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Applied nutritional investigation

## Pharmac nutrition revisited for critically ill patients with coronavirus disease 2019 (COVID-19): Does selenium have a place?



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### ABSTRACT

Coronavirus disease 2019 (COVID-19) is a global pandemic causing one of the biggest challenges for critical care medicine. Mortality from COVID-19 is much greater in elderly men, many of whom succumb to acute respiratory distress syndrome (ARDS) triggered by the viral infection. Because there is no specific antiviral treatment against COVID-19, new strategies are urgently needed. Selenium is an essential trace element with antioxidant and immunomodulatory effects. Poor nutritional status increases the pathogenicity of viruses and low selenium in particular can be a determinant of viral virulence. In the past decade, selenium pharmac nutrition studies have demonstrated some reduction in overall mortality, including how reduced incidence of ventilator-associated pneumonia and infectious complications such as ARDS in the critically ill. Consequently, we postulate that intravenous selenium therapy, could be part of the therapeutic fight against COVID-19 in intensive care unit patients with ARDS and that outcomes could be affected by age, sex, and body weight. Our working hypothesis addresses the question: Could high-dose selenite pharmac nutrition, as an early pharmacologic intervention, be effective at reducing the incidence and the progression from type 1 respiratory failure (non-ARDS) to severe ARDS, multiorgan failure, and new infectious complications in patients with COVID-19 patients?

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### Coronavirus disease 2019 (COVID-19) background

At the end of 2019, in the city of Wuhan, Chinese health authorities reported the first cases of a potentially fatal disease in humans, characterized by severe pneumonia and acute respiratory failure due to a novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Coronavirus disease 2019 (COVID-19) subsequently spread rapidly worldwide and has now become a global pandemic, resulting one of the biggest challenges for critical care medicine [1]. According to the World Health Organization in May 2020 there were 5.5 million cases worldwide and ~350,000 deaths [2]. The estimated case fatality rate in China was 2.3%, while it was 7.2% in Italy. Mortality has been much higher in patients >80 y of age (20.2% in Italy and 14.8% in China), particularly in those with preillness comorbidities such as diabetes

mellitus, cardiovascular disease, obesity, cancer, and chronic respiratory disease [3]. Moreover, COVID-19 appears to be deadlier in men, with a fatality rate of 2.8% in Chinese men compared with 1.7% in women. To date, there is no specific antiviral treatment against SARS-CoV-2, and new strategies are urgently needed [3].

### The inflammatory response

Although current knowledge about the immune response to COVID-19 is limited, recent evidence after histopathologic examinations of lung tissues have found severe alveolar epithelial damage with nonspecific innate immune response, swelling, hyperplasia, and necrosis [4]. Acute respiratory distress syndrome (ARDS) is a sepsis-related process fueled by a cytokine storm, which is triggered by a viral infection. Excessive lung parenchyma inflammation is responsible for severe, life-threatening hypoxemia requiring mechanical ventilation and prolonged stay in the intensive care unit (ICU) and hospital [5]. Both respiratory failure phenotypes: type 1 (non-ARDS or isolated viral pneumonia), and type 2 (“true” ARDS or “typical” ARDS with low pulmonary compliance) exhibit an exaggerated immune response from the cytokine storm [5]. Early diagnosis

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and differentiation is crucial as there are clinical implications that can determine first-line treatment.

Hypercytokinemic inflammation in patients with COVID-19, as in other viral infections, shows a cytokine profile similar to the macrophage activation syndrome characterized by very high levels of proinflammatory cytokines, notably interleukins (IL)-6, IL-1 and IL-17, granulocyte macrophage-colony stimulating factor, and tumor necrosis factor (TNF)- $\alpha$  [6]. Notably, the elderly and others with comorbidities have exhibited the most aggressive inflammatory response, a phenomenon that has not so far been well understood. Unfortunately, with no specific treatment for SARS-CoV-2 infection, the overall ICU mortality in many countries remains unacceptably high at >60%, underlining the urgent need for new therapeutic strategies [7].

