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Selenium (Se) plays a key role in the biological effects of some viruses: Implications for COVID-19

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ABSTRACT

Host nutrition is an important factor affecting disease progression. Selenium (Se) is an essential trace element for the human body with anti-inflammatory, antioxidant, and immune effects, and Se deficiency increases RNA-virus replication and virulent mutations, which lead to more severe tissue damage and symptoms. Low Se status in the host may be an important cause of health complications induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this article, we describe the metabolic mechanisms by which Se is involved in anti-inflammatory, antioxidant, and immune effects, and review the role and clinical effects of Se in viral infection. We then discuss the potential relationship between Se and coronavirus disease 2019 (COVID-19). The association between soil Se level and the incidence of COVID-19 was observed in different cities of Hubei Province. The incidence of COVID-19 was more than 10 times lower in Se-enriched cities (Enshi, Shiyan, and Xiangyang) than in Se-deficient cities (Suizhou and Xiaogan). Although the relationship between soil Se levels and the incidence of COVID-19 in Hubei still needs further study, these findings provide baseline information demonstrating the effect of Se levels on SARS-CoV-2, which could contribute to the prevention and management of COVID-19.

1. Introduction

The ongoing pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in over 200 countries has led to a global health emergency (Khursheed et e al., 2020; Zhang et al., 2020a). As the outbreak spreads, mass use of antiviral drugs is imminent (Kumar et al., 2020, 2021). However, due to increased antiviral-drug resistance and the mutation rate of the virus, the treatment of COVID-19 is facing new challenges. Thus, new antiviral strategies like antiviral nanotherapeutics and nutritional therapy have been proposed (Mukherjee et al., 2020). Some essential trace elements, such as zinc, selenium (Se), and iron, are thought to be helpful in immune-system regulation (Moghaddam et al., 2020). Since severe alveolar epithelial-cell damage with nonspecific innate immune response, swelling, hyperplasia, and necrosis have been found in COVID-19 patients (Zhang et al., 2020a), nutritional therapy has been suggested for some COVID-19 patients (Bae et al., 2020; Méplan and Hughes, 2020).

Se is an important and essential trace element in mammalian redox biology (Zhang et al., 2020a), and its positive effects on viral diseases (including Ebola and hantavirus disease) have been reported in both experimental and clinical applications (Fang et al., 2015; Eimoemen et al., 2016; Guillin et al., 2019). Dietary Se deficiency can affect host immunity and alter virus virulence (Hiffler et al., 2020). Hence, we hypothesized that the incidence of COVID-19 in Hubei might be related to Se levels in the local environment. Here, we review the relationship between Se in the environment and human health, explore the mechanism and efficacy of Se in different viral diseases, and discuss the positive role of Se in the recovery and treatment of SARS-CoV-2 by statistically analyzing cases in Hubei Province as an example. The goal was to provide suggestions for the prevention and treatment of COVID-19.

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2. Relationship of Se status with diseases and the immune system

2.1. Se intake and endemic diseases

Se is widely found in rocks, soils, and plants. In the natural environment, Se is distributed unevenly on the earth's surface, which leads to large differences in Se content among geological regions (Tan et al., 2002). The average Se content in the earth's crust is about 0.05 mg/kg, although levels up to 0.5 mg/kg have been recorded, while the global average soil Se content is 0.4 mg/kg (range: 0.1–2.0 mg/kg) (Kumar et al., 2014). Soil Se content is closely related to the geological parent materials (Dinh et al., 2018). Atmospheric deposition and anthropogenic emissions also contribute to Se accumulation in soil (Blazina et al., 2014).

Most Se intake by humans is derived from food; the major sources of Se in the food chain are soil, water, and livestock (Dinh et al., 2018). Therefore, local Se deficiency can affect dietary Se intake and cause endemic diseases (Fang et al., 2015). According to a World Health Organization (WHO) report, more than 40 countries are Se deficient, with the lowest levels observed in Finland, Slovakia, New Zealand, sub-Saharan Africa (SSA), and a long belt extending from northeastern to south-central China (Harthill, 2011). Daily dietary Se intake in China and SSA is as low as 10–17 μg, which is far lower than the recommend consumption of 55 μg Se per day in the US. Blood Se levels can be substantially lower than 1 μmol/L in Se-poor regions of China, SSA, and some eastern European countries (Fig. 1). The most typical diseases related to Se deficiency are Keshan disease and Kashin–Beck disease (Shi et al., 2017). The epidemics of Ebola fever and acquired immunodeficiency syndrome (AIDS) in West Africa are also thought to be linked to Se deficiency (Melse et al., 2007; Steinbrenner et al., 2015). In addition, Se deficiency affects the physical development of children's immune systems, which has led to immune impairment of adolescents in Africa (Ramanathan and Taylor 1997; Matson et al., 2020). Given that Se is apparently strongly linked to diseases, how exactly does it affect them? That is what we will discuss next.

2.2. The role of Se in the immune system

Se is an essential component of several major metabolic pathways, including antioxidant, anti-inflammatory, and immune functions (Guillin et al., 2019). It is an important component of selenocysteine (SeCys) and selenomethionine (SeMet). SeMet translates to SeCys by trans-selenation, and the SeCys is lysed into HSe^- by β-lyase; part of the HSe^- is converted into methylated metabolites, while the other part is used for selenoprotein and selenoenzyme synthesis (Fig. 2). Many selenoenzymes are antioxidants, such as glutathione peroxidases (GPxs) and thioredoxin reductases (TrxRs) (Steinbrenner et al., 2015). GPx is an important catalyst for the mutual conversion of glutathione (GSH) and glutathione disulfide (GSSG) (Fig. 3). The GSH and GSSH redox system

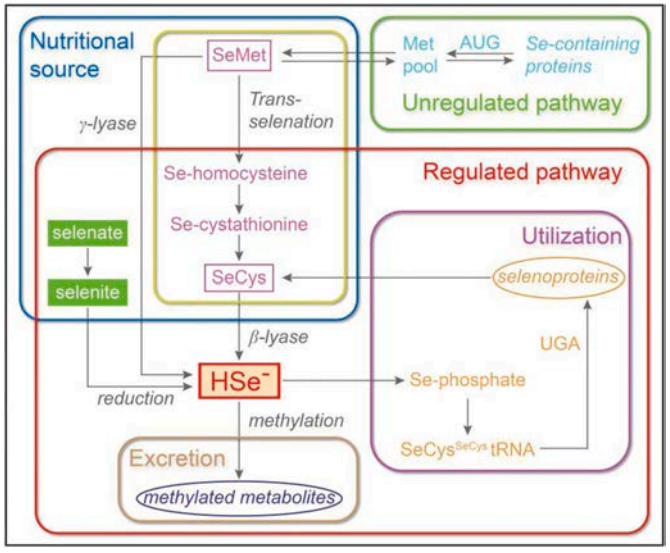

Fig. 2. Metabolism of Se and process involved in the synthesis of selenoprotein (based on Melse et al., 2007). Part of the SeMet is involved in the selenoproteins through selenation translation and β-lyase. Other part of SeMet is excreted by methylation after cracking.

