Biological Trace Element Research
https://doi.org/10.1007/s12011-022-03208-4

Selenium in the Prevention of SARS-CoV-2 and Other Viruses

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Received: 14 February 2022 / Accepted: 15 March 2022

Abstract
The rapid spread of new pathogens (SARS-CoV-2 virus) that negatively affect the human body has huge consequences for the global public health system and the development of the global economy. Appropriate implementation of new safety regulations will improve the functioning of the current model supervising the inhibition of the spread of COVID-19 disease. Compliance with all these standards will have a key impact on the health behavior of individual social groups. There have been demonstrably effective treatments that proved to be effective but were rapidly dismissed for unknown reasons, such as ivermectin and hydroxychloroquine. Various measures are used in the world to help inhibit its development. The properties of this element provide hope in preventing the development of the SARS-CoV-2 virus. The aim of this review is to synthesize the latest literature data and to present the effect of sodium selenite in reducing the incidence of COVID-19 disease.

Keywords Selenium · Selenite sodium · COVID-19 · Pandemic

Introduction

The coronavirus pandemic in 2019 caused a sudden change in current treatment regimens, and to ensure global health security. Several virus outbreaks have been reported worldwide in recent years, such as the Ebola virus in West Africa, the acute respiratory syndrome coronavirus (SARS-CoV — severe acute respiratory syndrome coronavirus), the ZIKA virus, the respiratory syndrome coronavirus (MERS-CoV — Middle East respiratory syndrome coronavirus), and the H1N1 influenza [1]. With the onset of a worldwide pandemic, the occurrence of severe disease in human bodies is becoming an increasingly important health problem. One such example is the coronavirus (SARS-CoV), which causes severe acute respiratory syndrome resulting in the outbreak of COVID-19 disease. Practically in every country in the world, well-established cases of human infection with this virus are observed every day. The elderly and those burdened with comorbidities are at a higher risk of a severe course of coronavirus infection. We even learn every day that the majority of deaths from COVID-19 are people with additional diseases. The development of comorbidities is influenced by age, but also by the presence of, *inter alia*, chronic inflammation, diseases of the cardiovascular and respiratory systems, and various metabolic disorders. In fact, due to changes in the immune system associated with many diseases, such people are much more likely to develop complications from COVID-19. Such a picture is presented throughout the world, including China, where the first cases of the SARS-CoV2 virus took place [2]. It is worth emphasizing that the sudden appearance of this mysterious virus and its rapid spread around the world has had serious health and economic consequences. Direct contact with the virus has paralysized economies and, consequently, the entire states.

It is worth emphasizing that some groups of infected people endure a difficult disease course, requiring intensive supervision and medical treatment. Epidemiological and preventive actions aimed at reducing the number of cases may be very important to reduce the mortality rate associated with the COVID-19 pandemic. Such actions are aimed at avoiding the situation of a drastic increase in their numbers in a very short time. Bearing in mind the safety and health of citizens during the current pandemic, all preventive measures should be taken. Due to the high rate of virus transmission in the current epidemiological crisis, it is very important to ensure that the number of sick people does not

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increase dramatically. To take significant action against the development of this harmful disease, many authors have stated [3, 4] that selenium deficiency may affect the course of COVID-19. The higher the selenium status in the population, the higher the recovery rate from this disease [5]. This review was conducted to discuss the effect of selenium on the possible prevention of COVID-19 infections.

Characterization of the SARS-COV-2 Virus

The emergence of a new virus in the Chinese city of Wuhan in December 2019 [6] was officially announced by the Chinese authorities on January 7, 2020, as a pathogen causing acute pulmonary insufficiency [7] is a very big threat to the whole world. The International Committee on Taxonomy of Viruses (ICTV) announced on February 11, 2020, the name of the virus, SARS-CoV-2, while the WHO (World Health Organization) announced the official name of the disease as COVID-19 [2]. When deciding to give such a name to the new virus species, the genetic similarity to the SARS-CoV virus, as well as the similarity of clinical symptoms occurring in patients, was taken into account. The SARS-CoV-2 coronavirus was previously known as the 2019 novel coronavirus (2019-nCoV), as named by the WHO [8]. As in the case of other coronaviruses (SARS-CoV and MERS-CoV), the dominant human-to-human transmission of SARS-CoV-2 is the droplet route, e.g., through the oral mucosa [9]. It can also be transmitted indirectly by touch [10]. Research by Gu et al. [11] showed that the virus can also be transmitted through food. It is currently estimated that the median incubation period for COVID-19 is 4 to 8 days and is transferable from asymptomatic individuals [12].