### Selenium and viruses

Reducing the incidence of severe ARDS, multiorgan failure, and new infectious complications, especially in elderly men where micronutrient deficiencies have been associated with severe adverse events during viral infections, is a worthwhile aim [8,9]. In this clinical scenario, early repletion of micronutrients such as selenium should be a mandatory part of critical care nutrition. Specifically, we would argue that pharmaconutrition with high-dose selenium, as intravenous (IV) sodium selenite, is worthy of re-investigation.

Selenium is an essential trace element for humans, present in selenoproteins as the 21st amino acid selenocysteine [10]. The antioxidant, immunologic, and anti-inflammatory properties of selenium have made it one of the most extensively studied micronutrients in the critical care setting [10]. The glutathione peroxidase (GPx) family catalyses the interconversion of glutathione (GSH) and its oxidized form, glutathione disulfide (GSSG) [11]. The GSH/GSSG redox system facilitates the reduction of various hydroperoxides and oxidized forms of other antioxidants. Inadequate selenium status not only compromises GPx status but also cellular and humoral immunity, which are linked to an inflammatory response involving the production of free radicals and redox control processes [10,11]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS), including free radicals, increase expression of proinflammatory cytokines such as IL-6, and TNF- $\alpha$  through upregulation of nuclear factor- $\kappa$ B activity where the selenium status of the host may play a role in viral evolution, which has been associated with sepsis [11,12].

In plants and food, selenium is mainly present as the amino acids selenomethionine and selenocysteine [13]. However, these organic forms of Se<sup>2+</sup> are not available for IV supplementation. Thus, in the critical care setting selenium has been mostly administered as inorganic selenite or selenious acid [10]. It is important to note that the conversion of selenite substrates to the element's divalent form facilitates oxidation of sulphhydryl groups in protein disulphide isomerase (PDI), which plays an important role in viral pathogenesis and the spread of infection [14]. Thus, the divalent form of selenium shows oxidizing capacity reacting with thiol groups in the active site of viral PDI, converting them to inactive sulphhydryl groups. In this way, selenium as selenite may be able to inhibit the entrance of SARS-CoV-2 in host cells, impeding its ability to infect healthy individuals [14].

It is well established that poor nutritional status of the host increases pathogenicity of viruses, increasing either susceptibility to illness or its severity in nutrient-deficient animals [15]. According to the literature, several host nutritional factors have long been associated with an effect on a viral pathogen, specifically by altering its genome, which can affect the viral expression, producing a

new pathogenic viral phenotype [12]. Viral infection and T helper 1-related cytokines trigger the production of high amounts of ROS and RNS due to the induction of inducible nitric oxide synthase enzyme [16]. Concomitantly, the synthesis of antioxidant selenoenzymes such as GPx-1, GPX3, and selenoprotein P (SELENOP) is downregulated in the infected cells. Thus, oxidative/nitrative stress and depletion of endogenous antioxidant levels enhance viral replication and the viral RNA mutation rate, inducing severe tissue damage in the infected host [12,15,16].

Over the past 4 decades, various studies have demonstrated the role of selenium status as a determinant of viral virulence. An elegant Chinese mice study in 1980 showed that the lower the selenium status, the higher the heart injury in coxsackievirus B4-infected animals [17]. Also, a benign strain of coxsackievirus B3 may become virulent and cause myocarditis in selenium-deficient mice. Interestingly, Levander et al. [18], in another mouse model, showed that selenium deficiency increased the virulence of an already virulent strain of coxsackievirus B3 and selenium deficiency was associated with the conversion of a non-virulent strain into virulent coxsackievirus with mutations in the viral genome.

In the early 1930s, clinical observations of juvenile cardiomyopathy by Chinese researchers during the outbreak of Keshan disease [18], found a higher incidence of the disease in selenium-deficient regions, as well as a protective and preventive effect of selenite supplementation. Clinicians also found a seasonal and annual variation, which suggested the presence of a viral agent [18,19]. This suspicion was later confirmed by analysis of tissues from patients with Keshan disease, which revealed the presence of coxsackieviruses. Similarly, selenium deficiency has been demonstrated in other infections caused by RNA viruses that include common human pathogenic viruses influenza A, HIV, hepatitis C virus, Ebola virus, and potentially the novel coronavirus SARS-CoV-2 [12].

