effects of some essential and toxic metals/metalloids in COVID-19: A review

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## ARTICLE INFO

Handling Editor: Dimitrios Kouretas

### Keywords:

Metals  
Metalloids  
COVID-19 patients  
Deficiencies  
Toxic effects

## ABSTRACT

Thousands of studies have been conducted in order to understand in depth the characteristics of the novel coronavirus SARS-CoV-2, its infectivity and ways of transmission, and very especially everything related to the clinical and severity of the COVID-19, as well as the potential treatments. In this sense, the role that essential and toxic metals/metalloids have in the development and course of this disease is being studied. Metals/metalloids such as arsenic, cadmium, lead, mercury or vanadium, are elements with known toxic effects in mammals, while trace elements such as cobalt, copper, iron, manganese, selenium and zinc are considered essential. Given the importance of metals/metalloids in nutrition and human health, the present review was aimed at assessing the relationship between various essential and toxic metals/metalloids and the health outcomes related with the COVID-19. We are in the position to conclude that particular attention must be paid to the load/levels of essential trace elements in COVID-19 patients, mainly zinc and selenium. On the other hand, the exposure to air pollutants in general, and toxic metal/metalloids in particular, should be avoided as much as possible to reduce the possibilities of viral infections, including SARS-CoV-2.

## 1. Introduction

It is well known that metals and metalloids play an essential role in numerous biological, chemical and molecular processes. While trace elements such as cobalt, iron, zinc, manganese or copper are essential for humans, other elements (arsenic, lead, cadmium, mercury) have not any known functionality in the human body and are toxic at certain levels (Batista et al., 1996; Esplugas et al., 2019). For non-occupationally exposed individuals, exposure to metals/metalloids – either essential and/or toxic – occurs mainly through the diet, being inhalation and dermal minor exposure pathways. Essential trace elements regulate cellular homeostasis, humoral and cellular immune responses, and they also act as cofactors of a number of enzymes and antioxidant molecules (Cannas et al., 2020). By contrast, chronic/acute exposure to toxic metals/metalloids – or even to essential elements at high doses – may cause adverse effects, including cancer (e.g., arsenic, cadmium chromium, nickel), skin lesions (e.g., arsenic, beryllium, tin), neurological disorders (e.g., mercury, manganese, thallium), learning disability (e.g., lead), immunotoxicity (e.g., cadmium, lead), or respiratory problems (e.g., vanadium, chromium, cadmium) (Domingo et al., 2017; Esplugas et al., 2019; Nadal et al., 2011).

In recent months, the current pandemic situation due to the new viral infection caused by SARS-CoV-2 has generated thousands of investigations directly or indirectly related with COVID-19. On March 17, 2021, Pubmed (<https://pubmed.ncbi.nlm.nih.gov/>) includes around 113,000 publications containing the term COVID-19. However, among them, only about 400 papers are shown with the search term “metals and COVID-19”. Given the importance of heavy metals and trace elements in nutrition and human health, the present review was aimed at assessing the relationship between various essential and toxic metals/metalloids and COVID-19. Zinc, selenium, copper and iron were hereby included as essential trace elements, while the review of toxic metals did not exclude any element. The databases PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and Scopus (<https://www.scopus.com/>) were used for the bibliographic search. The search terms used were as follows: “metals”, “metaloids”, “trace elements”, “COVID-19” and “SARS-CoV-2”. The combination of search terms was done with the Boolean operator AND.

## 2. Metals/metalloids, the immune system and COVID-19

A proper functioning of the human immune system is absolutely key

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to prevent the infections caused by a number of respiratory viruses (Calder et al., 2020a; Jayawardena et al., 2020). Among the factors that can significantly influence the role of the immune system to fight against these viruses – including SARS-CoV-2 – there is a notable influence of nutritional and nutrigenetic factors, including nutraceuticals (Caccialanza et al., 2020; Calder, 2020b; Di Stadio et al., 2020; Galmés et al., 2020; Jayawardena et al., 2020; Junaid et al., 2020; Iddir et al., 2020; Im et al., 2020). In relation to this, the European Safety Authority (EFSA) reported that six vitamins (A, B<sub>6</sub>, B<sub>12</sub>, C, D and folate), as well as four trace elements (zinc, selenium, copper and iron), were essential for the proper functioning of the immune system. These micronutrients have impacts on some aspects of the immune function as a result of clinical deficiencies. In addition, increased susceptibilities to infections and poorer outcomes have been commonly found in cases of undernutrition (Lockyer, 2020).