The genetic material of coronaviruses is single-stranded, positive-sense RNA [13]. The SARS-CoV-2 genome is approximately 30 kb [14], while the total content of guanine and cytosine (G + C) is approx. 38% [15], which is typical of most coronaviruses [16]. Usually coronaviruses are surrounded by a spherical bilayer lipid envelope with a diameter of approx. 120 nm. On the surface of the shell, one can observe the presence of surface protrusions, commonly called spines, consisting of highly glycosylated type I glycoprotein [17]. As a result, this group of viruses gets their name from the insets that give it a crown-like appearance. These elements are involved in the recognition of receptors on the surface of the host cell and penetration into its interior.

The process of replication of this virus is very similar to other RNA viruses, which include, among others, the influenza virus, Ebola, Coxsackie, Hantavirus, or immunodeficiency (HIV) [5]. Information provided by Inal [18] and Bourgonje et al. [19] showed that the SARS-CoV-2 virus belongs to the Coronaviridae family of the Nidovirales order [20], responsible for the occurrence of severe acute respiratory syndrome, and binds through the interaction of its protein (S) with the angiotensin-converting enzyme 2 (ACE2 protein receptor) or the dipeptidyl peptidase IV protein (DPP-4) host [21, 22]. The interaction of the transmembrane spike glycoprotein receptor binding domain with the ACE2 receptor is further facilitated by the presence of human transmembrane serine protease or cathepsins, which cleave the viral spike protein and introduce further penetrant changes. Such mechanisms mediate the direct ability to infect human cells [20, 23]. According to the data presented by Davies et al. [24], the coronavirus also binds to human cells through the use of the neuropilin-1 (NRP1) protein receptor, which is found in olfactory epithelial cells. Thus, virtually every cell that has a virus specific receptor is a potential target for it. As a consequence, these processes lead to the occurrence of acute respiratory distress syndrome with cytokinin release, which is caused by dysregulation of the immune system response [25]. Previous assumptions have been that COVID-19, whose genotype is practically 82% similar to SARS-CoV, will behave in a similar way [26]. This suggests the presence of highly homologous 2 β-coronavirus B lines and angiotensin II converting enzyme (ACE2), previously known as the host cell entry receptor for SARS-CoV [19]. It should be emphasized that SARS-CoV-2 is more pathogenic compared to other coronaviruses, at least partly due to the almost 20-fold increased affinity for the ACE2 receptor (SARS-CoV from 2003) [19, 26].

The typical symptoms of this virus infection are highly nonspecific and include dyspnea, fever, and cough [27, 28]. The second most common symptom is diarrhea and nausea a few days before the onset of fever [21, 29]. The infectious doses of SARS-CoV-2 virus are not fully known. Research by Zou et al. [30] showed that there is a higher viral load in the nasal cavity compared to the throat, with no difference in viral load between symptomatic and asymptomatic individuals. There are also reports in the literature that patients' infectivity may persist for 2 weeks [31]. According to He et al. and Cao [32, 33], COVID-19 can lead to liver damage, especially when experiencing very severe, life-threatening symptoms of the disease. It should be emphasized, however, that in the absence of respiratory symptoms, an underestimation of the cases of people suffering from COVID-19 may persist, as studies in patients showing mild symptoms are not conducted in most cases [31]. The mainstay of clinical treatment is symptomatic treatment and oxygen therapy with mechanical ventilation in patients with respiratory failure. While several antiviral drugs, including the nucleotide analog remdesivir, are actively tested, none has been approved for the treatment of COVID-19 [33]. There are many hypotheses for the appearance of the SARS-CoV-2 virus. Data presented by Graliński and Menachery [34] show that the source of the virus was animal products (seafood, snakes, bats, birds) sold at a market in Wuhan city in Hubei province in China. Serological data by Wang et al. [35] showed that the virus is very similar to the SARS virus that appeared in China in 2002. Other authors [36], however, believe that the virus originated in the laboratory.

In order to evaluate all these data, it is necessary to conduct further research aimed at explaining and meticulously characterizing the SARS-CoV-2 virus and its biochemical properties. This will allow future application of an appropriate strategy to counteract the COVID-19 disease in order to save human lives. The development of a solid and durable system of diagnostics that counteract crises related to the spread of epidemics should be a priority for many research centers around the world.

