

The Effect of Selenium on Pathogenicity and Mortality of COVID-19: Focusing on the Biological Role of Selenium

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Abstract

In the last two years, coronavirus infections increased the mortality rate among the elderly and especially patients who suffer from chronic diseases. Despite vaccination, many people are still dying from COVID-19. Among these, the role of minerals in increasing the function of the immune system and combating coronavirus infection has been proven. Selenium (Se) is a crucial valuable element for human health with a determinative in decreasing the amount of ROS produced in response to different viral infections within the body. The role of selenoprotein enzymes in struggling oxidative caused by ROS overproduction is very important. The overall function of cytotoxic cells increases by the presence of selenium. Recent clinical trials carried out on patients with COVID-19 have demonstrated that the deficiency of selenium is obvious in patients who suffer from acute respiratory infections. Due to the role of selenium in viral inflammation, it is expected that this substance will prevent the cytokine storm and ultimately mortality of infected people by reducing the production of inflammatory cytokines. The present study investigates the role of selenium and selenoproteins and their possible mechanisms in the pathogenesis of viral infections. Further comprehension on the the role of the pathogenesis of viral infections and their mortality could be achieved through identifying potential selenoproteins in the COVID 19 genome by means of computational tools. The following core competencies are addressed in this article: The effect of selenium on pathogenicity and mortality of COVID-19.

Keywords: COVID-19, Selenium, Mortality, Morbidity, Coronavirus.

DOI: 10.47750/pnr.2022.13.S03.038

INTRODUCTION

COVID-19 is a respiratory disease that was first identified in Wuhan in December 2019 and later spread to other countries. The new epidemic of COVID-19 was declared by World Health Organization (WHO) in March 2020. WHO warned all countries around the world to take preventive measure against the immediate spread of the virus (1).

The Covid epidemic now affects 19 million people and has caused major health and economic disruptions worldwide. Although mortality is declining with the start of vaccination, new infections are steadily increasing due to mutated strains. Nutrition and immunity are two vital factors in the successful fight against coronavirus. Recent studies revealed a significant positive correlation between the survival rate of COVID-19 patients and their selenium levels in comparison with non-survivors (2). Selenium is an essential trace element and its situation is varies based on the region in the world. Recent studies in European (48 studies) and Middle East (44 studies) have reported that the normal range of selenium is 98.7 ng /ml serum at which optimizes

glutathione peroxidase activity. However, previous studies reported that the normal range of selenium was 150-170 ng/ml (3,4). In patients who are affected by viral infections, administration of inflammatory mediators in high dosage causes acute lung injuries which increases the potential of acute respiratory distress syndrome (ARDS) and in some cases may leads to death. The release of innate immune cells activated by proinflammatory cytokines, leads to acute lung damage and local inflammation. Additionally, in patients with viral infection, one of the main causes of ARDS with increased oxygen species (ROS) is detected to be oxidative stress. Such a condition activates the inflammatory pathways and leads to a marked increase in inflammatory cytokines, leading to death in some cases (5, 6). Studies show that impaired antioxidant defense in the acute respiratory syndrome of SARSCoV infection is due to a decrease in the function of certain enzymes called selenoproteins. At the center of these enzymes is the trace element selenium, which has a crucial role in decreament of the production of ROS which may be produced as a response to different viral infections. Selenium is also

involved in inhibiting NF- κ B activation and reducing inflammation (6).

Examining the pathology of respiratory virus infections is very important in diagnosing, preventing and providing treatment strategies, as well as developing new therapies. Since many studies indicated low levels of selenium in patients with COVID-19, so in this study we intend to investigate the relationship between the level of this micronutrient and the severity of COVID-19 disease. The present study is trying to investigate the main role of selenium and Selenoprotein mechanisms in the pathogenesis of viral infections.