In addition to northeast China, many other geographic regions, including parts of east Asia, Australasia, Europe, Africa, and South America have populations with low selenium status, which mostly depends on selenium content in soils [10,12]. Increasing mortality has been associated with decreasing selenium intakes [11]. Recently, in a retrospective Chinese study, Zhang et al. [20] analyzed data from the Baidu website. The authors looked for associations between regional or city mean hair selenium content and recovery outcomes in COVID-19 patients. Through weighted linear regression models, the authors found a positive correlation between selenium status and the cure rate, concluding that the higher the selenium intake and selenium status, the better the COVID-19 cure rate [20]. This constitutes the first report showing a higher SARS-CoV-2 pathogenicity and mortality rate in selenium-deficient Chinese patients with COVID-19, but supports the results from an earlier volunteer study in the United Kingdom [21], where the low selenium status may have accelerated viral replication by downregulating the immune response and increasing the permissiveness of the host for viral replication. These data could have implications for other RNA viruses, leading us to speculate that increasing GPX3 activity with selenium supplementation could improve immune function and downregulate systemic inflammation in patients with COVID-19.

### Selenium pharmaconutrition

In critically ill patients with sepsis/septic shock we and others have previously demonstrated an early reduction in serum/plasma selenium levels due to capillary leakage [22]. SELENOP is the major selenoenzyme, accounting for  $\leq$ 60% of plasma selenium [11]. As critical illness is characterized by low plasma selenium concentration, SELENOP decreases early in ICU patients with systemic

inflammation and multiorgan failure. In 2009, this was demonstrated by Forceville et al. [23], who found that SELENOP decreases earlier than GPX3 activity in those patients with sepsis and septic shock. Low selenium status in sepsis negatively correlates with illness severity and when measured at ICU admission may be useful as an early predictor of ICU survival [22]. In this context, high-dose parenteral selenium monotherapy has been extensively studied in different ICU patient populations and early results were encouraging [10]. The majority of randomized clinical trials (RCTs) published between the late 1990s and 2015 reported that selenium pharmaconutrition with IV selenite as sodium selenite/selenious acid was well tolerated, optimized selenium status, and enhanced activity of antioxidant selenoenzymes such as GPx and SELENOP [10]. These trials all demonstrated some improvement in clinical outcomes, such as overall mortality and reduced incidence of ventilator-associated pneumonia (VAP) and infectious complications in the critically ill [10].

Everything changed in 2015, when the REDOXS (Reducing Deaths due to Oxidative Stress) study [24] of high-dose glutamine dipeptide and antioxidants (including selenium) concluded that antioxidant supplementation conferred no therapeutic benefit for the critically ill. The choice of patients and inappropriate “off-label” dosage of the dipeptide has been a common criticism of this study. Indeed, it could be postulated that an insufficient dose of selenium or an ineffective dosing schedule may have been employed for the selenium arms of the investigation. Furthermore, absence of an effect from selenium pharmaconutrition might have been due to the fact that many patients were not selenium depleted. North Americans mostly have adequate selenium status, in contrast to other populations which, as indicated earlier, are frequently selenium deficient [10,11].

Subsequently, SISPECT (Placebo Controlled Trial of Sodium Selenite and Procalcitonin Guided Antimicrobial Therapy in Severe Sepsis) [25], the German multicenter RCT of selenium pharmaconutrition, compared high-dose selenium against procalcitonin (PCT)-guided antimicrobial therapy in >1000 patients with severe sepsis and septic shock. In this 2 × 2 factorial design, Bloos et al. [25] administered an initial bolus of 1000 µg (12.7 µmol) selenium as selenite, followed by a daily infusion of 1000 µg (12.7 µmol) selenium for 21 d or until ICU discharge. However, they were unable to show any difference in 28-d mortality between the four patient groups. It is important to note that selenium therapy did significantly shorten hospital length of stay (LOS) for sepsis patients by 3 d (26 vs 29 d;  $P = 0.02$ ) and there was a trend toward a reduction in ICU LOS ( $P = 0.08$ ).