Selenium as an Element

Selenium is one of the most interesting trace elements. Since its discovery in 1817, knowledge about it has expanded significantly. Initially, it was argued that this non-metal was only a toxic substance. The progress of research on this micronutrient, however, has revealed that selenium is a component of many compounds necessary for the proper functioning of many organisms [37]. The range of actions of this microelement is wide, and it should be remembered that there is a fine line between a deficiency and an excess of this element in a living organism. Therefore, it is very important to extend the current knowledge about selenium content in food and to estimate its actual consumption by the population. The recommended daily allowance (RDA) for selenium for adults is 55 µg/day, while the tolerable upper intake for adults is 400 µg/day. Selenium is incorporated into the polypeptide chain of proteins as a component of the amino acid selenocysteine (Sec), which is the 21st amino acid in the genetic code [38]. Selenium found in the human body is a component of many compounds regulating its functioning (e.g., enzymatic proteins, selenoproteins), which is important for protection against oxidative stress. Thanks to this, it ensures the proper functioning of the thyroid gland and regulates the immune and reproductive systems [37, 39, 40]. Moreover, it exhibits anti-inflammatory properties [41] and supports the progression of the cell cycle, making it essential for optimal immune response [42]. Selenium influences gene expression and cell growth by activating transcription factors [43]. The chemical form of selenium is an important factor influencing biological activity. This non-metal occurs in an inorganic form in certain forms of selenite(IV) and selenate(VI), while in the organic form, it occurs in certain amino acids, e.g., selenocysteine and selenomethionine [44, 45].

Selenium compounds, due to their functions in the human body, are an inseparable element of biochemical changes taking place in the body. The lack of one of the selenoproteins can have negative consequences for humans in the form of various diseases (e.g., thyroid). So far, 25 different genes responsible for the biosynthesis of selenium proteins have been identified [46] and are involved in defense mechanisms against ROS (reactive oxygen species) and catalyze many redox reactions and cell signaling [47]. Among these genes are glutathione peroxidases (GPX), thioredoxin reductases (TXNRD), and iodothyronine deiodinases (DIO) [48]. It should be noted that the catalytic function of some selenoproteins has not yet been fully identified [38]. It is suspected that the selenoprotein P (SELENOP), which is the most common in plasma, is responsible for selenium transport, signaling the redox reaction, and is an important regulator of pancreatic β-cells [49, 50]. In the case of selenoprotein V (SELENOV), it is assumed that it is involved in protection against oxidative stress [51]. According to Kryukov et al. [52], SELENOR, also known as MsrB1 (Methionine Sulfoxide Reductase B1), is an important antioxidant enzyme especially expressed in immune cells. Selenoproteins K and S are involved in the degradation of misfolded proteins on the endoplasmic reticulum. Selenoproteins K (SELENOK) and N (SELENON) are involved in the maintenance of Ca^{2+} ion homeostasis. They also take an active part in the response to the occurrence of oxidative stress. According to Rocca et al. [48], selenoprotein T (SELENOT) shows an intriguing cardioprotective effect by reducing ischemic damage to the heart muscle.

Selenium is a natural component of soils, though selenium soil content varies greatly in different regions of the world. Therefore, the level of selenium in food products from a given region is proportionally dependent on its presence in the soil. In areas rich in this element, the selenium enrichment trait was reflected in animal feed crops and local human food. A particularly high content of this element is noted in high-protein products. High levels of this element can be found in beef (1.8 µg/g) [53], and leading amount are contained in the kidneys (about 1.45 µg/g) [39], seafood (mussels, lobsters, oysters, shrimps), and fish [54]. The concentration of selenium in cereals ranges from 0.01 to 0.55 µg/g fresh weight [55]. Dairy products contain varied selenium content, which is directly related to the presence of this element in animal feed. On the other hand, its content in fruit and vegetables, depending on the species, is negligible and usually does not exceed 0.10 µg/g [56]. The exception to this rule is garlic and legumes (lentils), in which the content of this element is very high and may vary even between 5.8 and 39 µg/g [57, 58]. The presence of selenium in water is minimal (10–20 µg/L) [59]; however, there are regions of the world with high levels of selenium content in water, among them areas of the USA, Venezuela, and China.

Selenium, due to its strong anti- and pro-oxidative properties, is used in anti-cancer therapy [60]. The element contributes to cell apoptosis by modifying proteins, which leads to the inactivation of transcription factors and may inhibit the cell cycle. Currently, research focuses on the use of selenium in the form of nanoparticles for the treatment of cancer. Selenium-containing nanoparticles may prove to be a promising therapy because they are more effective and less toxic than conventional forms of selenium. Additionally, such nanoparticles can be conjugated with appropriate ligands, directing them to the appropriate tissues covered by the tumor. It is worth noting that the effectiveness of nanoparticles depends on the dose used and the size of a single nanoparticle. Research by Wang et al. [61] shows that smaller sized nanoparticles are more effective.