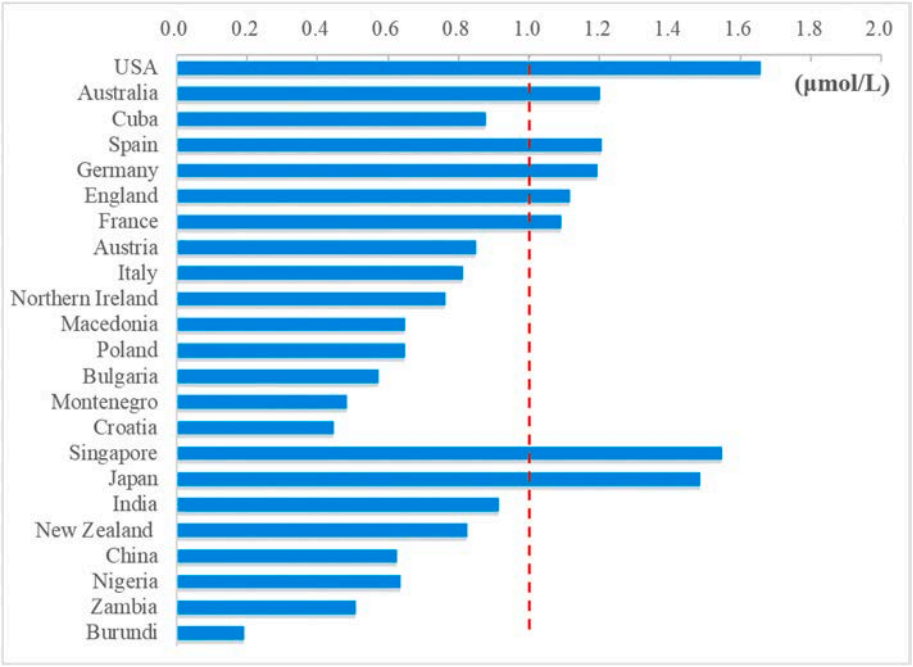

Fig. 1. Se concentrations in serum or plasma of healthy adults worldwide (See supplemental table for details).

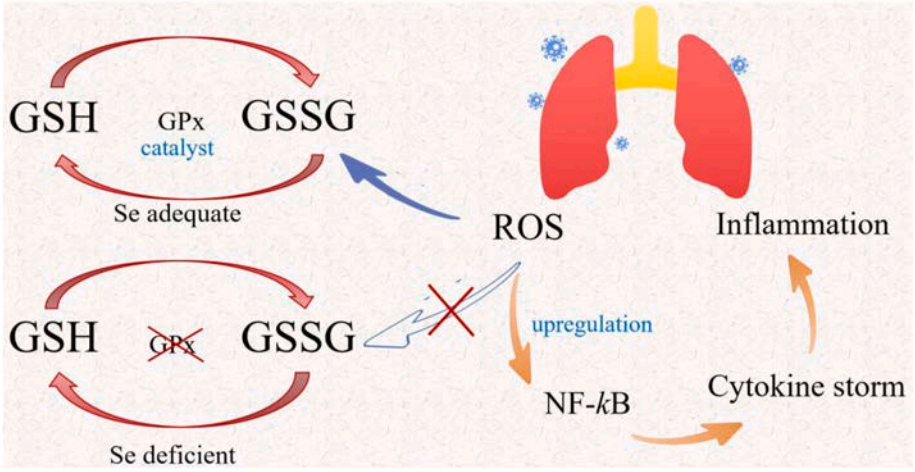

Fig. 3. Potential inflammation mechanism underlying different Se status. Viral infection induces an increase in ROS, and generally, GPx catalyzed GSSG reduction to decrease ROS in host cell; when the host is in Se-deficient, the GPx status will be destroyed. The ROS and free radicals cannot be reduced, thus stimulating the production of various pro-inflammatory cytokines and chemokines by upregulating the NF-*k*B and further causes the inflammatory response. The above process explains how viral infection is related to oxidative stress.

promotes the reduction of harmful reactive oxygen (ROS) (Manzanares et al., 2021). Once GPx status been compromised, ROS and free radicals cannot be reduced and subsequently upregulate nuclear factor *kappa*-B (NF-*k*B). The activation of NF-*k*B plays an important role in controlling the production of various pro-inflammatory cytokines and chemokines. Overproduced cytokines can induce a "cytokine storm", which then causes an inflammatory response in patients (Song et al., 2020). Thus, the above process explains how viral infection is related to oxidative stress, which may be also explain the pathophysiological mechanisms potentially underlying low Se status in severe COVID-19.

Se not only contributes to the function of the host immune system but also has direct effects on viral pathogens. (Reilly, 2006). Since GPx is a virus homologue (Fig. S1), RNA viruses target cellular selenoprotein mRNA via antisense interactions to hijack the selenocysteine insertion sequence ("SECIS" element) of the host cellular mRNA to express the viral selenoprotein and increase virus adaptability (Taylor et al., 2016). The mRNA subtypes of TrxR seem to be targeted in these processes. This condition will also lead to the decrease of host TrxR, thus affecting the antioxidant capacity of host cells (Guillin et al., 2019). Supplementation of selenite can restore the biosynthesis of TrxR in host cells, thereby rebuilding the DNA-synthesis and antioxidant capacities of cells (Hiffler et al., 2020; Kieliszek et al., 2020).