The trial had a number of shortcomings. There was a markedly uneven distribution of patients, with for example, significantly more high-risk sepsis patients requiring renal replacement therapy in the selenium group. Inexplicitly, the mortalities observed (~25% in all groups) were significantly lower than the 40% expected mortality in German ICUs [26], raising questions about the basic assumptions in the study protocol design. The intention-to-treat analysis also found a statistically significant interaction between selenium and PCT, which had previously been reported [27]. This interaction adds further confusion to the interpretation of the results and is considered a major limitation of the study.

### Pharmaconutrition and the guidelines

Notwithstanding any limitations, the large SISPECT trial [25] heavily influenced the most recent systematic review and meta-analysis on selenium pharmaconutrition in the critically ill [28]. Aggregation of data from 14 selenium monotherapy RCTs and 7 RCTs with selenium and other antioxidants, failed to demonstrate

any improvement in clinical outcomes [8]. In the latest guidelines from the European Society for Clinical Nutrition and Metabolism [29], the Manzanares data [28] outweighs the previous meta-analysis published by Alhazzani et al. [30], which analyzed nine RCTs and 792 septic patients and concluded that high-dose selenium may reduce mortality. Singer et al. now recommend that antioxidants as high-dose monotherapy should not be administered without proven deficiency [29].

On the other hand, the American Society of Parenteral and Enteral Nutrition/Society of Critical Care Medicine guidelines in 2016 [31] recommended the provision of a combination of antioxidant micronutrients “in safe doses” (ie, 5–10 times the Dietary Reference Intake). The latest Canadian Critical Care Recommendations [32] also conclude that parenteral selenium does not improve clinical outcomes, with the proviso that parenteral selenium may be associated with a reduction in mechanical ventilator days. When the four studies investigating VAP were aggregated, selenium supplementation was associated with a significant reduction in the occurrence of VAP (risk reduction, 0.69; 95% confidence interval, 0.55–0.86;  $P = 0.0008$ ) [32].

### The hypothesis

With an appreciable level of disagreement between expert committees worldwide, it is an opportune moment to pose the question: Is IV selenium therapy, as part of the therapeutic fight against acute respiratory failure in the ICU, worthy of reinvestigation in patients with COVID-19? Our affirmative answer and working hypothesis is as follows:

Early pharmacologic interventions, including high-dose selenite pharmaconutrition could be effective at reducing the incidence and the progression from type 1 respiratory failure (non-ARDS) to severe ARDS, multiorgan failure, and new infectious complications.

To test our hypothesis, a comprehensive research program needs to address a number of issues and key questions by treating pharmaconutrients as drugs not as simple nutrients. Investigations need to be carried out on the pharmacokinetics (PK) and pharmacodynamics (PD) determining the optimum daily dosage (posology) based on body mass index (BMI); evaluating any sex differences in metabolism; and investigating any age-related influences on drug efficacy.

### Selenium PK and PD

The first step will be to better understand the PK and PD involved and explore a potential link between plasma/serum selenium, related antioxidant selenoenzymes, and the risk for contracting SARS-CoV-2 infection. Few studies have evaluated selenium kinetic profiles in the critically ill. In healthy individuals, maximal activity of GPX3 is achieved at a daily intake of 55 to 70 µg (0.70–0.89 µmol) selenium and is associated with a plasma selenium in the normal physiologic range of 90 to 125 µg/L [33,34]. Nonetheless, according to studies published between 1995 and 2003 in European countries, serum or plasma selenium levels in healthy adults show a wide range from 50.22 to 145.29 µg/L [35]. However, critically ill selenium-depleted ICU patients may require much higher doses. So far, IV sodium selenite or selenious acid is the most effective way to deliver a sufficiently high dose of selenium for PK/PD investigations and to produce beneficial clinical effects in ICU patients. In a sheep model of sepsis, an initial IV-loading dose of 2000 µg (25.3 µmol) sodium selenite produced