Effects of Selenium on SARS-CoV-2 and Other Viruses

Since the outbreak of the SARS-CoV-2 coronavirus outbreak, research has been carried out on drugs that guarantee safety and could have a positive effect on human health. Currently, there is an increasing amount of speculation regarding the use of various antiviral drugs to prevent SARS-CoV-2 infections. Based on the experience of SARS and MERS, antiviral drugs such as lopinavir-ritonavir have been used. There is experience with the use of remdesivir (GS-5734) as an adenosine analog prodrug [62], a broad-spectrum anti-RNA drug developed for the Ebola virus. Due to the possibility of inhibiting viral RNA polymerase, this drug could be effective in the treatment of COVID-19 [27]. However, recent literature data show that the drug remdesivir [63], hydroxychloroquine, the antibiotic azithromycin, and lopinavir-ritonavir show little effect on the inhibition of mortality due to the development of COVID-19 disease [63]. Dexamethasone is the first drug to show life-saving efficacy in COVID-19 infected patients [64]. Data presented by the recovery team [65] showed that the administration of 6 mg of dexamethasone from the corticosteroid group caused a reduction in COVID-19 mortality compared to those undergoing standard care [66]. Oseltamivir should be administered as soon as possible and used because of its proven beneficial activity against the MERS virus [67]. However, there is currently no evidence that a similar effect is seen with infections from the new coronavirus. To prevent transmission of this virus, it is recommended that the infected person be quarantined and adhere to good hygiene practices.

It is estimated that 1 billion people have very little selenium intake [68]. This worrying scenario could worsen in the future due to projected climate changes that will reduce the selenium content of the soil, mainly in agricultural areas. Such activities will have huge consequences for the content of this element in food. It is known that selenium deficiency can affect the functioning of the entire immune system responsible for the production of macrophages and lymphocytes. The malfunctioning of this system in the human body will affect the occurrence of various disease states. Such a persistent burden on the body can even lead to death.

It should be noted that most critically ill COVID-19 patients experience bleeding disorders that carry a high risk of gastrointestinal bleeding [21]. That is why an alternative to the possible inhibition of SARS-CoV-2 virus proliferation may be the use of selenium, and more precisely its inorganic form — sodium selenite. Selenium plays an important role in regulating blood clotting by affecting the thromboxane/prostacyclin ratio and the functioning of the complement system. Research published by Beck et al. [69], Hiffler and Rakotoambinin [5], Cheng et al. [70], and Moya et al. [71] showed that selenium deficiency increased virulence of RNA viruses. It is well known that the SARS-CoV-2 virus in the first stage of infection must introduce its genome inside the cell. In order to do so, it has to overcome the barrier which is the cell membrane. The virus enters the host cell using the transmembrane serine protease type 2 enzyme (TMPRSS2) and the ACE2 receptor protein, leading to the phenomenon of endocytosis with the host cell (human) [22].

Understanding the rivalry between virus and host is still developing. By better understanding the defense mechanisms of both sides, scientists want to discover how the proliferation of this virus can be inhibited. It is sodium selenite that exhibits oxidizing properties that affect the possible change in the conformation of virus proteins responsible for penetration into the host cells. Similar mechanisms of this chemical compound occur in the circulatory system where sodium selenite reacts with the -SH groups of proteins and prevents the formation of large aggregates of protein polymers rich in disulphides (parafibrin) [72]. It is worth noting that selenium acts as a protective agent by its normal route, which is the incorporation into selenoproteins as selenocysteine. Lowering selenoprotein expression may increase the risk of bacterial and viral infection [73].

According to data presented by Vavougios et al. [74], appropriate selenium status contributes to the modulation of organisms' immunity. Adequate selenium supplementation is associated with a marked increase in the number of cytotoxic lymphocytes in healthy people. Moreover, selenium is involved in the regulation of many metabolic pathways (pathways of the immune response) towards cell proliferation, e.g., the development of T lymphocytes, in the presence of lymphopenia [75]. A possible mechanism of selenium action before the development of COVID-19 in the body is also preventing the process of damage to the vascular endothelium, and thus the occurrence of coagulopathy by increasing the synthesis of selenocysteine released [76].

It is worth noting that glutathione peroxidases and thioredoxin reductase are selenoproteins that play a very important role in antiviral defense through their redox signaling and homeostatic activity [77]. There has been an association between the COVID-19 cure rate and basal selenium status in various regions of China [51]. To confirm this observation, a deficiency of elemental selenium and its transporter proteins was noted in patients with COVID-19 in Germany [78]. The studies presented by Moghaddam et al. [79] showed that the average serum selenium level of patients (Germany) was about 84 ng/mL in the control group, while the average serum selenium levels in COVID-19 patients were lower (51 ng/mL). A control group of patients in India had an average serum selenium level of 79 ng/mL, which was significantly higher than that of COVID-19 patients [80]. Decreased serum selenium levels may be a risk factor for COVID-19 infection. It is worth noting that recent studies from China [51] showed a relationship between the cure rate of patients infected with SARS-CoV-2 and selenium status in a geographic areas poor in this element. Selenium deficiency in people causes lipid peroxidation, increasing oxidative stress, which in turn reduces immune resistance and possibly increases the risk of hemorrhages.