Oxidative stress in viral infections

Generally, the changes in Oxidation happen during different cellular processes, such as metabolism, signaling, differentiation, and proliferation. Maintaining redox homeostasis has a crucial role in pathology. Any decrement in degradation systems or accumulation RNS and/or ROS could cause inflammation, oxidative stress, and chronic activation of immune responses. Due to the capability of ROS in reacting with almost any type of biological molecules such as nucleic acids, lipids, and proteins, their rapid increase to a chronic level could lead to apoptosis, organ dysfunction, and genome instability (7-9). As a result, it can be stated that oxidative stress increases with viral infection.

The role of antioxidant functions is prominent in reducing reactive oxygen species and cell damage

The term "reactive oxygen species (ROS)" includes intermediates with short reactivity oxygen life. ROS chemical mainly include hydrogen peroxide (H₂O₂), hydroxyl radical (HO), and superoxide anion (O₂⁻). The choice of antioxidant pathways, which are activated in response to ROS, depends on their position in a cell (10). Some ROS, such as lipid peroxides due to peroxidation of membrane phospholipids (e.g., malondialdehyde), can affect blood circulation and cell membranes, disrupting normal cellular processes such as membrane transfer and mitochondrial respiration. Therefore, ROS is often recognized as the cause of cell damage (8).

Disruption of antioxidant pathways provides the conditions for viral replication

The total oxidant status (TOS) would be affected by viruses following which the main balance between peroxidants and antioxidants in the body would be disturbed. ROS-inducing enzymes may disrupt the antioxidant balance. These enzymes include nicotinamide adenine dinucleotide phosphate oxidase (NADPH and Nox oxidases) and xanthine oxidase (XO). The increment of ROS and the subsequent oxidative stress which is caused by viral

infection is capable of providing a favorable environment for virus replication and survival (11, 12). In fact, activation of phagocytes is associated with oxidative stress when infected with the virus because active phagocytes may secrete prooxidant cytokines such as tumor necrosis factor (TNF) and interleukin-1, which increase iron uptake, by the reticuloendothelial system (13).

Antioxidant enzymes increase during increased cellular stress

The oxidative stress caused by viral infections could be relieved by antioxidant enzymes (14). These enzymes could be regulated easily by 2 transcription factor which is similar to nuclear factor E2 (Nrf2). In situation when the level of ROS is normal, the transcription factor nrf2 could be controlled in the cytoplasm and for degradation of the ubiquitin pathway. However, increasing the amount of ROS more than normal leads to the retention of Nrf2 in the cytoplasm and its transfer its transfer to the nucleus finally causes transcription of antioxidant enzymes (14, 15).

Viruses tend to inactivate the antioxidant pathway

Various types of viruses are capable of activating the above pathways in varied ways. An increment in this pathway could be seen in the mice models affected by the influenza virus. It's while Respiratory syncytial (sin-SISH-uhl) virus (RSV) because of proteasomal degradation pathways of the transcription factor nrf2 causes an incorrect regulation in this pathway. Briefly, it could be noted that viruses could adjust the Nrf2 pathway, control oxidative stress, and also are capable of keeping a desirable cellular environment for survival and proliferation (16).

Selenium and viral infections

Selenium is an essential valuable element that helps in maintaining the homeostasis of the human body. Due to the antioxidant properties of selenium, it is capable of creating an immune response against oxidative stress which is known to be its most vital function. Some clinical trials have demonstrated that the supplements of selenium are capable of protecting the body against many harmful biological and chemical agents. These supplements have a crucial role in protecting the body from any available side effects of drugs, heavy metals, pesticides, toxins, and other oxidative stressors (17).

The selenium in selenoproteins is capable of protecting the body against viral infections

In a study by Jones et al (2017) it was reported that the deficiency of selenium affects nearly 1 billion people worldwide mainly because of inadequate dietary intake (18). One of the most important biological functions of selenium is its presence in selenoproteins There is a total of 25

selenoproteins in the human body, some of which have a crucial role in protecting the body against viral infections, controlling thyroid hormone signaling, protecting the body against oxidative stress, improving mitochondrial health, and protein folding. Selenoproteins are also essential for an effective immune response to infections. Some other roles of selenium supplements are such as decrement of allergic asthma, increment of vaccine response, and also decrement of progression of tuberculosis or HIV-1 (19).

