Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Selenium and mercury concentrations in biological samples from patients with COVID-19

Ghulam Qadir Chanihoon\textsuperscript{a}, Hassan Imran Afridi\textsuperscript{a,\ast}, Ahsanullah Unar\textsuperscript{b,\ast}, Farah Naz Talpur\textsuperscript{a}, Hadi Bakhsh Kalochi\textsuperscript{a}, Rayan Nassani\textsuperscript{c}, Nazia Laghari\textsuperscript{a}, Najam Uddin\textsuperscript{a}, Ali Ghulam\textsuperscript{d}, Anees UR Rahman Chandio\textsuperscript{a}

\textsuperscript{a} National Centre of Excellence in Analytical Chemistry, University of Sindh Jamshoro, Sindh, 76080, Pakistan
\textsuperscript{b} School of Life Sciences, University of Science and Technology of China, Hefei, Anhui, China
\textsuperscript{c} Center for Computational Biology, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, United Kingdom
\textsuperscript{d} Computerization and Network Section, Sindh Agriculture University, Sindh, Pakistan

ARTICLE INFO

Keywords:
Coronavirus disease 2019
Selenium
Mercury
Biological samples
Respiratory disease recurrence

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a systemic disease affecting multiple organs. Furthermore, viral infection depletes several trace elements and promotes complex biochemical reactions in the body. Smoking has been linked to the incidence of COVID-19 and associated mortality, and it may impact clinical effects, viral and bacterial conversion, and treatment outcomes.

Objectives: To study the relationship between severe acute respiratory syndrome coronavirus type 2 and the elemental concentrations of selenium (Se) and mercury (Hg) in biological samples from smokers and nonsmokers infected with the virus and in healthy individuals.

Method: We evaluated changes in the concentrations of essential (Se) and toxic (Hg) elements in biological samples (blood, nasal fluid, saliva, sputum, serum, and scalp hair) collected from male smokers and nonsmokers (aged 29–59 years) infected with COVID-19 and from healthy men in the same age group. The patients lived in different cities in Sindh Province, Pakistan. The Se and Hg concentrations were determined using atomic absorption spectrophotometry.

Results: Se concentrations in all types of biological samples from smokers and nonsmokers with COVID-19 were lower than those of healthy smokers and nonsmokers. Hg concentrations were elevated in both smokers and nonsmokers with COVID-19.

Conclusions: In the current study, persons infected with COVID-19 had higher concentrations of toxic Hg, which could cause physiological disorders, and low concentrations of essential Se, which can also cause weakness. COVID-19 infection showed positive correlations with levels of mercury and selenium. Thus, additional clinical and experimental investigations are essential.

1. Introduction

COVID-19 is a rapidly spreading disease that first appeared in December 2019 and has already killed hundreds of thousands of people around the world [1]. The virus that causes this condition is SARS-CoV-2, which is highly contagious and spreads predominantly through respiratory droplets [2]. Coronaviruses are a group of viruses that can infect both humans and animals [2]. Trace elements are nutritional components that are only necessary at trace levels but play critical roles in the immune system. In the context of viral infections, they mostly serve as catalysts in enzymatic reactions. A powerful association has been discovered between an imbalance in trace element levels (for example, iron, zinc, copper, selenium and magnesium) [3,4].

Selenium is a trace element present in selenocysteine, and its primary biological role is mediated by the selenium protein that contains 21 amino acids. The main source of selenium in the human body is dietary selenium from animals and plants, while the soil selenium content and soil selenium bioavailability for crops are the key factors that determine the amount of selenium in the human diet [4–8]. Selenium, found as selenocysteine in the catalytic centers of several selenoproteins, is an

* Corresponding authors.
E-mail addresses: hassan.afridi@usindh.edu.pk (H.I. Afridi), aunar@mail.ustc.edu.cn (A. Unar).