3. Overview of the relationship between Se and RNA viruses

Studies increasingly demonstrate that Se is essential to human health and plays key roles in the treatment of viral diseases (Taylor et al., 2016; Kieliszek and Lipinski, 2020). We further explored the mechanism of Se in the treatment of viral diseases caused by human immunodeficiency virus (HIV), Ebola virus, coxsackievirus, influenza, and hantavirus.

3.1. HIV

HIV is the etiologic agent of human AIDS, and is an enveloped, linear, positive-sense, single-stranded RNA virus (Guillin et al., 2019). As a zoonotic disease, HIV-1 is more infective and has spread worldwide, whereas HIV-2 is mainly confined to western Africa. More than 35 million people are infected with HIV and around 1.5 million people die annually from AIDS and related disease worldwide (WHO, 2003). The HIV-1 positive rate in the population has been used as a surrogate indicator of Se deficiency in Africa (Taylor et al., 1997) since HIV-1 infection rates are significantly higher in Se-poor areas of Africa. It was reported that Se deficiency was significantly associated with mortality in 125 HIV-1-seropositive drug-using men and women (Baum et al., 1997).

Supplementation with 200 μg Se per day can suppress the progression of the HIV-1 viral burden and indirectly improve CD4 T cell counts (Hurwitz et al., 2007). A clinical trial showed that long-term Se supplementation can safely delay the progression of HIV in the early stages of infection (Baum et al., 2013). This is because Se deficiency can damage GPx status, which leads to immune damage to host cells and humors, thereby resulting in an inflammatory response (Manzanares et al., 2021). Furthermore, HIV-1 completes its own selenoprotein expression by hijacking host Se and enhancing viral adaptability (Taylor et al., 2016). These mechanisms may also explain the relationship between Se and SARS-Cov-2, which is also an RNA virus.

3.2. Ebola virus

The Ebola virus is a filamentous, unsegmented, negative-sense RNA virus of the family Filoviridae and can cause hemorrhagic fever (Matson et al., 2020). It has attracted worldwide attention due to its multiple outbreaks in Africa. Eimoemen et al. (2016) examined the relationship between Se and Ebola in Africa and found that Ebola infection was closely linked to seriously low Se blood levels. A previous study suggested the involvement of Se in manifestations of hemorrhagic viral diseases because it plays an important role in regulating blood coagulation by influencing the ratio of thrombin to prostacyclin (Ramanathan and Taylor, 1997). Therefore, it suggests that Se levels affects clinical symptoms in patients through thrombin. It is reported that blood coagulation may increase mortality in patients with COVID-19 (Zhou et al., 2020).

In another study, the Ebola virus was compared to HIV-1 virus, which tethers the mRNAs of host selenoproteins by antisense tethering interactions to express virally encoded selenoprotein modules (Taylor et al., 2016). Since a potential viral selenoprotein may contain multiple Se atoms per molecule, the demand for Se in the host increases dramatically, leading to severe lipid peroxidation and cell-membrane destruction, as well as bleeding symptoms (Harthill, 2011). However, Se^{4+} can oxidize the sulfhydryl groups at the active site of virus protein disulfide isomerase (PDI) to inactive disulfide, thus rendering it unable to penetrate the healthy cell membrane (Kieliszek and Lipinski, 2020), as follows:

$$PDI-(SH)_2+Se^{4+}\rightarrow PDI-S-S-PDI+Se^{2+}$$

A clinical study found that the death rate of viral hemorrhagic fever in very severe and less severe cases fell from 100% to 37% and from 22% to zero, respectively, with oral sodium selenite treatment (Hou, 1997). Thus, sodium selenite inhibition of protein disulfide exchange can prevent thrombo-hemorrhagic events, suggesting selenite may be an inhibitor of Ebola (Lipinski, 2015). The mechanism might be also used to relieve thrombo in COVID-19 patients.

3.3. Coxsackievirus

Coxsackievirus is an RNA virus classified into A and B types. Coxsackievirus type A infects mucous membranes and causes hand, foot, and mouth disease, whereas coxsackievirus B (CVB) tends to infect internal organs, causing systemic inflammation (Germano et al., 2019). Although both viruses typically cause mild, self-limiting symptoms such as fever, rash, and upper respiratory illness, severe CVB infections can cause more life-threatening and endemic diseases like Keshan disease, which occurs in a well-known area with Se deficiency in China (Fang et al., 2015). The degree of myocardial injury in patients with Keshan disease is correlated with oxidative stress, and selenoenzymes are also considered to be involved in its pathogenesis (Pei et al., 2013; Hiffler et al., 2020). Severe oxidative stress responses were found in patients with COVID-19 (Manzanares et al., 2021). As shown in Fig. 3, selenoenzyme is an important participant in the process of oxidative stress in patients with viral diseases, therefore, it is believed that Se may be one of the important factors affecting oxidative stress in COVID-19 patients.

A mouse-model study in China showed that lower levels of Se in mice infected with CVB4 were associated with more severe heart damage (Cao et al., 2003). Beck et al. (1995) showed that CVB3 infection in mice causes myocarditis similar to that found in humans. The inoculation of non-cardio-virulent CVB3 (Figs. S2 A–B) into mice showed that the virus mutated and was found at higher levels in Se-deficient mice, whereas it showed no genetic variation in mice with adequate Se levels (Guillin et al., 2019). Inoculation of CVB3 (Figs. S2 B–C) recovered from the hearts of Se-deficient mice into Se-adequate mice causes severe myocardial damage, suggesting that Se deficiency initiates changes in the viral genome, making the virus more virulent (Beck et al., 1995; Guillin et al., 2019). It appears that adequate levels of Se in the host may prevent the virus from mutating. For example, Se supplementation among residents of the Chinese Keshan area greatly decreased the number of deaths (Li et al., 2013). Moghaddam et al. (2020) proposed that individuals with low baseline Se status y spread the SARS-CoV-2 efficiently and allow viral replication and rapid evolution of particular pathogenic viral species. Thus, the Se levels in host might influence SARS-CoV-2 mutation.