an anti-inflammatory action that significantly reduced IL-6, and was associated with a significant improvement of hemodynamic parameters [36]. IL-6 is one of the most prominent cytokines up-regulated during SARS-CoV-2 infection [37]. Thus, in the early phase of COVID-19 disease, selenium pharmacotherapy, following an initial loading dose, could regulate production of IL-6 and other cytokines, hence moderating ARDS, the most severe and frequent consequence of the cytokine storm. In 2010, our phase I dosing study [38], evaluating two different parenteral selenium regimens, found that after an initial bolus injection of 1000  $\mu\text{g}$  selenium, followed by continuous infusion of 1000  $\mu\text{g}$  (12.7  $\mu\text{mol}$ ) over 24 h, the concentration-time curve showed that selenium concentration does not normalize until day 10. Moreover the PD profile showed that maximum GPX3 activity was achieved at day 7, suggesting that high-dose supplementation, somewhere between 100 (1.3  $\mu\text{mol}$ ) and 1000  $\mu\text{g}/\text{d}$  (12.7  $\mu\text{mol}/\text{d}$ ) is required to optimize SELE-NOP, GPX3 and antioxidant status by increasing the bioavailability of reduced GSH [38].

### Posology and BMI

Further refinement in posology, based on body weight or BMI, is necessary to eliminate an important variable, not considered in earlier studies. As we previously indicated, in the SIC (Selenium in Intensive Care) study [39], the mean BMI was  $27.1 \pm 8 \text{ kg}/\text{m}^2$ , but 10% of patients had low BMI ( $<20 \text{ kg}/\text{m}^2$ ) and 7.5% had a high BMI ( $>40 \text{ kg}/\text{m}^2$ ). Each patient received a fixed selenium dose of  $\sim 1071 \mu\text{g}/\text{d}$ , which equates to a daily mean of  $14 \mu\text{g}/\text{kg}$ , but those with the lowest BMI would have received  $\sim 19 \mu\text{g}/\text{kg}$  daily and those with high BMI only  $11 \mu\text{g}/\text{kg}$  daily, a significant 67% difference that might have affected outcome. Likewise, in SISPECT [25], the patients had a mean BMI of  $28 \pm 7.5 \text{ kg}/\text{m}^2$  (i.e., some patients were  $\sim 70\%$  heavier than others). Thus, providing a fixed daily selenium dose to all patients meant that the actual amount of selenium administered per kg of body weight could have varied significantly from one patient to another. Indeed, although patients in the selenium intervention group received a mean daily infusion of  $22 \mu\text{g}/\text{kg}$  selenium, the actual individual dosage varied from 300 to  $1352 \mu\text{g}/\text{d}$ . This equates to a four- to five-fold difference that could have influenced their response and outcome. Future studies should calculate the pharmacotherapy dose of selenium from the patient's BMI.

### Obesity

Evidence from Italy, where COVID-19 has been most virulent, suggests that overweight and obese patients have a higher risk for severe clinical symptoms during SARS-CoV-2 infection. Italians with obesity require more frequent hospitalization and admission for intensive care with assisted ventilation during SARS-CoV-2-related pneumonia. In a small study of 92 elderly ( $70.5 \pm 13.3 \text{ y}$ ) predominantly male (61.9%) patients with COVID-19, Busetto et al. [40] report that overweight and obese patients, despite their younger age ( $67 \pm 12.6 \text{ y}$ ) were more likely to be admitted to the ICU. Moreover, they had a higher need for non-invasive ventilation for pneumonia than normal weight patients  $76.1 \pm 13 \text{ y}$  of age ( $P < .01$ ) [40]. Further support for our contention that any future pharmacologic therapy should be administered on the basis of the weight and/or BMI of the patient.

