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THE EFFECT OF SELENIUM ON THE HEALTH OF PATIENTS WITH COVID-19

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STRESZCZENIA / ABSTRACTS

Selenium (Se) is one of the trace elements necessary for the normal functioning of the human body. Deficiency or excess of this element may pose a potential threat in maintaining the homeostatic mechanisms of the body, including disruption of the immune system. Se deficiency significantly reduces the body's immunity by facilitating infections with various pathogens, including SARS-COV-2 infections. This paper reviews the literature covering issues of the impact of Se deficiency on the incidence and course of COVID-19, and considers its preventive significance.
Keywords: Selenium, immunological immunity, COVID-19 patient, SARS-CoV2.

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INTRODUCTION

Selenium is a non-metal belonging to the oxygen group. In inorganic form it occurs in the form of selenate (VI) and selonate (IV), while in organic form it builds two basic amino acids - selenomethionine and selenocysteine. Both amino acids were formed by replacing the sulfur atom present in cysteine and methionine with a selenium atom. Thus, selenocysteine has a selenium group (-SeH) instead of a thiol group, while selenomethionine has a selenium atom at the 4th carbon instead of a sulfur atom [1]. In the environment, it occurs in three allotropic varieties, however, in these forms it has no biological activity.

Selenium (Se) belongs to the group of trace elements. The demand for Se and its content in the body are small, but this small amount is essential for life and proper functioning. In the 1960s, it became known as the "element of life" because it has been proven to be essential for the maintenance of normal human body functions, including proper development and growth [2,3,4,5]. Se is an element that only in a narrow range of concentrations should be considered useful, in excess it has a harmful effect [6]. The daily requirement for Se is age-dependent. In 2000, the United States National Academy of Sciences (NAS) published data on recommended dietary Se intakes. It found that the Estimated Average Daily Requirements (EAR) and Recommended Dietary Allowance (RDA-Recommended Dietary Allowance) for Se for adult women and men are 45 μg selenium/day. According to a report by the U.S. Food and Drug Administration (FDA-Food and Drug Administration), published in 2008, the reference daily intake of Se (defined as RDI-Reference Daily Intake) is 70 μg/day. The demand for Se increases in pregnant and lactating women, due to the needs of the developing foetus and the secretion of this element with milk. The recommended daily intake of Se is then 60-70 μg Se/day. The toxic dose is estimated at 5 mg/day [1,5,6].

Selenium was discovered in 1817 by Swedish chemist Berzelius and was considered a toxic element until 1957. Ever since Klaus Schwartz discovered the beneficial importance of Se in an animal experiment, interest in this element in relation to human health has increased [5].

METHODS

A literature review was conducted from PubMed, Scopus, Google Scholar databases to evaluate the effect of selenium on morbidity during the COVID-19 pandemic and its prophylactic effect. Analysis of the data obtained will allow the creation of prevention scenarios with selenium supplementation in immunocompromised patients. Search keywords included: Selenium, COVID-19 patient, SARS-CoV2, morbidity, immunity.

FUNCTIONS OF SELENIUM IN THE HUMAN BODY

Selenium is involved in the construction of important enzyme proteins. During analysis of the human genome, 25 genes that encode selenoproteins were detected [7,8]. Se is a component of many enzymes with antioxidant activity: glutathione peroxidase, selenoprotein P, thioredoxin reductase and phospholipid hydroperoxide glutathione peroxidase. Being part of glutathione peroxidase, it has an important function as an antioxidant and is involved in scavenging free radicals. Its action is to inhibit harmful processes of peroxidation of lipids, nucleic acids (DNA, RNA), and thus protects cells from deformation and genetic damage [9].There are 3 main families of enzymes in the structure of which Se is present: glutathione peroxidases, iodothyronine deionidases and thioredoxin reductases.

In addition, 12 individual selenoproteins with antioxidant, anti-inflammatory and chemoprotective properties have also been detected in the human body. The element is found in amino acids important for the proper functioning of living organisms, such as selenocysteine and selenomethionine, which in turn are the building blocks of dozens of proteins that play both structural and enzymatic roles.

The metabolism of selenium in the body is very complex and depends mainly on the form in which it enters the body. It can be absorbed in organic and inorganic forms. Inorganic forms include selenate (VI) and sodium selenite (selenate IV), while organic forms we can include selenomethionine and methylated selenocysteine. It has been shown that humans absorb organic forms to a greater extent than inorganic salts [10].Studies have shown that selenomethionine was absorbed in 98% and sodium in selenate 84% [11,12].

Se participates in the metabolism of thyroid hormones as a catalyst for the synthesis of their active forms. It stimulates the immune system, as it exhibits anti-inflammatory and antiviral properties (for example, it inhibits the progression of HIV infection, limiting the development of AIDS disease). Se is necessary for the normal growth of nerve cells, and plays an important role in the transmission of nerve impulses in the central nervous system. It participates in the elimination of free radicals and heavy metals: arsenic, cadmium, silver and mercury [13,14, 10].