https://doi.org/10.1016/j.jtemb.2022.127038
Received 12 March 2022; Received in revised form 26 June 2022; Accepted 13 July 2022
Available online 16 July 2022
0946-672X/© 2022 Elsevier GmbH. All rights reserved.
essential nutrient for mammalian redox biology [9,10]. For the synthesis of selenocysteine, which is integrated into selenoproteins, an appropriate amount of the amino acid serine is essential [11]. A selenium deficiency in the diet can affect both the immune response and the pathogenesis of a virus [12–14]. A viral genome can be altered by Selenium (Se) depletion, causing a typically benign or mildly pathogenic virus to become extremely virulent in the deficient, oxidatively stressed hosts [15]. Even host with regular nutrition can be damaged by the emerging pathogenic strain once viral changes occur [15]. After entering the host, a viral genome can be changed from a generally slightly pathogenic virus to a highly virulent agent due to nutritional selenium insufficiency and elevated oxidative stress [16]. It has been suggested that Se deficiency may play a significant role in the development of SARS-CoV [17]. The role of selenium as a key cofactor in a group of enzymes that, in conjunction with vitamin E, serve to limit the generation of reactive oxygen species, explains its possible protective effect (ROS). Excessive ROS can cause oxidative alterations in both invading bacteria and host cells [18].

Furthermore, selenium deficiency has been associated with a higher incidence of viral genome mutations in RNA viruses such as HIV, Ebola, Coxsackievirus Hantavirus, Influenza virus, and SARS-CoV [19–21]. Trace element imbalances combined with the structure of enzymes facilitate these processes (for antioxidant protection). Copper, zinc and manganese are essential for superoxide dismutase activity, and the presence of active selenium in the active center structure specifies the specific action of antioxidant enzymes (glutathion peroxide and glutathion transferase) [21]. There are some reasons to believe that adequate inhibition of oncological pathology deterioration after surgical involvement and/or radiotherapy (which causes the generation of free radicals) should be achieved by taking into account the content and quantity of toxic elements (cadmium, lead, nickel, arsenic and mercury) [19]. Toxic elements increase the risk of hypertension [22–26]. Mercury causes hypertension by inhibiting catecholamine-0-methyltransferase, which increases levels of epinephrine, norepinephrine, and dopamine in the blood and urine. This has the effect of increasing blood pressure. This link is well understood; according to Houston (2011), "Mercury toxicity should be evaluated in every patient with hypertension." Heavy metals have also been associated with diabetes and obesity [27–31]. However, COVID-19 fatalities seem to be associated with the immune system initiating a "cytokine storm," in which abnormally high quantities of cytokines are generated, initiating a cascade of events that might result in death. Mercury increases proinflammatory cytokines that affect the cytokine response. Interleukin-1 (IL-1) cytokines, which are the same cytokines that mercury elevates, are the center of COVID-19-induced cytokine storms [32–34].

Selenium counteracts some of the negative effects of mercury (Hg) in tissues by generating a less toxic seleno-mercury complex [35]. Mercury-related cardiovascular illness and cerebrovascular accidents are reduced when people consume more Se [38]. Glutathione peroxidase, which detoxifies hydrogen peroxide and lipoperoxides, has selenium at its active core [4]. Mercury influences the distribution and retention of other heavy metals by acting as a catalyst for lipid peroxidation [36]. Mercury promotes free radical generation, inactivates antioxidant defenses, and forms seleno-mercury complexes with thiol-containing compounds [37] and Se, reducing Se availability for glutathione peroxidase activity [38].

Toxic elements (TEs) such as aluminum (Al), arsenic (As), cadmium (Cd), mercury (Hg), nickel (Ni), and lead (Pb) have been hypothesized as causal agents of cigarette smoke-induced physiological illnesses, and smoking is a major source of exposure to these TEs [39]. In fact, a study found that significant symptoms (intense desires to smoke, anxiety, or failed attempts to quit smoking) occurred in young people within weeks or days of starting to smoke [40]. Tobacco usage is the leading cause of disease and mortality around the world. Tobacco-related morbidity results from repeated inhalation exposure to a variety of toxic constituents in cigarette smoke, which are created by pyrolysis or released during combustion. Tobacco smoke is carcinogenic, poisonous, genotoxic, and mutagenic [41].

In this study, we determined the concentrations of selenium and toxic (mercury) elements in scalp hair, blood, serum, nasal fluid, sputum, and saliva samples from smokers and nonsmoking COVID-19 patients age range 29–59 years. Although the associations between essential trace and toxic element exposure and COVID-19 patients are not well understood before that, that is why this sort of study is necessary to elucidate the precise mechanism of metal-induced carcinogenesis.

2. Materials and methods

2.1. Approval from the ethical committee

Before sample collection, the protocol of the study was approved (Approval Number: DIR/665/2021) by the ethical committee of NCEAC, University of Sind, Jamshoro, Pakistan.