Specifically regarding to COVID-19, Galmés et al. (2020) showed that the intake of micronutrients, particularly vitamins B<sub>12</sub>, C, D and iron, were inversely associated with higher COVID-19 incidence and mortality, especially in those groups of individuals who were genetically predisposed to a low micronutrients status. Interestingly, one of the main conclusions of this ecological study was that those countries whose populations showed the lowest intake of the above indicated nutrients, were also among the most affected by the COVID-19. It is well established that both metal deficiency and overload can result in abnormal cellular function or damage. However, from a clinical perspective, alterations of the concentrations of some metals can result in increased or decreased susceptibility to infection, which often also occur in response to infections (Chaturvedi et al., 2004; Weiss and Carver, 2018). Immunomodulatory agents – including micronutrients – are among some of the current therapies applied in clinical settings for the COVID-19 (Gasmi et al., 2020; Zhang et al., 2020a). In a recent review on the influence in the course and outcome of COVID-19, Fedele et al. (2021) highlighted the relevance of the nutritional status of the patients. With respect to trace elements, attention was paid to selenium, zinc and copper since these elements are basic due to its antioxidant role and ROS balance in inflammatory processes (selenium), reducing ROS in viral infections (zinc), and having a role in immunity, antimicrobial action due to its own toxicity, and also because its enhancement in macrophage activity in lung infection (copper). It was concluded that the efficiency of trace elements would strongly affect the COVID-19 prognosis. In turn, according to Ferrer et al. (2020), ensuring a balanced intake of trace elements and vitamins should be particularly beneficial for those patients with severe forms of COVID-19 suffering from critical immune dysregulation.

de Jesus and de Araújo Andrade (2020) and also more recently Dharmalingam et al. (2021) have reviewed this topic. Thus, de Jesus and de Araújo Andrade (2020) highlighted the challenges found in studies focusing on viral infections, as well as the implications for COVID-19, in a review on the role of trace elements in the immune system and the state of the art in metallomics. It was shown that trace elements play important roles in viral infections such as promoting the activation of immune cells, production of antibodies, and inhibition of virus replication. Nevertheless, these authors also noticed that the relationship between trace elements and infections caused by viruses is complex, taking into account that a number of specific functions of various elements remain still undefined. In turn, Dharmalingam et al. (2021) reviewed the role of trace elements in viral infections, paying special attention to COVID-19 and their interactions with the immune system. Trace elements supporting the function and development of the human immune system such as zinc, selenium and copper would reduce the risks of COVID-19. Although trace elements have immunomodulatory effects at various aspects, molecular mechanisms of many of them, which are related to both innate and acquired immunity, are not yet fully understood.

### 3. Essential trace elements and COVID-19

#### 3.1. Zinc

Zinc is after iron the most abundant trace element in the human body. This metal possesses strong immunogenic properties, being also known to bind to a number of proteins and modulating their activities. The importance of zinc for the development and function of the immune system has been demonstrated in a number of studies conducted in various species. Moreover, zinc has been also used in viral infections control. Based on its potent immunoregulatory and antiviral properties, the use of this trace metal was rapidly suggested for the potential treatment of COVID-19. Thus, in recent months, a number of studies on the impact of zinc supplementation on COVID-19 pathogenesis have been conducted. We next summarized some of the most relevant results.

Razzaque (2020) reported that consuming 40 mg/day of zinc could be beneficial against the SARS-CoV-2 infection, possibly by reducing the viral load and by enhancing the host resistance against the viral infection. Wessels et al. (2020) reviewed the available data on the role of zinc homeostasis during viral infections, focusing mainly on the potential benefits of zinc supplementation to prevent and treat SARS-CoV-2 infections. These researchers found that those patients suffering chronic diseases, especially older subjects, but also those individuals belonging to a COVID-19 risk group, were the most benefited by zinc supplementation. It was concluded that due to the direct antiviral properties of zinc, it might be assumed that administration of this essential element would be beneficial for most people, and especially for those with sub-optimal zinc status. Recently, the same authors arrived again to a similar conclusion, showing that zinc deficiency would mean a potential risk factor for increased susceptibility and severe progression of the COVID-19 (Wessels et al., 2021). In turn, Mayor-Ibarguren et al. (2020) hypothesized which could be the role of zinc in the immunological pathways related to COVID-19. They indicated that interleukin-6 (IL-6) plays an important role in severe lung injury due to COVID-19, whereas low levels of zinc are associated with higher IL-6 responses. On the other hand, zinc inhibits SARS-CoV-2 RNA polymerase, and therefore, its replication capacity. Based on these points, it was suggested that zinc supplementation could be a suitable treatment for those individuals at high risk of deficiency of this trace metal, who develop severe pneumonia due to COVID-19 (Mayor-Ibarguren et al., 2020).