3.4. Influenza viruses

The influenza A virus is classified into 16 hemagglutinin (HA) subtypes and nine neuraminidase (NA) subtypes according to antigenicity (Neumann et al., 2009). Influenza viruses have yearly outbreaks, sometimes killing millions of people. Influenza pandemics occurred in 1918, 1957, 1968, and 2009 due to the introduction of novel influenza viruses from poultry and swine hosts (Yewdell et al., 2013). Point mutations and recombination of influenza viral genomes have led to the emergence of new variants or strains with pandemic or pandemic potential (Neumann et al., 2009). Beck et al. (2001) reported that the pathogenicity of the influenza virus changes rapidly in Se-deficient hosts. Host Se deficiency promotes rapid genomic evolution of viruses in HA and NA genes compared to Se-rich animals (Beck et al., 2001). Se deficiency can cause significant changes to the morphology of respiratory epithelial cells, altering their response and increasing their susceptibility to viral infection (Jaspers et al., 2007).

Se supplementation provide immune benefits to influenza vaccine (Jayawardena et al., 2020). Tests of Se supplementation and Se deficiency in mice infected with H1N1 virus resulted in 25% and 75% mortality, respectively (Yu et al., 2011). In addition, in Se-deficient mice, viral mutations of influenza virus H3N2 increased and more severe lung tissue damage was seen (Nelson et al., 2001). Similarly, clinical trials have also demonstrated the positive effect of Se on influenza immune response. Patients with influenza (H1N1) pneumonia had greater Se deficiency than the control group, and patients with H1N1 whose blood Se levels were best for GPx activity recovered more easily and had a higher survival rate than patients with low Se levels (Hiffler et al., 2020). Based on the above response between Se and influenza virus, nanomaterials containing Se have been developed to fight H1N1 virus, and these drugs have shown positive effects in inhibiting virus-induced apoptosis and preventing viral infection in Madin–Darby Canine Kidney cells (Li and Lin, 2018; Wang et al., 2020). Considering that the Se might affect the survival rate of influenza virus hosts through regulating of GPx, the similar mechanism might be applied to the COVID-19.

3.5. Hantavirus

Hantavirus is a single-stranded RNA virus of the bunyavirus family (Vaheri et al., 2013). Hantavirus infection causes hemorrhagic fever with renal syndrome (HFRS), a zoonotic disease characterized by fever and renal failure, which are accompanied by bleeding and shock (Goeijenbier et al., 2013). HFRS is common in Se-deficient areas; a previous study found that in vitro Se supplementation reduced viral replication in endothelial cell models with low-level multiple infection, and areas with severe ($\leq$0.02 ppm) and moderate (0.03–0.05 ppm) Se deficiency had HFRS incidence about 6-fold and 2-fold higher, respectively, than regions with adequate Se levels (Fang et al., 2015). Kieliszek et al. (2020) reported that sodium selenite inhibits the entrance of viruses into healthy cells and abolishes their infectivity. There is a close relationship between the incidence of HFRS and soil Se distribution in China (Fang et al., 2015). Recent research has also shown that the cure rate and death rate of COVID-19 are significantly related to human Se levels (which reflect Se intake and distribution) in China (Zhang et al., 2020b).

In addition, Kieliszek et al. (2020) reported that sodium selenite inhibits the entrance of viruses into healthy cells and abolishes their infectivity. And the mortality of patients with severe cases of hantavirus infection decreased by nearly 60% with oral sodium selenite supplementation (Hou, 1997). Therefore, the SARS-CoV-2 might be inhibited as well by supplementation of sodium selenite.

3.6. SARS-CoV

Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by the coronavirus SARS-CoV (Kuiken et al., 2003; Drosten et al., 2003). SARS virulence in humans begins with the entry of the novel coronavirus into pulmonary cells; infection severely impairs respiratory function by affecting epithelial cells in the lower respiratory tract (Kuiken et al., 2003). SARS spread from Asia, where the first outbreak occurred in 2003, to Europe and America, infecting 8437 people and causing 813 deaths worldwide (WHO, 2003).

Suboptimal health related to deficiency of the trace element Se is one of the main causes of atypical pneumonia (Lin, 2003). Raymond et al. (2004) also suggested that dietary supplementation with nutrients like Se can improve immunity against potential SARS infections. Studies have shown that the activation of NF-*k*B in cells infected with SARS-CoV nucleocapsid protein contributes, at least partly, to severe lung inflammation and lesions in SARS (Liao et al., 2005). DeDiego et al. (2014) reported that in a SARS-CoV-induced mouse experiment, the survival rate of mice was higher when inhibiting NF-*k*B. Se can inhibit NF-*k*B activation, which may help to reduce virus-induced apoptosis and alleviate inflammation and lesions (Hiffler et al., 2020). Therefore, it is particularly important to take the host's nutrition levels into account when new infectious diseases emerge or old diseases reappear with new pathogenic properties, such as with SARS (Beck et al., 2004) and SARS-CoV-2.

4. Implications of Se for SARS-CoV-2

SARS-CoV-2 is an enveloped, single-stranded, positive-sense RNA virus (Chan et al., 2020). People infected with SARS-CoV-2 may experience severe pneumonia and acute respiratory failure (Zhou et al.,

2020). Like other RNA virus, SARS-CoV-2 infection is thought to induce oxidative stress by producing ROSs and altering the cell's antioxidant defenses, including GPx and TrxR (Mahmoodpoor et al., 2019). SARS-CoV-2 induces endotheliitis, which leads to endothelial-cell infection in different organs and host inflammation directly (Varga et al., 2020). GPx and TrxR are important to endothelial-cell function. Supplementation of selenite can enhance the activity of GPX and TrxR, thereby reducing the oxidative damage to human endothelial cells (Hiffler et al., 2020; Bae et al., 2020). In addition, up to 20% of COVID-19 cases develop severe disease with fever and pneumonia, thereby inducing acute respiratory distress syndrome (ARDS) (Moore & June 2020), which is a sepsis-related process caused by a cytokine storm due to NF-*k*B activation by the virus (Manzanares et al., 2021). Supplementation of Se, especially selenite, in ARDS cases modulated GPx and NF-*k*B, which are important for restoring the antioxidant capacity of lungs, alleviating inflammatory responses, and improving respiratory mechanics (Mahmoodpoor et al., 2019; Hiffler et al., 2020). Therefore, Se deficiency may be a risk factor for incidence, mortality, and cure rate of COVID-19.