Literature data presented by Ivory et al. [81] showed that selenium supplementation has been shown to strengthen the immune system against the influenza virus. The 200 μg/day dose of selenium enriched yeast increased the secretion of interleukin 10 (IL-10) and decreased the number of granzyme + CD8 cells in the blood [78]. Thus, it is possible that the two effects may work together to inhibit antiviral responses. Given the current COVID-19 pandemic, in which there is no effective and curative treatment, the proper functioning of the immune system is one particularly invaluable weapon. One of the most important and positive factors in addressing COVID-19 is a correct diet, which has a very large impact on the proper functioning of the immune system [78]. According to the data presented by Beck [82], the nutritional status of the host with selenium and vitamin E may inhibit the development of the Coxsackie virus. Both selenium and vitamin E act as antioxidants. Yu et al. [83] conducting clinical trials proved that supplementing selenium yeast (in a dose of 200 μg Se) inhibits the development of hepatitis B virus (HBV) infection and reduces the incidence of neoplastic diseases (primary liver cancer) in China, where infection with this virus has become epidemic. As reported by Majeed et al. [77], nutritional status of patients is associated with the risk and the possibility of infection with SARS-CoV-2 virus. Selenium status positively correlates with the survival of patients infected with COVID-19 compared to those who, unfortunately, did not. Adequate nutrition is required to protect against viral infection, and the lack of a properly balanced diet can be one of the many factors that make people more susceptible to SARS-CoV-2 infection. Studies presented by Alehagen et al. [84] showed that supplementation with organic selenium and coenzyme Q10 (ubiquinone) reduces the non-specific inflammatory response measured by CRP (C-reactive protein) in plasma. Increasing the level of this element in the body may therefore show a protective effect and may constitute a protective measure against coronavirus infections. However, the appropriate chemical form and dose of this element must be administered because unskillful selenium supplementation may have a detrimental effect on cellular immunity. According to data provided by Beck et al. [85], RNA viruses (as exemplified by Ebola, Marburg, Lassa hemorrhagic fever, influenza virus, HIV, Hantavirus) have high rates of mutations that occur in their genetic material. Such activities enable rapid evolution, leading to an increased adaptation of the virus to changes in its environment. Verma et al. [86] showed that selenium may be a key ingredient to protect cells infected with West Nile Virus (WNV) from death. Taylor and Radding [87] reported that the SARS-CoV-2 virus reduces the biosynthesis of glutathione (GSH) and selenoproteins in infected cells. The consequence of this is a decrease in the level of these antioxidant molecules, which leads to an increase in oxidative stress and the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Then, as a result of further metabolic pathways, NF-κB is an activator of the action of many pro-inflammatory cytokines, including interleukin 6 (IL-6, which may contribute to the intensification of inflammation and cytokine storms observed in COVID-19) [32]. It is also worth mentioning the use of sodium selenite in the prevention of Ebola virus infections in 2014 in West Africa [88, 89]. The authors showed that the use of sodium selenite reduced the number of Ebola virus infections and mortality by up to 50%.

Summing up, it can be said that constant research on this chemical form should continue. Se may be a key component of treatment for patients infected with the SARS-CoV-2 virus. The introduction of prophylactic selenium supplementation, especially in the elderly, is a safe way to increase immunity. It is worth emphasizing that sodium selenite is a cheap and readily available chemical.

Conclusion

The coronavirus pandemic is quite an unusual time for all of us. The virus has had a significant socio-economic impact around the world. The cited data show that current scientific reports are insufficient to clearly assess the role of selenium in various therapies. Therefore, research should continue on the nature of this element in order to expand existing knowledge. The occurrence of various chemical forms of selenium requires understanding their potential properties, each of which is characterized by different biological properties that can play a very important role in the overall prevention of COVID-19 disease. Currrent knowledge and intermediation in the use of the most effective treatments available will help minimize the global problems the virus poses. It is worth using selenium as a potential factor in the prevention of viral infections. During this challenge, which is the coronavirus, the whole world should ask God for health and safety and to stop the coronavirus epidemic in the world.

Declarations

Conflict of Interest The author declares no competing interests.

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