It is well known that a proper nutrition can help to support an optimal immune function. In this sense, it has been reported that a number of vitamins (vitamin A, B<sub>6</sub>, B<sub>12</sub>, folate, C, D, E) and trace metals (zinc, selenium, copper, magnesium) support the cells of the immune system, while their deficiencies could increase the susceptibility of a host to infectious diseases. Thus, the potential role of various micronutrients – with particular attention to zinc – against various viral infections has been investigated and/or reviewed by a number of researchers. In a recent review, based on the results of *in vitro* tests, observational studies and clinical trials, Pecora et al. (2020) concluded that the role of vitamins A, C, and D, omega 3 fatty acids, as well as that of zinc was important and evident to modulate the immune response. However, these researchers also indicated that although nutritional supplementations should not necessarily prevent infections, or cure diseases such as COVID-19, it might help to decrease symptoms and to facilitate the recovery. Specifically, with respect to zinc, its deficiency has been linked to an increased susceptibility to infectious diseases caused by various microorganisms, including viruses. This deficiency can be due to certain specific diseases, aging, and lifestyle-associated factors (diet). Zinc supplementation has the potential to enhance antiviral – innate and humoral – immunity and also to restore depleted immune cell function and/or to improve normal immune cell function, in particular in immunocompromised and/or elderly patients. In this same line, Kumar et al. (2020) also hypothesized that zinc administration might be beneficial for the prophylaxis and treatment of COVID-19. On the other hand, Hoang and Han (2020) suggested the possible

application of hinokitiol ( $\beta$ -thujaplicin), which is a natural monoterpene considered as a safe zinc ionophore for the prevention and treatment of COVID-19, as well as other viral infections. Hinokitiol would help zinc to be transported into cells. Moreover, after reviewing the role of zinc in regulating the host defense and viral replications mainly focused on COVID-19, [Sharma et al. \(2020\)](#) also concluded that assuming that zinc is a structural component of numerous enzymes in the cell, zinc supplementation could help in treatment and prophylaxis of COVID-19.

Similar conclusions have been also drawn in various recent reviews aimed at assessing the potential positive role of zinc in COVID-19 treatment ([Joachimiak, 2021](#); [Celik et al., 2021](#); [de Almeida Brasiel, 2020](#); [Name et al., 2020](#); [Pormohammad et al., 2021](#); [Rahman and Idris, 2021](#)). In another recent review on the role of nutritional supplements as potential therapeutic adjuvants in COVID-19, [Costagliola et al. \(2021\)](#) concluded that the supplementation of vitamin D, probiotics, lactoferrin and zinc, might be useful as an adjuvant treatment in COVID-19, as well as in the prevention of viral spreading.

However, in contrast to the conclusions of most of the above discussed papers, some authors have not reported beneficial effects of zinc supplementation in patients diagnosed with SARS-CoV-2 infection. Recently, [Thomas et al. \(2021\)](#) assessed whether high-dose zinc and/or high-dose ascorbic acid could reduce the severity or duration of symptoms compared with usual cares-among ambulatory patients diagnosed with SARS-CoV-2 infection. A total of 214 patients received during 10 days, zinc gluconate (50 mg), ascorbic acid (8000 mg), both agents, or standard cares. Neither these high doses of zinc gluconate, ascorbic acid, or the combination of both, did not significantly reduce the duration of the symptoms associated with the coronavirus in comparison with usual cares. In another observational study, [Yao et al. \(2021a\)](#) examined the ratio of survival of 242 patients with COVID-19. Among these patients, 81% received zinc sulfate at doses of 440 mg/day (100 mg elemental zinc), while the rest were controls. The results showed a causal association between zinc and the survival of hospitalized patients with COVID-19, but subgroup analyses stratified by severity or additional therapies did not yield significant causal associations. Notwithstanding, the authors noted that their results were limited by the retrospective nature of the study and the possibility of residual confounding. Anyhow, these results were questioned by [Khurana et al. \(2021\)](#), who suggested that before concluding that zinc supplementation did not lead to a statistically significant decrease in mortality (or other outcome parameters), data clarifying which patients were zinc deficient, and which were not before receiving zinc supplementation, were clearly necessary. In this sense to measure zinc concentrations in serum would be key. In their reply, [Yao et al. \(2021b\)](#) agreed with that suggestion.

Nevertheless, other clinical investigations have corroborated the relationship between zinc deficiency in COVID-19 patients with poorer clinical outcomes. [Jothimani et al. \(2020\)](#) conducted a prospective study of fasting zinc levels in COVID-19 patients at the time of hospitalization. An initial comparative analysis was performed between healthy controls and COVID-19 patients, being patients with zinc deficiency, compared to those patients with normal zinc levels. Although the authors indicated that there is not a clear evidence whether zinc supplementation after admission to hospitals could reduce the severity of disease, it was shown that COVID-19 patients were zinc deficient when compared to healthy control adults. Low baseline zinc levels in these patients were associated with more complications, leading to prolonged hospitalization and increased mortality. This has been recently corroborated by [Gonçalves et al. \(2021\)](#), who in an observational study including 269 patients, found that low serum zinc levels were very prevalent at admission to the ICU for critically ill patients infected by SARS-CoV-2. It was also observed that inflammation plays a key role in viral infection pathogenesis at local (pulmonary) and systematic (cytokine storm) levels. Therefore, development of clinical trials in order to establish therapeutic nutrition with zinc, for critically ill patients with COVID-19, was recommended. In another recent observational study, a similar conclusion