Glutathione-transferases is one of the important selenoproteins in oxidative stress

One of the main enzymes which contain selenium cofactor is known to be Glutathione Peroxidase (GPx). The main function of GPx is its role in the elimination of hydrogen peroxidase and lipid peroxidase which acts as a strong oxidative stress factor without causing any harmful effects on the body. Selenium deficiency leads to a decrease in the activity of these antioxidant enzymes, resulting in exacerbation of oxidative stress and more mutations in viruses (20, 21). As a matter of fact, this condition results from a viral infection that results in oxidative stress and increased proliferation. Moreover, the mentioned condition causes an accumulation of mutations in the viral RNA genome which finally causes host damage (22, 23).

Selenium is effective in the protein synthesis cycle of the immune system

Some special defense mechanisms such as chemical and mechanical barriers which are derived from skin epithelial cells are the first line of innate immunity against the virus which is capable of preventing the virus from entering the body. Inside the respiratory tract and on the mucosal surfaces, epithelial cells are immersed within the mucus and fluid which decreases the direct binding of viruses. Moreover, because of the presence of defense enzymes and peptides inside the mucosa, invasive agents could be eliminated easily. The synthesis of antioxidant enzymes and defense proteins could be increased due to the presence of selenium. Moreover, the presence of selenium is crucial for activating phagocytic cells which act as key components of the innate immune system. Inadequate selenium intake leads to a decrease in phagocytic levels in neutrophil cells as part of the body's defense line (24, 25).

Selenium prevents a strong cytokine response

Selenium has a crucial role in mediating inflammatory signaling pathways. The role of selenium in preventing inflammatory signaling pathways has significant effects in mediating many diseases. In a study by Maehira *et al.*, it was reported that selenium is capable of inhabiting the activation of the NF- κ B transcription factor at physiological levels which involved in the coding of inflammatory cytokine regulatory genes. In addition, decreased serum selenium

levels induced CRP synthesis by hepatocytes during the acute phase reaction (26).

Selenium regulates the antioxidant response during increased cellular stress

The damages to the lung due to sepsis could be reduced through over-regulation of Nrf2 signaling by selenium. Through activating the Nrf2 pathway, glutathione synthesis and abnormal regulation of the NF- κ B pathway could be increased that finally would cause lung damage. On the other hand, a knockdown of endogenous Nrf2 showed an abnormal regulation of the NF- κ B pathway and the inhibition of glutathione synthesis. It should be noted that selenium has a significant role in NF- κ B and Nrf2 signaling to regulate inflammatory cytokines. The supplements of selenium could decrease the production rate of inflammatory cytokines such as animal and human studies, and cell line studies (27, 6).

Selenium and coronaviruses

COVID-19 virus needs a suitable receptor to enter the host cell, including the ACE2 receptor. Selenium and selenoproteins affect viral activity indirectly through several defense mechanisms. Selenium has a critical role in supporting the structural integrity and integrity of the respiratory epithelial barrier and also prevents the possibility of entering virus into respiratory cells. In a study using influenza virus, it was reported that selenium nanoparticles activated by the antiviral agent of amantadine inhibited the binding of the H1N1 virus to the host cell via suppressing neuraminidase activity. Thus, selenium can be capable of altering the binding of COVID-19 virus to ACE2 receptors, resulting in reduction of the infection rate (Figure 1) (28).