Selenium (Se), due to its antioxidant properties, plays a role in protecting against oxidative stress and maintaining a functioning immune system[8]. It affects both non-specific macrophages - humoral response, and B and T lymphocytes, - cellular response. Se deficiency contributes to reduced proliferation of T lymphocytes, affects the activity of NK (Natural Killer) cells [15]. Se levels also affect macrophage differentiation. Under conditions of Se deficiency, more M1 macrophages are formed, while under conditions of Se excess, mainly M2 macrophages are formed. This pattern of action allows for the induction of a pro-inflammatory cellular immune response directed against viral and bacterial pathogens by Th1 lymphocytes, while protecting against an overly potent immune response [16]. Se deficiency can be dangerous in viral infections, as redox imbalance in the cell contributes to the development of infection. Se deficiency is unfavourable in infections with mutation-prone RNA viruses, which can assume a more virulent form under the influence of RFTs [16,17]. Se should be supplied to the human body with food of plant and animal origin. However, the main problem in the therapeutic use of this element is its narrow therapeutic range.

PREVENTION, COVID-19 DISEASE AND RECOVERY WITH SELENIUM IN MIND

SARS-CoV-2 infections underlie the current pandemic of coronavirus disease (COVID-19) and are responsible for a large number of deaths, especially among the elderly and those with comorbidities. The risk of mortality from severe illness, such as sepsis or multi-organ injury, is inversely proportional to Se status [18].

The observed association of mortality risk with selenium deficiency and the likely underlying feedback mechanism argue in favor of initiating intervention trials according to the highest quality standards so as not to miss a widely available, inexpensive and safe preventive measure and complementary treatment option[19]. Ongoing studies have reported that Se level were significantly higher in surviving COVID-19 patients compared to those who did not survive [18,19]. These findings reinforce the view of an important role for Se in recovery from COVID and support the discussion of complementary Se supplementation in severely sick Se-deficient patients [18,19].

Because SARS-CoV2 virus is transmitted by the droplet route, as well as through contact with surfaces that an infected person has come into contact with, it is important to pay attention to the efficiency of the immune system, which is largely dependent on diet [19].

A cross-sectional observational study conducted at two hospitals in Ghent, Belgium, to investigate whether Se deficiency on admission correlates with disease severity and mortality risk in COVID-19 patients with or without comorbidities, indicated that Se is an essential trace element needed for normal immune system response, cell signalling and antiviral defense [19,20]. Inadequate Se status on admission of patients was associated with higher mortality and more severe disease course in the entire study group, especially in the senior population. Compared to healthy European adults, patients with confirmed COVID-19 on hospital admission showed severely reduced total Se level. These studies have led to the contention that trace element assessment at hospital admission may contribute to better stratification from treatment of patients with COVID-19 and other similar infectious diseases, support clinical care, therapeutic interventions and supplementation needs, and may be particularly relevant for patients with significant comorbidities [21,22].

A sufficiently good supply of Se is an important and usable support, especially in disease prevention, as it is determined by the chosen nutritional profile. Knowing this link, this drawback presents itself as an avoidable and remediable challenge that can be dealt with by combining a conscious and balanced diet with targeted mineral (Se) supplementation [9], which can help improve immunity, which is essential during a pandemic [23,24].

Contemporary studies show a link between low levels of selenium in the body and respiratory failure. A prospective observational study of 83 people with respiratory disease showed that patients requiring intensive care had 28% lower Se level compared to those who did not require hospitalization (70.0 ± 26.4 and 97.9 ± 20.8 ng/ml, respectively; $p < 0.001$). Ongoing studies also found that lower Se level were associated with a decrease in lymphocyte and albumin levels [25]. The introduction of Se-containing supplements into the treatment of respiratory diseases has benefits, which have been confirmed by clinical studies [26]. The administration of sodium selenite (1 mg/24 h for 3 days and 1 mg/24 h for the remaining 6 days) by injection in patients with acute respiratory distress syndrome by alleviating inflammation occurring in the lungs may contribute to protection against lung damage. In this case, the administration of sodium selenite restored adequate levels of selenium in the body and lowered the levels of pro-inflammatory cytokines (IL-1b and IL-6), which contributed to improved respiratory mechanics in the patients. However, supplementation had no significant effect on survival, nor did it have a significant effect on the duration of mechanical ventilation [26]. A population-based retrospective analysis conducted in China during the COVID-19 pandemic showed that Se deficiency correlates with increased deaths from SARS-CoV-2 infection, and it was reported in the literature that those living in Hubei province had significantly lower cure rates [27]. There is an association between regional Se status and reported incidence of COVID-19 in China [28,29,30].

In addition, high levels of Se and its presence in the diet of residents of Enshi province compared to residents of Hubei correlated with higher recovery rates (36.4% for Enshi and 13.1% for Hubei, respectively). In Heilongjiang province, where residents had low Se level (0.26 mg/kg body weight) due to low daily Se intake (16 µg per day), the mortality rate was significantly higher compared to other provinces. Se deficiencies may contribute to a more severe course of COVID-19, and daily Se supplementation of 55 µg in adults and the elderly is recommended to improve body function [31].