has been also drawn by [Vogel-González et al. \(2021\)](#). These researchers have reported that having low levels of serum zinc ( $<50 \mu\text{g/dL}$  at the admission) is a risk factor that will determine the COVID-19 outcome, including a higher mortality. In turn, [Perera et al. \(2020\)](#) conducted a double-blind randomized controlled trial of daily high-dose intravenous zinc (0.5 mg/kg) versus placebo. There were 160 hospitalized participants, including 100 critically ill patients with confirmed COVID-19. The efficacy and safety of the zinc administration was assessed over a 7-day period, being the results positive. [Heller et al. \(2021\)](#) also investigated the zinc status of COVID-19 patients and its relevance for predicting survival. A profound and acute deficiency of this trace element in most COVID-19 patients – when admitted to the hospital – was observed in the 35 patients involved in this observational study. Results showed that when the serum zinc levels were within the reference ranges, high chances for survival were noted, while in zinc supplementation should be considered in those patients with substantial deficiencies.

### 3.2. Selenium

The metalloid selenium is basic for human health, being also particularly important for a well-balanced immune response. However, sub-optimal selenium status is not unusual across the world, especially in various areas/regions of China and Europe. Its essential role to human health is mainly due to the incorporation of this element into selenoproteins, which possess a wide range of protective functions. For example, the benefits of selenium supplementation were already demonstrated in viral infections, including HIV-1 ([Baum et al., 1997](#); [Steinbrenner et al., 2015](#); [Guillin et al., 2019](#)).

The levels of selenium were determined in hair samples of inhabitants of the Chinese region of Hubei in an ecological study conducted in China in February 2020 ([Zhang et al., 2020b](#)). This study was focused on associating the regional selenium and the reported outcome of COVID-19 cases. An increased virulence of COVID-19 was related with selenium deficiencies among other nutrients. GPX1 (glutathione peroxidase 1) is a cytosolic selenoenzyme that has known antiviral properties, which is clearly impacted by the selenium status. In relation to this, [Seale et al. \(2020\)](#) suggested that the interaction between the GPX1 detoxifying system, and the main protease ( $\text{M}^{\text{pro}}$ ) of SARS-CoV-2, could mean a novel molecular target for COVID-19. Although it has not been demonstrated yet, it might provide novel insights into mechanisms leading to the severity of COVID-19, as well as to identify the population groups taking benefit from selenium supplementation. Considering that selenium is found in various chemical forms and taking into account that various pharmacological preparations can drive to blood increased concentrations of selenium, [Kieliszek and Lipinski \(2020\)](#) have suggested that sodium selenite, but not selenate, can oxidize thiol groups in the virus protein disulfide isomerase, rendering it unable to penetrate the healthy cell membrane. Consequently, selenite would inhibit the entrance of viruses into the healthy cells, suppressing their infectivity. These authors indicated that sodium selenite could offer a real protection against COVID-19.

[Bae and Kim \(2020\)](#) reviewed the roles of vitamins C and D, as well as that of selenium in the immune system. The beneficial effects of these micronutrients to reduce the risk of infectious diseases in general, and COVID-19 in particular, were also reviewed. Based on the results of a number of studies, the immunomodulatory properties of selenium were clearly corroborated. Thus, this trace element prevents mutations in viral genome, being important for the function of cytotoxic effector cells, such as  $\text{CD8}^+$  T cells and natural killer cells. Selenium is also important for maintaining T cell maturation and functions, as well as for T cell-dependent antibody production. With respect specifically to COVID-19, the importance of higher selenium concentrations in the survival of COVID-19 patients was evident when compared to the levels of deceased patients. A higher recovery rate from COVID-19 in those patients showing higher concentrations of selenium was also observed. [Im et al. \(2020\)](#) conducted a study to assess the levels of various

nutrients in COVID-19 patients. The results showed that many of those patients were deficient in vitamin D (76%) and selenium (42%). However, no significant increases in the incidences of deficiency in patients with COVID-19 was observed for vitamins B<sub>1</sub>, B<sub>6</sub>, and B<sub>12</sub>, folate and zinc. In a recent review of the scientific literature on the role of selenium and viral infections, [Bermano et al. \(2021\)](#) suggested that selenium status might be an additional risk factor to be considered as determinant for the SARS-CoV-2 infection outcome. This factor could be especially relevant in those when selenium intake is sub-optimal or low, and therefore, selenium would be playing a crucial role in the immune and inflammatory responses caused by SARS-CoV-2. Selenium supplementation – as potentially beneficial in limiting the severity of symptoms of COVID-19 – was also suggested by this author. As an appropriate biomarker to monitor selenium status in COVID-19 patients, erythrocyte selenium was used by these researchers. Regarding biomarkers, [Pince-mail et al. \(2021\)](#) identified blood biomarkers of oxidative stress including antioxidants, trace elements, and oxidative damages to lipids in COVID-19 patients. They also analyzed the relationship with inflammation as a major source of ROS production. The systemic oxidative stress status was strongly altered in critically ill COVID-19 patients. An increased lipid peroxidation was observed, but also deficits in some antioxidants (vitamin C, glutathione, thiol proteins), as well selenium.