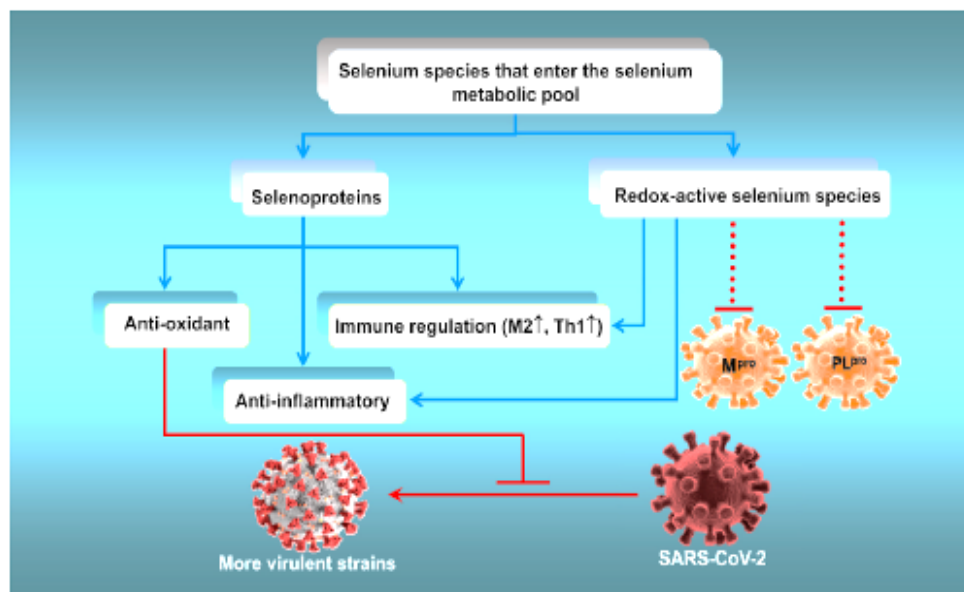


Figure 1: The proposed mechanism through which the level of selenium barricades severe mutation of SARS-CoV-2 and its life cycle. At the same time, oxidative stress caused by the virus reduces organ damage and cytokine storms (29)

Recently new evidence has emerged about the role of selenium in COVID-19 disease. However, the exact antioxidant and regulatory role of selenium in the immune system in coronavirus infections remains unknown. Examining the relationship between selenium level status and COVID-19 disease in China showed that the rate of improvement is higher and the mortality rate is lower in people with adequate selenium levels (30).

The clinical trials which evaluated the nutritional status of COVID-19 patients revealed that in 42% of these patients a low level of selenium is available. However, the comparison of patients who were survived from COVID-19 with non-survivors showed a higher level of selenium among survived individuals (32, 31). Normal levels of selenoprotein P combined with zinc have a significant effect on the chances of survival and reduction of severity of involvement in patients with COVID-19. Organoselenium compounds with a low molecular weight are proved to be strong potent papain-like protease inhibitors (PL pro CoV2) which are mandatory for replication of viruses within host cells (34, 33). Papain-like protease (PL pro) is one of the main enzymes that has a significant role in the pathogenesis of COVID-19, which facilitates the process of replicating the virus by collecting new viral particles in human cells. Recent clinical trials have also demonstrated that the targeting of various selenoproteins by means of protease cleavage prediction tools could be done easily. It has been proved that glutathione peroxidase 1 (GPx-1), Thioredoxin reductases 1 (TR1), and selenoprotein F have a crucial role in the pathophysiology of COVID-19 infection (35). Based on the proven role of selenium in improving the antioxidant capacity of the lungs in ARDS patients, Mahmoodpoor et al.

performed intravenous sodium selenite injection for COVID-19 patients where the healing process was very evident (27).

It has been shown that the deficiency of selenium possibly increases the mortality rate among COVID-19 patients. A recent study by Moghaddam et al (2020) demonstrated that the level of serum selenium in COVID-19 patients was significantly higher compared to patients who died of COVID-19 (32). Another study by Zhang et al (2020) in China revealed that the rate of recovery in COVID-19 patients was significantly associated with selenium levels (30). A study by Nelson et al. found that selenium-deficient mice were more likely to have lung damage because of influenza virus infection compared to the mice with adequate levels of selenium. Their study also demonstrated that the virus isolated from the lungs of mice with deficient levels of selenium five days following infection had mutations in their genome that made their health situation worse. The deficiency of selenium in mice infected with the flu virus caused severe interstitial pneumonitis compared to mice with adequate selenium levels (36).