2.2. Study design and pretreatment

We tried our best to obtain biological samples from COVID-19 patients. However, due to the global lockdown, we had to collect biological samples from our families, friends, and other family members (N = 115) who were affected by COVID-19 disorders. Entire patients who were admitted to different hospitals. These samples were obtained between October 2021 and January 2022.

For information purposes, an oral session was held at the patients’ home, during which the contributors/subjects were informed about the necessity and pattern. Before collecting samples, patients received a written consent form to fill out and sign. Another form was filled out with information on patients’ lifestyles, dietary habits, and employment histories. All COVID-19 patients were between the ages of 29–59 years. COVID-19 participants were separated into two groups for the comparison study: smokers and nonsmokers. Seventy-one smokers and 87 nonsmokers were among the 158 healthy referents. Among the COVID-19 patients, 63 were nonsmokers and 52 were smokers, for a total of 115 patients (Table 1). COVID-19 patients are categorized into three basic types based on the following clinical symptoms, according to the seventh edition of the COVID-19 diagnostic and treatment plan. (1) mild conditions: fever, respiratory or digestive symptoms, and chest computed tomography (CT)-diagnosed pneumonia; (2) severe conditions: shortness of breath and respiratory rate of 30 times per minute, oxygen saturation of 93 % at rest, or chest CT imaging showing progression of the lesion of more than 50 % within 24–48 h; (3) critical conditions: respiratory failure and need for mechanical ventilation, shock, or chest CT imaging showing progression of the lesion of more than 50 % in 24–48 h.

All of these participants were subjected to an RNA detection test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). PCR was used to perform this test on a nasopharyngeal/oropharyngeal swab (qualitative) (Table 2). Following a clinical examination by a specialist to confirm the existence of COVID-19, samples were collected in the presence of a specialist doctor at several hospitals around Sindh, Pakistan, after COVID-19 patients signed a permission form. Initially, we collected biochemical data from each participant (Table 2).

Healthy referents were chosen according to the following criteria: Have no fever and/or any respiratory tract-related disease/infection at the time of selection; and ii) no known history of tuberculosis in the previous 2 years from the time of sample collection. Healthy individuals were chosen using a probability sampling procedure. Prior to the collection of biological samples, all 158 healthy referents were examined by a specialist doctor.

All 115 COVID-19 patients underwent acid-fast bacilli sputum tests, as well as radiographic, clinical, and microscopic tests, which revealed abnormalities related to pulmonary TB in their samples. Patients with
COVID-19 had to be at least 25 years old and have a smear-positive case of pulmonary tuberculosis. Excluded patients were retreated for tuberculosis, had multidrug-resistant tuberculosis, and/or had extrapulmonary tuberculosis.

2.3. Ethical consideration

Before sample collection, multiple hospitals in Sindh, Pakistan, gave their ethical approval. The Declaration of Helsinki code was rigorously followed when collecting consent from volunteers and/or their legal guardians. To protect the identities of the volunteers, secret IDs were used to code them. All COVID-19 patient data were kept private, and access to it.

2.4. Sample collection

2.4.1. Blood sample collection

In the current study, all enrolled volunteers agreed to participate and donate blood samples. Blood samples were collected from each subject after fasting overnight using a BD (Oxford, UK) Vacutainer (trace element tube with potassium-EDTA) with folded aluminum foil to prevent blood samples from being exposed to sunlight. According to standard protocols, these blood samples were drawn with a sterile 10 cc syringe (Supplier BD, Pakistan) using a winged infusion set. Blood samples were centrifuged at 3000 rpm for 15 min to separate serum from blood cells. Hemolytic sera were discarded. After centrifugation, the obtained samples were stored at −20 °C for future analysis.

2.4.2. Saliva sample collection

Each volunteer received a sterile plastic container without any elemental or bacterial contamination. Each volunteer’s secret identity number was preprinted on the sterile container. To reach the 5 mL mark, each volunteer was instructed to collect saliva in their oral cavity and spit into a plastic container. This method of collecting saliva is known as direct collection.

2.4.3. Sputum sample collection

Male nurses were instructed to direct each volunteer patient and referent to fill a sterile plastic container with 5 mL of blood, which was provided to each participant with a prelabeled confidential identifier number. All of the samples were subsequently transported to Jamshoro’s National Centre of Excellence in Analytical Chemistry (NCEAC) for analysis in a sealed container to avoid exposure to direct sunlight. The use of nebulized 4.5% hypertonic saline to elicit sputum collection was used in healthy volunteers.