In another review on selenium and COVID-19, [Zhang et al. \(2020b\)](#) revised the evidences for the involvement of this metalloid, and selenium species, or selenoproteins, in viral infections. The following issues were specifically examined: a) the role of the selenoproteins in combatting viral infection; b) the evidence for the effects of selenium/selenoproteins on viral pathogenicity, including data that link them with SARS-CoV-2/COVID-19; c) the effect of selenium/selenoproteins on immunity and production of inflammatory cytokines; d) the possible viral targeting of selenoprotein mRNAs by antisense and related mechanisms; e) the potential mechanisms by which selenium species, including selenoproteins, might affect COVID-19 outcome; and f) whether selenium supplementation could benefit SARS-CoV-2 infected subjects. According to the bibliographic data, it was concluded that would be very unlikely that a supranutritional dose of selenium could result in toxicity in COVID-19 patients, being in contrast potentially beneficial for those individuals with moderate-to-severe symptoms. The use of selenium in the therapy of COVID-19 patients has been also proposed by [Manzanares et al. \(2021\)](#). These authors, based on the sufficient evidence on the anti-inflammatory, immunologic and antioxidant properties of selenium, have suggested to conduct in-depth investigations on the metabolic and clinical aspects of selenium pharmaconutrition as a potential adjuvant therapy against COVID-19. The supplementation of various nutrients, including selenium, has been also suggested by [Shakoor et al. \(2021\)](#).

[Majeed et al. \(2021\)](#) determined the serum selenium levels in COVID-19 patients from India and control subjects, in order to understand the correlation between the concentrations of this element, the viral infection and recovery. COVID-19 patients showed significantly lower selenium concentrations:  $69.2 \pm 8.7$  ng/mL than control individuals  $79.1 \pm 10.9$  ng/mL. In turn, [Moghaddam et al. \(2020\)](#) hypothesized that severe selenium deficiency could be prevalent among COVID-19 patients with poor survival. In a cross-sectional study, serum samples from COVID-19 patients were collected and analyzed for total Se and selenoprotein P. It was found that selenium status was significantly higher in serum samples from surviving COVID-19 patients than in those of non-survivors: selenium,  $53.3 \pm 16.2$  vs.  $40.8 \pm 8.1$  µg/L, and selenoprotein P,  $3.3 \pm 1.3$  vs.  $2.1 \pm 0.9$  mg/L. The observed association of mortality risk with selenium deficit suggests once more the interest of supplementation of this trace element in COVID-19 patients. In this same line, [Heller et al. \(2021\)](#) carried out a study focused on the prediction of survival odds in COVID-19 by age, zinc and selenoprotein P as composite biomarker. The results showed that zinc and selenoprotein P status – within the reference ranges –

would indicate high survival odds in COVID-19. Therefore, it was assumed that correcting a diagnostically proven deficit in selenium (also in zinc), by a personalized supplementation, could support convalescence.

### 3.3. Copper

Copper is another essential trace element that plays a key role in immune function and free-radical defense. This metal is essential for both, pathogens and the hosts, in viral infections. Therefore, copper has been clinically used to reduce the risks of bacterial and viral contamination. Copper, as other transition metals, has a notable affinity for biological ligands and redox properties. This makes it ideal to drive biochemical reactions involving redox and oxygen chemistry. However, these same chemical properties, which make copper a superb enzymatic cofactor, render the metal potentially toxic, being especially notorious for unicellular microbes. Thus, the antimicrobial properties of copper make it useful as effective biocides for pathogens from COVID-19 to eukaryotic pathogens ([Culbertson and Culotta, 2020](#)).