In ongoing studies on the relationship between Se and COVID-19 in China, the territorial aspect was also considered, and it was found that a selenium deficiency belt runs from northeast to southwest across China. Conducted studies actually confirmed that China in this belt has the lowest Se level in the world[32]. This discovery shed light on a disease caused by Se deficiency, known to cardiomyopathy as Keshan disease. When the population was supplemented with Se, the incidence of Keshan disease dropped dramatically. Significant clinical benefits of selenium supplementation have also been demonstrated in other viral infections, including HIV-1. Se may be important for many evolutionary processes of various viruses, through potential immunomodulatory effects with many of Se's primary roles in the immune system, especially when deficient [32,33]. The study provided the basis for the hypothesis that Se status was associated with the incidence of COVID-19 in China [34].The results of the study showed that in Chinese provinces with low selenium, which includes Keshan, there was a significantly higher mortality rate at 2.4% than in other regions. The results show an association between reported cure rates for COVID-19 and Se status [35,36,37]. However, there were many limitations to this in the study, so the need for continuation toward the association between Se status and disease is indicated.

Sufficiently high Se level is a prerequisite for an initial immune response, and this is true for people living in Se-deficient areas where endemic diseases are known to be preventable[38]. Selenium biomarkers strongly decline during pregnancy, severe illness or COVID-19, reaching critically low concentrations. It should be noted that these conditions are associated with an increased risk of autoimmune diseases (AID) [39,40,41,42,43,30]. Positive effects on the immune system are observed with Se supplementation during pregnancy and autoimmune

thyroid disease [41]. The current need for research into the relationship between AID and Se deficiency is particularly evident in rheumatoid arthritis and type 1 diabetes. Se deficiency can lead to depression, myopathy, muscular dystrophy and calcification, and promotes impaired cardiac muscle contraction, vascular degeneration, impotence and a general decline in vitality [44,42].

Despite these gaps in knowledge, it appears that severe Se deficiency can induce AID in susceptible individuals. Therefore, a properly balanced, qualitatively diverse diet, or Se supplementation, are effective ways to avoid severe Se deficiency, thereby reducing the risk of AID, and may contribute to the improved immunity that is needed during the COVID-19 pandemic [45,46,47]. An individualized approach is needed during therapy but a population-wide approach should be considered for areas with habitually low Se intake, e.g., Finland has been adding Se to its food chain for more than 35 years [45,46]. It is unfortunate that the health risks of Se deficiency are often ignored, while the possible side effects of Se supplementation are exaggerated, leading to disregard for this safe and promising preventive and complementary treatment option. This is important in cases of pregnancy, severe illness or COVID-19, where massive Se deficiencies have developed and are associated with risk of AID, long-term health impairment and slow recovery [41,42,47,48].The risk of Se deficiency is expected to increase due to future climate change [49].

The introduction of Se-containing supplements into the treatment of respiratory diseases has benefits, which have been confirmed by clinical studies. Although elevated Se concentrations in the blood can be achieved with various pharmacological preparations, only one chemical form (sodium selenite) can provide effective protection. Sodium selenite, but not selenate, can oxidize thiol groups in the virus protein disulfide isomerase, preventing it from penetrating the healthy cell membrane, which is important in the prevention of COVID-19 coronavirus infection [50].Thus, selenite inhibits viral entry into healthy cells and abolishes its infectivity. Therefore, this simple chemical compound has potential applications in the fight against coronavirus outbreaks [51].In addition, Se enhances immunity in viral infections, with a particular focus on COVID-19 [52]. For the viral disease, COVID-19, prevention or treatment strategies are currently available. Where is the exact time to end the alarming situation, nutritional strategies to strengthen immunity are unknown. In addition to treating malnutrition and overweight, obesity, attention has been given to the potential preventive and therapeutic use of trace elements, including Se [53].

In the current global context, it is difficult to obtain a balanced and varied diet. Therefore, achieving the recommended amount of calories and micronutrients will be a challenge, and planned micronutrient supplements may be beneficial especially for vulnerable populations such as the elderly [52,53].

SUMMARY

Content analysis from selected articles showed that there is a correlation between selenium deficiency and the risk of COVID-19 and the clinical course of the disease. Supplementation with this element may be helpful in preventing coronavirus infection and alleviating the symptoms of COVID-19. Individuals living in areas with poor baseline Se supply or using restricted nutrition and COVID patients with comorbidities or a long course of the disease are at increased risk of severe Se deficiency and may benefit from improving Se supply with dietary or supplemental measures. The bioavailability of this element varies and depends on the form of occurrence and composition of food, content in water and soil, and nutritional status of the individual. At the same time, many issues are still unexplained, and subsequent experiments bring further questions in addition to answers, demonstrating the need for further research into the importance of selenium, including its role in the treatment of COVID disease. Perhaps in the future this trace element will enter the therapeutic program permanently.

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