Zhang et al. (2020b) found a significant positive relationship between Se levels in human hair and the cure rate for COVID-19 in China. Another study reported that COVID-19 patients in Germany who survived had higher Se serum levels than patients who died (Moghaddam et al., 2020). In another report, COVID-19 patients in Korea with and without pneumonia were significantly deficient in Se (Im et al., 2020). Supplementation of Se may improve host immunity and prevent host-cell oxidative stress by regulating GPx and TrxR in the human body (Hiffler et al., 2020). Kieliszek et al. (2020) also proposed that sodium selenite can be a potential chemical compound used in the battle against COVID-19. Thus, we suggest that host Se status should be taken into account in clinical treatment of COVID-19, especially in regions exhibiting soil Se deficiency.

To explore whether there is a relationship between the incidence of COVID-19 and local Se levels, we collected data of diagnosed COVID-19 cases from different cities of Hubei from the website of the Health Commission of Hubei Province (2020), which updated the COVID-19 dynamics in real time (Table S2). The data were collected by April 30, 2020, when the city of Wuhan was unsealed. The incidence rate of COVID-19 was calculated for different cities in Hubei. The incidence rate was 6.3 per 100,000 inhabitants in Enshi city, which is famous for Se enrichment, while in other cities and counties except Wuhan, the incidence was between 14 per 100,000 inhabitants and 140 per 100,000 inhabitants (Fig. 4). Shiyan Xiangyang, Jingzhou, and Yichang cities also had a relatively low incidence, ranging from 14.4 per 100,000 inhabitants to 23.8 per 100,000 inhabitants. Surface Se-enriched soil in Hubei province is divided into two belts and three zones: the Shiyan–Danjiangkou (Shiyan city)–Zhongxiang (Jinmen city) belt and Badong (Enshi city)–Zigui (Yichang city)–Yichang belt; and the Enshi zone, Hanjiang plain zone and the zone southeast of Hubei (Xu et al., 2018). Among them, the Enshi area is extremely enriched in Se. Suizhou and Xiaogan are Se-deficient areas in Hubei, and the incidence in these two cities was also the highest apart from that in Wuhan city (Fig. 5). Therefore, we speculate that there is a relationship between the soil Se level and the incidence of COVID-19 in different areas of Hubei Province. The relatively high dietary Se intake in Se-rich areas can enhance human immunity, which may contribute to resisting SARS-CoV-2 infection.

5. Conclusion

Soil Se distribution may be an important risk factor affecting the occurrence of COVID-19 in Hubei province, and human Se levels may contribute to antioxidant, anti-inflammatory, and immune effects in COVID-19. Therefore, we suggest that serum Se levels in patients with COVID-19 and clinical selenite drug therapy should be considered to support disease treatment and management. In addition, the mutation of coxsackievirus in a mouse model showed that the synthesis of antioxidant selenoenzymes and selenoprotein P in infected cells decreases due to host Se deficiency, which enhances viral replication and mutation, thereby causing more severe tissue damage. Thus, it is important to pay attention to the effect of dietary Se deficiency in the development of COVID-19 in Se-deficient areas, especially in light of the recent occurrence of SARS-CoV-2 mutation (Greaney et al., 2021). Finally, the observed association of incidence rate in Se-deficient and Se-enrichment area, as well as the potential mechanism of Se on SARS-CoV-2 provide a basis for high quality intervention research, while, further studies are

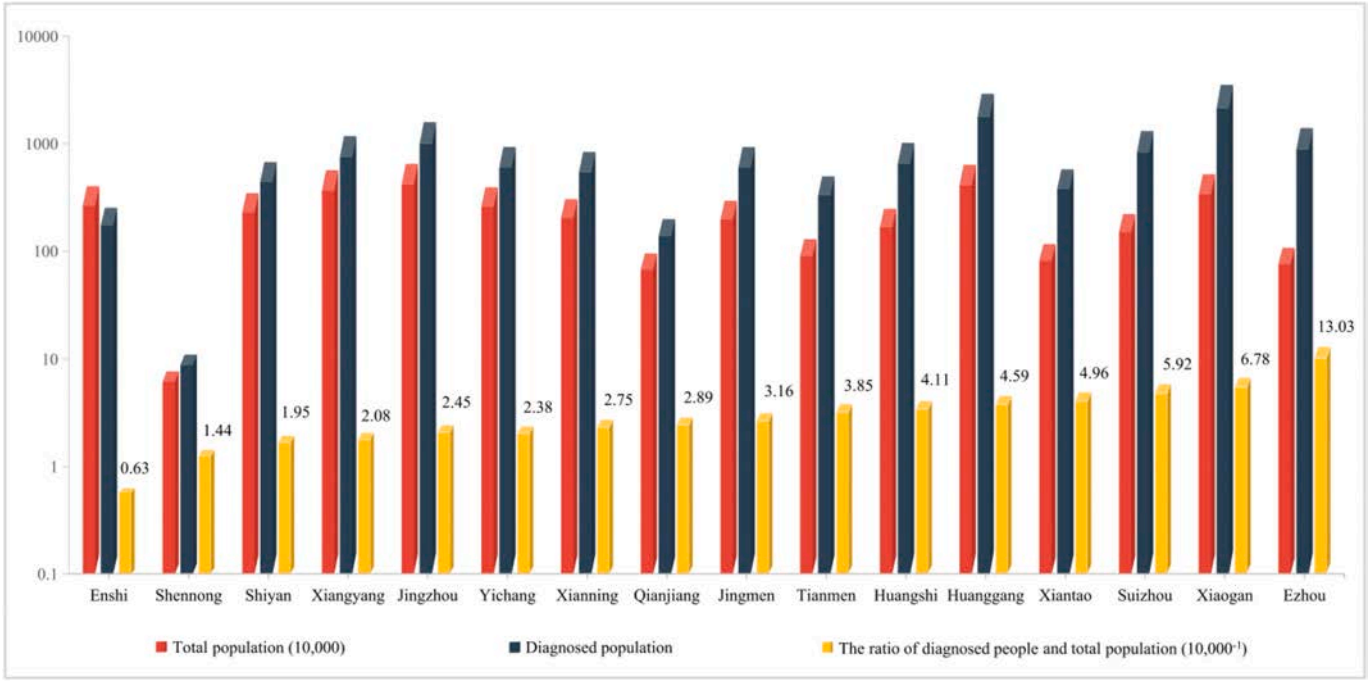

Fig. 4. The incidence of COVID-19 cases in different cities of Hubei province (data were collected by April 30th, 2020).