Recently, [Cortes and Zuñiga \(2020\)](#) reviewed the scientific literature about the use of copper to prevent the potential transmission of influenza viruses and SARS-coronaviruses. According to these authors, the published data would support the use of this essential metal to inactivate viruses and a wide range of microorganisms. The reviewed studies also suggested that copper could be effective to help reducing transmission of infectious diseases, such as the coronavirus. However, these authors were cautious in their conclusions, suggesting that more research should still be conducted to support the potential use of copper in the SARS-CoV-2 infections. Regarding this, [Fooladi et al. \(2020\)](#) also suggested that, based on the available data, clinicians should consider copper insufficiency in their critically ill COVID-19 patients. Notwithstanding, these authors also remarked that attention should be paid to the copper toxicity, the potential adverse responses depending on copper dose, as well as the duration of copper misbalance. The current US Recommended Intake of copper is 0.9 mg/day, but dietary studies have suggested that even 1.03 mg of copper per day might be insufficient for adult men. In this sense, [Raha et al. \(2020\)](#) suggested that an optimal intake level of copper for humans could be 2.6 mg/day. Based on their estimations, these authors suggested that nowadays, a large portion of the general population might have insufficient dietary copper intake and mild copper deficiency. Therefore, and taking into account the potent capacity of contact killing of various viruses, including SARS-CoV-2, these authors hypothesized that copper supplementation might mean some protection for COVID-19 patients. [Andreou et al. \(2020\)](#) reviewed the scientific literature regarding virucidal agents and investigational medicinal products for COVID-19, acute inflammation's mechanism, immune response to inflammation, and COVID-19 clinical manifestation. Since copper could play a role in the immune system response to inflammation, this trace metal was also included in the review. Since copper has shown strong virucidal effects, acting on the virus itself, the authors suggested that copper might be combined with N-acetylcysteine (NAC) at the early stages of the infection in order to decrease viral RNA levels. Consequently, it was concluded that in combination with the blocking of RNA replication by antivirals, copper, NAC and nitric oxide (NO) could potentially contain – or even stop – the infection at early stages. In a review entitled “The Yin and Yang of copper during infection”, an interesting hypothesis on the effects of copper during infection was raised a few years ago by [Besold et al. \(2016\)](#). These authors hypothesized that the animal host could also thwart pathogen growth by limiting their copper nutrients. This would happen in a similar way to the well-documented nutritional immunity effects for starving microbes of essential zinc, manganese and iron micronutrients.

### 3.4. Iron

Iron is another trace element that plays an important role in various

immune processes, being also essential for some enzymes that are involved in important activities of immune cells. The role of iron in the immune system seems to be linked to decreased numbers of naïve T-helper and T-cytotoxic cells, which have been observed in iron-deficient subjects. It would suggest that iron is required for the regeneration of new CD4<sup>+</sup> T cells and the maintenance of T-cell cytolytic processes. It has been also suggested that iron alters the balance between pro- and anti-inflammatory cytokines (Lockyer, 2020). Anyhow, the role that iron plays in COVID-19 is rather different from that of other essential trace elements, such as zinc and selenium.

Recently, Ersöz and Yılmaz (2021) reported the results of a retrospective observational study conducted to determine the levels of vitamin B<sub>12</sub>, vitamin D, folate, and iron in COVID-19 patients in the first quarter of the pandemic in Turkey. It was found that the iron levels in serum of the patients were low. The results showed that iron, folate, and vitamin D deficiency in serum, and excess of vitamin B<sub>12</sub>, were correlated with bad prognostic factors (hospitalization to ICU, intubation, and death). It was concluded that monitoring of micronutrient levels might be beneficial during the COVID-19 pandemic. Although ferritin – a representative of total body iron stores – is a more reliable marker showing iron levels in the body under normal conditions, it can reach very high levels in COVID-19 infection due to its acute phase reactant. For that reason, it was not directly measured in that study. In another retrospective observational study conducted in Pakistan focused on evaluating serum ferritin for the prediction of the severity and mortality of COVID-19, Ahmed et al. (2021) concluded that on the admission of patients to the hospital, ferritin concentration would be a predictor of mortality, although it might not reliably predict the severity of the disease. The ferritin levels in the non-survivor group of patients were significantly higher than those found in the survivors. On the other hand, Akhtar et al. (2021) have reviewed the role of nutrition in preventing and reducing the severity of COVID-19, with a focus on various micronutrients. With respect to iron, it was considered that its role in innate immunity would be to regulate production of cytokines and to improve phagocytosis, while in adaptative immunity, it increases T-cell proliferation and improves cytotoxic T-cell function. These authors also highlighted that deficiencies of micronutrients, including zinc, selenium and also iron, are being common among vulnerable populations in general, and in COVID-19 patients in particular, which might increase the risks of mortality in these patients.