Selenium has a crucial role in producing antibodies. Moreover, the deficiency of selenoprotein devastates the puberty of T cells, their function, and also T cell-dependent antibody response in mice (37). Any increment in the possibility of blood coagulation increases the rate of mortality in COVID-19 patients. COVID-19 patients with a low concentration of plasma selenium are more likely to experience tissue damages, infection, organ failure, and also the rate of mortality among them is higher. Additionally, the level of plasma selenium is associated with protein C activity, minimum plasma antithrombin activity, and

minimum platelet count in COVID-19 patients. In their study, Spyropoulos et al (2020) revealed that venous thromboembolism happen in nearly 30% of COVID-19 patients in the intensive care unit (38).

Research on the association of selenium levels with COVID-19 mortality

In the Northeast to the southwest of the globe, people are potentially deficient in selenium. Therefore, one of the marginal causes of COVID-10 disease in China can also be related to selenium (22). Another study demonstrated that the deficiency of selenium increases the mortality risk among COVID-19 patients (32).

Many articles have been written about the relationship between selenium and the mortality rate of COVID-19. However, some of them consider the deficiency of this micronutrient as a risk factor in its incidence and mortality, and some have considered it unrelated. Anyway, more detailed clinical studies should be done to investigate the productiveness of selenium in patients with COVID-19. A similar study by Younesian et al., revealed that the level of

serum selenium in COVID-19 patients was significantly lower in comparison to the healthy control group individuals. However, they did not show any significant association between selenium and the rate of disease mortality (39). In another study, it was revealed that the level of selenium has a significant effect on the treatment of COVID-19 patients (32). Similarly, a study in Germany reported that the rate of mortality in patients with a lower level of selenium was higher compared to those with a higher level of selenium (30).

In the study of Jahromi et al. in 2021, the relationship between Se and Zn status and the severity of COVID-19 was investigated. The level of serum selenium in patients who suffer from severe COVID-19 was significantly lower compared to the patients with mild to moderate levels of COVID-19 disease (41). Similarly, a clinical trial in China demonstrated a significant association between the level of selenium and the treatment rate of patients with COVID-19. This study showed that with increasing Se concentration in the population, the rate of recovery of COVID-19 also increased (32).

Findings	Title of article	Author/Year
Based on the data from the present study, it was observed that any increment in the level of serum selenium decreases the possibility of being affected with COVID-19. However, there is not any significant association between the level of selenium and the severity and mortality rate of COVID-19 disease.	Decreased Serum Selenium Levels of COVID-19 Patients in Comparison with Healthy Individuals	Ommolbanin Younesian et al., 2021 (39)
The present study demonstrated that there is a significant association between the treatment rate of COVID-19 patients and the level of selenium. These results are in line with the previous studies which provided evidence for antiviral effects of selenium.	Association between regional selenium status and reported outcome of COVID-19 cases in China	Zhang et al., 2020 (29)
SARS-CoV-2 infection reduces serum selenium levels and this is associated with the severity of COVID-19. Selenium supplementation has been suggested to improve the outcomes of COVID-19 in sickle cell disease populations	Selenium supplementation may improve COVID-19 survival in sickle cell disease	George D. Henderson. 2021 (40).
This study provides a precise introduction for conducting further clinical trials with larger population. Moreover, it suggest that the supplementation of selenium could effectively decrease the side effect of this virus.	An exploratory study of selenium status in healthy individuals and in patients with COVID-19 in a south Indian population: The case for adequate selenium status	Muhammed Majeed et al., 2021 (2)
The results show that the increment of Zn level could decrease the level of serum CRP. However, the significant relationship of Se and Zn with disease severity disappeared after adjusting the intervention factors.	The correlation between serum selenium, zinc, and COVID-19 severity: an observational study	Jahromi et al., 2021 (41).
The results emphasis the fundamental role of Selenium in the recovery of Covid-19 patients and support the discussion of See adjuvant supplements in critically ill patients and patients with See deficiency.	Decrement of the selenium level increases the mortality of COVID-19 patients.	Moghaddam et al., 2020 (32)