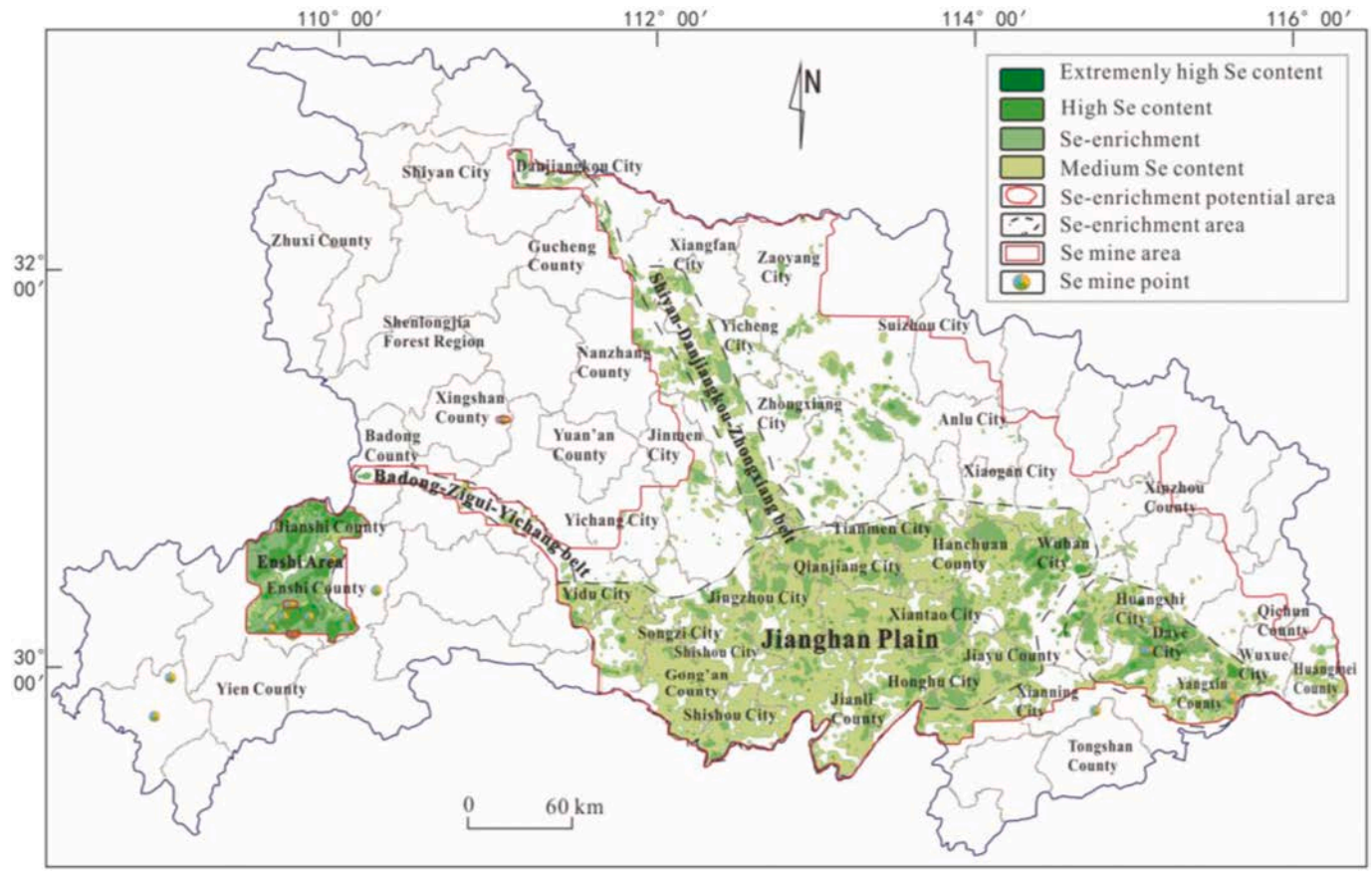

Fig. 5. Distribution of Se in soil of Hubei province (based on Xu et al., 2018).

needed to elucidate the mechanism of Se on SARS-CoV-2 and the relationship between SARS-CoV-2 mutation and host Se status.

Credit author statement

Qiyuan Liu and Xiaoli Zhao analyzed data and wrote the paper. Jin Ma and Fengchang Wu designed research, Yunsong Mu, Ying Wang, Shuhui Yang, Yihang Wu, and Yongzhang Zhou collected data.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.110984.