In contrast to the above data suggesting that iron supplementation in iron deficient individuals offers immune enhancing benefits, it has been also reported that this trace element can exacerbate infections and inflammation (Ganz and Nemeth, 2009). Evidence in the context of SARS-CoV-1 and MERS-CoV suggests that iron is important for viral replication (Liu et al., 2020). According to Augustine et al. (2020), oral iron supplementation in the presence of inflammation might lead to enhanced oxidative stress and adverse gut microbiome. This, together with the hypothesis that iron chelators could be considered as adjuvants to treat COVID-19 (Liu et al., 2020; Habib et al., 2021), led these authors to be concerned about the safety and effectiveness of iron supplementation programs during COVID-19 pandemic (Augustine et al., 2020). On the other hand, various manifestations of COVID-19, such as inflammation, hypercoagulation, hyperferritinemia, as well as immune dysfunction, are also reminiscent of iron overload. It would point to the assumption that iron overload could be a potential contributor to the pathogenesis of COVID-19 (Habib et al., 2021). Since the iron chelator lactoferrin exerts immunomodulatory and anti-inflammatory effects, and it can bind to various receptors used by coronaviruses thereby blocking their entry into host cells (Kell et al., 2020), Habib et al. (2021) have suggested that a supplementation of lactoferrin would benefit the immune system, and would reduce inflammation by modulating cytokine and ROS production, which in turn reduces iron overload. Moreover, Mohseni et al. (2021) did not find significant differences between groups in the percentages of vitamin C, D<sub>3</sub>, zinc, iron and multivitamin supplements intake in the last six months, when the role of body mass

index and the history of nutritional supplementation were examined in relation to the severity of COVID-19.

#### 4. Essential trace elements and COVID-19: clinical results

Muhammad et al. (2021) measured in Nigeria the concentrations of various antioxidants and oxidative stress markers in 50 COVID-19 patients. The levels of the trace elements selenium, zinc, magnesium, copper and chromium were determined in plasma, being the results compared with the concentrations corresponding to 21 healthy subjects. The levels of selenium, zinc, magnesium and copper were significantly lower in COVID-19 patients than in controls, while chromium did not show significant differences. On the other hand, Zeng et al. (2021a) determined in COVID-19 patients the urinary levels of various essential and toxic metals/metalloids, including arsenic, cadmium, chromium, copper, lead, manganese, mercury, selenium and thallium, in order to establish the potential relationship with the severity of the disease (either severe or non-severe) and the outcomes (recovered or deceased). The urinary concentrations of most analyzed elements were found to be higher in severe patients than in the non-severe cases. Among the severe cases, the levels of these elements were also higher in the deceased subjects than in those in the recovered group. It was concluded that urinary concentrations of these trace elements were associated factors for the prognosis of severe COVID-19. On the other hand, Taheri et al. (2020), by reviewing the available scientific information on the concentrations of various serum electrolytes and micronutrients in patients with COVID-19, concluded that the trace elements and electrolytes levels (zinc, selenium, iron, potassium, sodium, calcium, magnesium and copper) in the blood circulation had important roles to alleviate or increase the severity of the disease, resulting affected the mortality rates of the COVID-19 patients.

#### 5. Toxic metals/metalloids and COVID-19

In recent decades, a considerable number of studies have demonstrated that increases in outdoor air exposure affect people's health outcomes, directly and indirectly. Although air pollution is a major environmental health hazard for the general population, the scientific literature regarding the extent, range, and nature of the influence of outdoor air pollution with respect to human health is not especially abundant. On the other hand, the role of respiratory viruses in the pathogenesis of severe respiratory infections is an issue of great importance. In this sense, the outbreak of the severe acute respiratory syndrome (SARS), the emergence of the Middle East respiratory syndrome (MERS), but very especially the appearance of the SARS-CoV-2, have brought an extraordinary attention to these serious pathogens, particularly in respiratory tract infections (Domingo and Rovira, 2020). Since initially COVID-19 was already characterized as severe acute respiratory syndrome, it does not seem a banal hypothesis that those environmental pollutants, which can negatively affect the respiratory system, can also have a significant influence on the severity of the respiratory problems in COVID-19 patients. In relation to this, particulate matter (PM), sulfur dioxide, nitrogen oxides, ozone, carbon monoxide, volatile organic compounds (VOCs) and polycyclic aromatic hydrocarbons (PAHs) are among the outdoor air pollutants that in humans may cause adverse respiratory effects. In a recent review of the scientific literature, we found clear evidences supporting an association between air concentrations of some pollutants and human respiratory viruses interacting to adversely affect the respiratory system (Domingo and Rovira, 2020). Particular attention has been paid to the association between air pollutants and the transmission and severity of the effects caused by SARS-CoV-2 (Domingo and Rovira, 2020; Domingo et al., 2020; Marquès et al., 2021). Based on the results of most studies, we concluded that chronic exposure to certain air pollutants is leading to more severe and lethal forms of COVID-19 and delays/complicates the recovery of patients suffering this disease (Domingo et al., 2020).