### Age and sex

In the developed world,  $<10\%$  of the population is  $>65 \text{ y}$  of age with a male-to-female ratio of 0.75 and by 2030, one in five people will be classified as old ( $75\text{--}84 \text{ y}$ ) or old old ( $\geq 85 \text{ y}$ ). Classical drug

PK take into consideration changes with age in absorption, distribution, metabolism, and excretion (ADME) There are well-established age-related physiologic changes (e.g., decreased lean body mass, decreased renal and hepatic flow, decreased cell-mediated immunity) that can affect the ADME of pharmacotherapy such as selenium. Intracellular levels of various nutrients are known to vary between the young and the elderly and between men and women [41].

Brazil, China, Iran, and New Zealand have both selenium-rich and selenium-poor regions. Consequently, patients from these regions, might have different "normal" selenium values. In a recent Brazilian investigation [42], almost half the participants were  $>60 \text{ y}$  of age with low selenium intakes and selenium status well below normal. Men had a mean selenium plasma concentration of  $24.62 \pm 16.70 \mu\text{g}/\text{L}$  (median =  $22.5 \mu\text{g}/\text{L}$ ) and women's levels were significantly lower at  $19.36 \pm 6.40 \mu\text{g}/\text{L}$ . In contrast, mean hair selenium levels in Enshi, a Chinese city with a high recovery rate from COVID-19 [20], were  $3.13 \text{ mg}/\text{kg}$  in women compared with  $2.21 \text{ mg}/\text{kg}$  in men.

Similarly, in Iran, healthy male serum levels at  $102.2 \pm 12 \text{ SD } \mu\text{g}/\text{L}$  were also significantly higher than female levels of  $93.9 \pm 14 \text{ SD } \mu\text{g}/\text{L}$  ( $P < 0.005$ ), with a positive correlation between higher selenium serum and age in men  $>16 \text{ y}$  ( $P < 0.001$ ) [43].

How might these age and sex differences affect metabolic and clinical responses to supplementation?

Under normal conditions, the whole body half-life of L-selenomethionine is  $\sim 252 \text{ d}$ , which is much longer than selenite half-life of  $102 \text{ d}$  [44,45]. In selenium-deficient male animals, the reproductive organs assume greater importance, with the testes, epididymis, and sperm taking up a high proportion of the administered selenium dose [46]. Clearance from the body is slower and the elimination half-life is extended further. Conversely, selenium-deficient females retain larger amounts of selenium in all tissues, except the brain and reproductive organs [47]. Selenium is essential for spermatogenesis and is present in the capsule surrounding the sperm mitochondria. Consequently, selenium status and supplement efficacy is likely influenced by sex-linked hormonal patterns, so that we should monitor selenium status and ADME separately in both men and women after at least 2 to 3 months follow up in future supplementation studies [46].

In a subgroup analysis of data from the REDOXS study, Heyland et al. [24] showed that antioxidant (selenium) supplementation actually improved 28-d mortality for those  $<65 \text{ y}$  of age but not for those older. Age and sex differences are not immediately obvious in the SISPECT [25] study where the mean age was  $65 \text{ y}$  but the male-to-female ratio was 0.6 with more than a four-fold difference in daily doses and according to the authors, age and disease severity marker differed considerably between the study groups. Clearly, age and sex differences have been an invisible confounder in many pharmacotherapy studies. Currently, in the COVID-19 era, it is surely not a coincidence that age and sex differences are increasingly being identified as important factors influencing the severity of the response to the virus.

### Future clinical investigations

Simultaneous to the new PK/PD studies, we propose that large-scale RCTs aimed at addressing the questions of age, sex, BMI, and optimum posology need to be designed. Groups of severely ill patients with COVID-19 admitted to the ICU, will receive an initial loading dose of high-dose IV sodium selenite, followed by selenium monotherapy by parenteral route starting as soon as possible after admission to the ICU for up to 14 d with follow up on selenium status and outcome measures for up to 100 d.

We believe there is sufficient evidence on the anti-inflammatory, immunologic, and antioxidant properties of selenium that allows us to initiate further in-depth investigations into metabolic and clinical aspects of selenium pharmaconutrition as adjuvant therapy aimed at combating this global pandemic.

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