References

Bae, M., Kim, H., 2020. The role of vitamin C, vitamin D, and selenium in the immune system against COVID-19. Molecules 25 (22), 5346.
Baum, M.K., Campa, A., Lai, S., et al., 2013. Effect of Micronutrient supplementation on disease progression in asymptomatic, antiretroviral-naive, HIV-infected adults in Botswana a randomized clinical trial. J. Am. Med. Assoc. 310 (20), 2154–2163.
Baum, M.K., Shorposner, G., Lai, S., et al., 1997. High risk of HIV-related mortality is associated with selenium deficiency. J. Acquir. Immune Defic. Syndr. Hum. Retrovirol. 15 (5), 370.
Beck, M.A., Handy, J., Levander, O.A., et al., 2004. Host nutritional status: the neglected virulence factor. Trends Microbiol. 12 (9), 417–423.
Beck, M.A., Nelson, H.K., Shi, Q., et al., 2001. Selenium deficiency increases the pathology of an influenza virus infection. Federation Amer. Soc. Exp. Biol. 15, 1481–1483.
Beck, M.A., Shi, Q., Morris, V.C., et al., 1995. Rapid genomic evolution of a non-virulent Coxsackievirus B3 in selenium-deficient mice results in selection of identical virulent isolates. Nat. Med. 1, 433–436.
Blazina, T., Sun, Y.B., Voegelin, A., et al., 2014. Terrestrial selenium distribution in China is potentially linked to monsoonal climate. Nat. Commun. 4717 (5), 1–7.
Cao, D.Y., Zhong, X.K., Liu, Y., 2003. Exerimental research on myocardial injury and mechanism of apoptosis induced by CVB4 in Se-deficient mice. Chin. J. Ctrl. Endemic Disenaces 18 (1), 3–5 (In Chinese).
Chan, J.F., Yuan, S., Kok, K.H., et al., 2020. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 10223 (395), 514–523.
DeDiego, M.L., Nieto-Torres, J.L., Regla-Nava, J.A., et al., 2014. Inhibition of NF-kappaB-mediated inflammation in severe acute respiratory syndrome coronavirus-infected mice increases survival. J. Virol. 88 (2), 913–924.
Dinh, Q.T., Cui, Z., Huang, J., et al., 2018. Selenium distribution in the Chinese environment and its relationship with human health: a review. Environ. Int. 112, 294–309.
Drosten, C., Günther, S., Preiser, W., et al., 2003. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N. Engl. J. Med. 348 (20), 1967–1976.
Eimoemen, N.A., Menshawy, A., Negida, A., et al., 2016. Ebola outbreak in west Africa; Is selenium involved? Int. J. Pept. Res. Ther. 22 (1), 135–141.
Fang, L.Q., Goeijenbier, M., Zuo, S.Q., et al., 2015. The association between Hantavirus infection and selenium deficiency in mainland China. Viruses 7, 333–351.