In addition to the above indicated pollutants, exposure to certain toxic metals/metalloids such as arsenic, cadmium, chromium, lead or vanadium can also cause negative effects on the human respiratory system (González et al., 2021; Grzywa-Celińska et al., 2020; Oh et al., 2014). Recently, Park et al. (2020) investigated the association between cadmium and mortality from influenza and pneumonia in US adults. The results suggested that a higher cadmium burden is associated with higher mortality from influenza/pneumonia. Based on the evidence showing that cadmium's mode of pulmonary toxicity probably occurs through immunotoxicity and amplifying inflammation, these researchers suggested that would be possible that higher cadmium burdens could worsen outcomes from COVID-19 infections, for which evidence suggests that the main mechanism involves marked amplification of inflammation (Fu et al., 2020). On the other hand, Zeng et al. (2021a) showed that the urinary concentrations of various metals/metalloids (chromium, manganese, copper, cadmium, mercury, arsenic and thallium) were associated with the prognosis of severe COVID-19. These authors have recommended that trace elements should be persistently monitored, not being only useful for the identification of COVID-19, but also as a help for the evaluation of the dynamic changes that appear in COVID-19 patients. Recently, this same research group reported the results of a retrospective study in a cohort of 306 confirmed COVID-19 patients from Wuhan, China (from February 10 to March 15, 2020), which was aimed at determining potential associations of whole blood levels of various essential and toxic metals/metalloids with the severity of the disease and mortality (Zeng et al., 2021b). Among the severe COVID-19 patients, the levels of chromium and cadmium were higher, while the concentration of arsenic was lower in the deceased group. It was concluded that iron and arsenic levels in whole blood, as well as age and sex, were independent factors associated with the disease severity. In turn, the whole blood concentrations of cadmium and chromium, as well as comorbidities of cardiovascular diseases, were independent factors associated with respect to the mortality. Recently, in an excellent paper by Skalny et al. (2020), data on the potential role of four toxic metals (arsenic, cadmium, lead and mercury) in the development of respiratory dysfunction, immunotoxicity, and interference of metal toxicity with viral diseases, were reviewed. This review was based on epidemiological and experimental studies to demonstrate the potential crossroads between metal exposure and the COVID-19 severity risk. It was noted that human exposure to arsenic, cadmium, lead and mercury was associated with respiratory dysfunction and respiratory diseases. An association between toxic metal exposure and the severity of viral diseases was also found, which could be considered a consequence of the adverse effects of metal exposure on adaptive immunity. The authors concluded that a reduction of toxic metal exposure should be taken into account in order to decrease the susceptibility and severity of viral diseases affecting the respiratory system, including COVID-19.

On the other hand, it is evident that the immunologic system plays a key role in the development and prognosis of COVID-19. In turn, the link between environmental pollution and immunity is of particular interest as various pollutants may provoke immunotoxic effects. Among these pollutants, some toxic metals can cause immunotoxicity in humans (Cohen, 2018; Hultman and Pollard KM, 2015; Quinete and Hauser-Davis, 2021). Environmental factors, such as air and drinking water contaminants, may contribute to the increased prevalence of allergies and autoimmune diseases, many of which are due to the activity of Th17 T cells (Tsatsakis et al., 2020). Cadmium is one of the toxic metals with more information available. Various studies have pointed to this toxic metal as an important health hazard for the immune system. This element attenuates the macrophage response to lipopolysaccharide through inhibition of the NF- $\kappa$ B pathway (Cox et al., 2016), while the ability of cadmium in the modulation of the innate, adaptive and mucosal immune responses related with the release of chemokine, gene expression, and susceptibility to microbial infections has also been demonstrated (Hossein-Khannazer et al., 2020). Cadmium induces also immune alterations that might compromise host defense against

pathogenic microorganisms and homeostatic reparative activities (Mirkov et al., 2021).

## 6. Conclusions

In this paper, we reviewed the scientific literature regarding the role of zinc, selenium, copper and iron, as well as that of the toxic metals/metalloids, on the infectivity of SARS-CoV-2, and the development and prognosis of COVID-19 in infected subjects.

The deficits of zinc and selenium seem clearly to play a negative role in COVID-19 patients, being their supplementation recommended in many cases. On contrary, the supplementation of copper and iron to COVID-19 patients is not obvious. Anyhow, the role of these trace elements is clearly linked to the immune system of the COVID-19 patients, which is crucial in this disease.

On the other hand, the role of the toxic metals/metalloids in COVID-19 patients is well defined. Human chronic exposure – and tissue accumulation – to toxic elements such as arsenic, lead, cadmium, chromium or vanadium, among others, means that at certain levels and time of exposure they can cause immunotoxicity, as well as adverse effects on the respiratory system. Therefore, those individuals whose immune and respiratory systems can already be negatively affected by chronic exposure to toxic elements – and other environmental pollutants – very probably will suffer from COVID-19 with greater severity.

In summary, in COVID-19 patients, special attention must be paid to their load/levels of essential trace elements, mainly zinc and selenium. On the other hand, the exposure to air pollutants in general, and toxic metal/metalloids in particular, should be avoided as much as possible to reduce the possibilities of viral infections, including SARS-CoV-2.

## Credit authors statement

Both authors Jose L Domingo and Montse Marquès equally contributed to prepare this Review-Manuscript: searching of the scientific literature (PubMed and Scopus), writing the paper, reviewing it and editing it.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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