DISCUSSION

For several reasons, the essential trace element Se is particularly effective for viral infections among nutritional agents. Selenium has a crucial role in the production of antibodies. In a study carried out in mice, it was observed that selenoproteins deficiency spoils the function and maturation of cells, and also the response of T cells which are dependent to antibodies (42). Low plasma selenium concentrations are also associated with increased tissue damage, infection, organ failure, and increased mortality in ICU patients (43). Due to the association between thromboembolism and infection, venous thromboembolism has been reported to occur in 27% of patients with COVID-19 in the ICU (42). Generally, it has been proved that any decrement in the level of serum selenium increases the risk of being affected with COVID-19 (32, 30, 39- 41).

However, some of them did not find significant results regarding the relationship between this micronutrient and mortality in patients with COVID-19 (39). Due to the very important role of selenium as an antioxidant against oxidative stress and cytokine storms, this substance is of great importance. However, further studies are needed to investigate the association of selenium levels with COVID-19 mortality.

Recent studies have revealed that selenium supplementation are essential for prevention of age-related diseases mostly in old individuals. In addition, age is detected to be a risk factor for COVID-19 diseases, so the use of selenium supplements in older people is very important (44). In addition to selenium, many micronutrients are important in COVID-19. Jahromi *et al.* Conducted one of the first studies to examine the relationship between the status of Zn and Se and their effect on the recovery of COVID-19 patients (41). A similar study, revealed that there is a significant association between the levels of SRP and Selenium. Another study which consisted of 137 ill children, showed that there is an inverse relation between the levels of serum selenium and CRP (45).

Recently, a lot of studies have investigated the key role of some antioxidant minerals such as magnesium, zinc, and selenium in modulating the immune system when face with viral infections. It has been proved that all the mentioned materials have significant role in modulating antibacterial and antiviral immunity which potentially regulates the inflammatory response. The deficiency of these materials could result in a swifter prevalence of respiratory infections and endothelial dysfunction.

It has been proved that these features are associated with COVID-19 pathophysiology, and providing appropriate levels of selenium, magnesium, and zinc micronutrients potently boost the immune system during the infection in COVID-19 patients. However, more precise clinical trials should be carried out in this regard (46). Nowadays, it has

been proved that the lack of selenium causes an increment in the susceptibility of the host to be affected with viral infections. Anyway, it should be noted that the lack of selenium has a significant effect on virus-infected host which mainly depends on the type of pathology.

CONCLUSION

The properties of immune-modulating agents and the consequences of the lack of supplements or micronutrients in individuals with viral infectious diseases such as COVID-19 is being an important challenging issue for scientists. Many studies show that patients with Covid-19 are deficient in at least one nutrient in the body. Selenium, as a micronutrient, also plays a very important role in the immune system and the control of oxidative stress. Due to the role of selenium in maintaining the maturity of T cell function and the production of T cell-dependent antibodies, it therefore has a very important role in the immune system.

Studies have shown that very low levels of selenium may play a role in the increment of the inflammatory responses. Moreover, it has been shown that selenium supplements could have a crucial role in modulating the immune system through regulating inflammatory cytokine production pathways. Administration of selenium supplements for the management of patients with COVID-19 has created novel opportunities in this regard as there is conclusive evidence that selenium is involved in antioxidant mechanisms.

Given the potential benefits of selenium, it is suggested that the role of selenium be preferably tested in patients with COVID-19 in a randomized controlled trial. It is also suggested that these clinical trials be performed based on basal selenium status in the analysis of immunological phenomena in patients with COVID-19. Scientists are trying to investigate the importance of the administration of selenium supplementation in patients with SARS-COV-2 infection and its survival benefits through the decrement of the severe immune response. In this regard, they suggest conducting further clinical trials to discover this functional role more.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil.

CONFLICTS OF INTEREST

There are no conflicts of interest.

ETHICAL CONDUCT OF RESEARCH

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting, and reproducibility guidelines set forth by the EQUATOR

network. The authors also attest that this clinical investigation was determined not to require institutional review board/ethics committee review.

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