Germano, J.F., Sawaged, S., Saadaeijahromi, H., et al., 2019. Coxsackievirus B infection induces the extracellular release of miR-590-5p, a proviral microRNA. Virology 529, 169–176.
Goeijenbier, M., Wagenaar, J., Goris, M., et al., 2013. Rodent-borne hemorrhagic fevers: under-recognized, widely spread and preventable-epidemiology, diagnostics and treatment. Crit. Rev. Microbiol. 39 (1), 26–42.
Greaney, A.J., Loes, A.N., Crawford, K.H., 2021. Comprehensive mapping of mutations to the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human serum antibodies. Cell Host Microbe 29, 1–14.
Guillin, O.M., Vindry, C., Ohlmann, T., et al., 2019. Selenium, selenoproteins and viral infection. Nutrients 2102 (11), 1–33.
Harthill, M., 2011. Review: micronutrient selenium deficiency influences evolution of some viral infectious diseases. Biol. Trace Elem. Res. 143 (3), 1325–1336.
Hiffler, L., Rakotoambinina, B., 2020. Selenium and RNA virus interactions: potential implications for SARS-CoV-2 infection (COVID-19). Front. Nutr. 7, 164.
Hou, J.C., 1997. Inhibitory effect of selenite and other antioxidants on complement-mediated tissue injury in patients with epidemic hemorrhagic fever. Biol. Trace Elem. Res. 56 (1), 125–130.
Hurwitz, B.E., 2007. Suppression of human immunodeficiency virus type 1 viral load with selenium supplementation. Arch. Intern. Med. 167 (2), 148–154.
Im, J.H., Je, Y.S., Baek, J., et al., 2020. Nutritional status of patients with coronavirus disease 2019 (COVID-19). Int. J. Infect. Dis. 100, 390–393.
Jaspers, I., Zhang, W., Brighton, L.E., et al., 2007. Selenium deficiency alters epithelial cell morphology and responses to influenza. Free Radic. Biol. Med. 42 (12), 1826–1837.
Jayawardena, R., Sooriyaarachchi, P., Chourdakis, M., et al., 2020. Enhancing immunity in viral infections, with special emphasis on COVID-19: a review. Diab. Met. Synd. Clin. Res. Rev. 14 (4), 367–382.
Khursheed, A., Alam, S., Tyagi, V.K., et al., 2020. Future liasing of the lockdown during COVID-19 pandemic: the dawn is expected at hand from the darkest hour. Groundw. Sustain. Dev. 11, 100433.
Kieliszek, M., Lipinski, B., 2020. Selenium supplementation in the prevention of coronavirus infections (COVID-19). Med. Hypotheses 143, 109878.
Kumar, M., Mazumder, P., Mohapatra, S., et al., 2021. A chronicle of SARS-CoV-2: seasonality, environmental fate, transport, inactivation, and antiviral drug resistance - ScienceDirect. J. Hazard Mater. 405, 124043.
Kumar, B.S., Priyadarsini, K.I., 2014. Selenium nutrition: how important is it? Biomedicine & Preventive Nutrition 4 (2), 333–341.
Kuiken, T., Fouchier, R.A., Schutten, M., et al., 2003. Newly discovered coronavirus as the primary cause of severe acute respirarory syndrome. Lancet 362 (9380), 263–270.
Kumar, M., Kuroda, K., Dhangar, K., et al., 2020. Potential emergence of antiviral-resistant pandemic viruses via environmental drug exposure of animal reservoirs. Environ. Sci. Technol. 54 (14), 8503–8505.
Li, Y.H., Lin, Z.F., et al., 2018. Inhibition of H1N1 influenza virus-induced apoptosis by functionalized selenium nanoparticles with amantadine through ROS-mediated AKT signaling pathways. Int. J. Nanomed. 13, 2005–2016.
Li, Q., Liu, M., Hou, J., et al., 2013. The prevalence of Keshan disease in China. Int. J. Cardiol. 168 (2), 1121–1126.
Liao, Q.J., Ye, L.B., Timani, K.A., et al., 2005. Activation of NF-kappaB by the full-length nucleocapsid protein of the SARS coronavirus. Acta Bioch. Biophy. Sin. 37 (9), 607–612.
Lin, Z., 2003. Atypical pneumonia and trace elements. Guangdong Trace Elem. Sci. 10 (2), 23–25 (In Chinese).
Lipinski, B., 2015. Can selenite be an ultimate inhibitor of EBOLA and other viral infections? Br. J. Med. Med. Res. 6 (3), 319–324.
Mahmoodpoor, A., Hamishehkar, H., Kamran, S., et al., 2019. The effect of intravenous selenium on oxidative stress in critically ill patients with acute respiratory distress syndrome. Immunol. Invest. 48 (2), 147–159.
Manzanares, W., Moreira, E., Hardy, G., 2021. Pharmaconutrition revisited for critically ill patients with coronavirus disease 2019 (COVID-19): does selenium have a place? Nutrition, 81, 110989.
Matson, M.J., Chertow, D.S., Munster, V.J., et al., 2020. Delayed recognition of Ebola virus disease is associated with longer and larger outbreaks. Emerg. Microb. Infect. 9 (1), 291–301.
Melse, A., Hogenkamp, P., Lungu, O., 2007. Mitigating HIV/AIDS in Sub-saharan Africa through Selenium in Food (A Report), pp. 23–28.
Méplan, C., Hughes, D.J., 2020. The role of selenium in health and disease: emerging and recurring trends. Nutrients 12 (4), 1049.
Moghaddam, A., Heller, R.A., Sun, Q., et al., 2020. Selenium deficiency is associated with mortality risk from COVID-19. Nutrition 12 (7), 2098.
Moore, J.B., June, C.H., 2020. Cytokine release syndrome in severe COVID-19. Science 368 (6490), 473–474.
Mukherjee, S., Mazumder, P., Joshi, M., et al., 2020. Biomedical application, drug delivery and metabolic pathway of antiviral nanotherapeutics for combating viral pandemic: a review. Environ. Res. 191, 110119.
Nelson, H.K., Shi, Q., Dael, P.V., et al., 2001. Host nutritional selenium status as a driving force for influenza virus mutations. Federation Amer. Soc. Exp. Biol. 15 (10), 1127–1138.
Neumann, G., Noda, T., Kawaoka, Y., et al., 2009. Emergence and pandemic potential of swine-origin H1N1 influenza virus. Nature 459, 931–939.
Pei, J., Fu, W., Yang, L., et al., 2013. Oxidative stress is involved in the pathogenesis of Keshan disease (an endemic dilated cardiomyopathy) in China. Oxid. Med. Cell Longev. 2013, 474203.
Ramanathan, C.S., Taylor, E.W., 1997. Computational genomic analysis of hemorrhagic fever viruses. Viral selenoproteins as a potential factor in pathogenesis. Biol. Trace Elem. Res. 56, 93–106.
Raymond, C.H., Joshua, K., 2004. Severe acute respiratory syndrome and sport, facts and fallacies. Sports Med., 34 (15), 1023–1033.
Reilly, C., 2006. Selenium in health and disease IV: The immune response and other selenium-related conditions. Selenium in Food and Health. Springer, pp. 134–148.
Shi, Z., Pan, P., Feng, Y., et al., 2017. Environmental water chemistry and possible correlation with Kaschin-Beck Disease (KBD) in northwestern Sichuan, China. Environ. Int. 99, 282–292.
Song, P., Li, W., Xie, J., et al., 2020. Cytokine storm induced by sars-cov-2. Clin. Chim. Acta 509, 280–287.
Steinbrenner, H., Al-Quraishy, S., Dkhil, M.A., et al., 2015. Dietary selenium in adjuvant therapy of viral and bacterial infections. Adv. Nutr. 6 (5), 73–82.
Tan, J.A., Zhu, W.Y., Wang, W.Y., et al., 2002. Selenium in soil and endemic diseases in China. Sci. Total Environ. 284 (1), 227–235.
Taylor, E.W., Bhat, A., Nadimpalli, R.G., et al., 1997. HIV-1 Encodes a sequence overlapping env gp41 with highly significant similarity to selenium-dependent glutathione peroxidases. J. Acquir. Immune Defic. Syndr. Hum. Retrovirol. 15 (5), 393–394.
Taylor, E.W., Ruzicka, J.A., Premadasa, L., et al., 2016. Cellular selenoprotein mRNA tethering via antisense interactions with Ebola and HIV-1 mRNAs may impact host selenium biochemistry. Curr. Top. Med. Chem. 16 (13), 1530–1535.
Zhou, F., Yu, T., Du, R., et al., 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395, 1054–10626, 10229.
The Health Commission of Hubei province. http://wjw.hubei.gov.cn/bmdt/ztzl/fkxxgzbdgrfyyq/xxfb/202005/t20200501_2256977.shtml.
Vaheri, A., Strandin, T., Hepojoki, J., et al., 2013. Uncovering the mysteries of hantavirus infections. Nat. Rev. Microbiol. 11 (8), 539–550.
Varga, Z., Flammer, A.J., Steiger, P., et al., 2020. Endothelial cell infection and endotheliitis in endothelial cell infection and endotheliitis in COVID-19. Lancet 395, 1417–1418, 10229.
Wang, C.B., Chen, H.Y., Zhao, M.Q., et al., 2020. The inhibition of H1N1 influenza virus-induced apoptosis by surface decoration of selenium nanoparticles withβ-thujaplicin through reactive oxygen species-mediated AKT and p53 signaling pathways. ACS Omega 5 (2), 30633–30642.
World Health Organization, 2003. Severe Acute Respiratory Syndrome (SARS): Status of the Outbreak and Lessons for the Immediate Future. https://www.who.int/csr/media/sars_wha.pdf.
Xu, C.Y., Ding, X.Y., Yan, J.L., 2018. Geological characteristics and usage regionalization of Se-enriched resources in Hubei. Glob. Geol. 37 (1), 140–147 (In Chinese).
Yewdell, J.W., Spiro, D.J., Golding, H., et al., 2013. Getting to the heart of influenza. Sci. Transl. Med. 5 (191), 1–2.
Zhang, H., Zhou, P., Wei, Y., et al., 2020a. Histopathologic changes and SARS-CoV-2 immunostaining in the lung of a patient with COVID-19. Ann. Intern. Med. 173 (4), 629–632.
Yu, L., Sun, L., Nan, Y., et al., 2011. Protection from H1N1 influenza virus infections in mice by supplementation with selenium: a comparison with selenium-deficient mice. Biol. Trace Elem. Res. 141 (1–3), 254–261.
Zhang, J.S., Taylor, E.W., Bennett, K., et al., 2020b. Association between regional selenium status and reported outcome of COVID-19 cases in China. Am. J. Clin. Nutr. 111 (6), 1297–1299.