2.4.4. Nasal fluid sample collection

Nasal fluids were collected using a small plastic spoon with dimensions of 10 mm × 5 mm × 2 mm. After collecting 1.5 mL of material into Eppendorf tubes, each sample was centrifuged.

2.4.5. Scalp hair sample collection

Hair samples weighing approximately 0.5 g (0.5–2.0 cm long) were collected from each ill and healthy subject using stainless steel scissors. Before and after cutting the hair of each participant, the scissors were carefully washed and sanitized with an alcohol swab. Hair samples from the back of the head were taken and stored in sterile plastic bags. Following the collection of samples, each participant’s bag was labeled with a confidential identification number. These plastic bags were affixed to each volunteer’s questionnaire and kept for digestion and further examination.

2.5. Apparatus

A double beam Perkin-Elmer atomic absorption spectrometer model Analyst 700 (Norwalk, CT, USA) equipped with a graphite furnace HGA-400 (PerkinElmer) and an autosampler AS-800 was used to analyze Hg and Se (PerkinElmer). The MHS-15 chemical vapor generation device was used to determine the amount of mercury in samples and standard solutions (PerkinElmer). An atomic absorption spectrometer was used to calculate integrated absorbance signals, which were used throughout.
The hollow cathode Hg and Se lamps were operated according to the manufacturer’s recommendations (Table 3). The biological samples were digested in a Pel (PMO23, Tokyo, Japan) household microwave oven with a maximum heating power of 900 W. For the production and storage of solutions, acid-washed polytetrafluoroethylene (PTFE) vessels and flasks were used.

2.6. Reagents and glassware

The ultrapure water used in the procedures was provided by Milli-Q USA. The company E. Merck, which makes analytical chemicals such as hydrogen peroxide and nitric acid, was used. All samples were verified for metal contamination before being used. Fluka Kamicia 1000 ppm Hg and Se standard solutions (Buchs, Switzerland) were used. HNO₃ (0.2 mol/L) was used to serially dilute the standard (stock) solutions. The solutions produced were kept at 4 °C in plastic bottles for future research. Certified reference materials (CRMs) of human hair BCR 397 (Brussels, Belgium) and Clincheck were used. Control lyophilized blood (Germany Munich, Recipe) were purchased to achieve a sensitive and selective technique. The plastic items and the apparatus were soaked for 24 h in 2 mol/L HNO₃ and then washed and rinsed with Milli-Q water.

2.7. Microwave-assisted acid digestion method

With the use of a microwave oven-based digestion procedure, duplicates of each sample were generated for elemental analysis. Six replication samples of the certificated reference materials (serum and blood) were prepared. For each sample, 200 mg of hair and 0.2 mL of nasopharyngeal fluid, serum, sputum, and blood were combined with 1 mL of the newly made H₂O₂ – HNO₃ mixture (1:2, v/v) in a PTFE flask. This combination flask was placed in an MW oven for 3 min before being exposed to 950 MW microwaves until complete sample digestion was achieved. The digested samples were allowed to cool to room temperature before being diluted with Milli-Q water to a final volume of 10 mL. ETAAS was used to assess the samples for Se and Hg. For the preparation of blank samples, the same process was used.

2.8. Data and statistical analyses

Data statistical analysis was performed using Excel X state and Minitab software. Certified reference materials from Hair BCR 397 and Clin check blood were used to test the accuracy of the analytical method. The approach was determined to be the most reliable compared to certified values of Hg and Se values, with a recovery rate of 95.7–98.4 % (Table 4). The linear ranges for Hg and Se from the quantification limit (LOQ) were 5.0 and 50 µg/L respectively, with correlation coefficients (r²) of 0.999 and 0.999 for Hg and Se, respectively. The limit of detection (LOD) and quantification (LOQ) were calculated by LOD = 3 × s/m and LOQ = 10 s/m, respectively, where s is the standard deviation of ten blank observations and m is the slope of the calibration graph. The LODs of Hg and Se were 0.145 and 0.057 µg/L respectively. Triplicate samples, reagent blanks, procedure blanks, and CRM samples were all analyzed to ensure that the process worked.

3. Results

COVID-19 patients had lower serum levels of cholesterol, HDL, LDL, triglycerides, total albumin, total protein and hemoglobin than the referents; however, COVID-19 patients had higher levels of leukocytes, ESR, and CRP than the referents (Table 2). Table 5 shows the mean amounts of selenium and mercury in biological samples (serum, scalp, blood, nasal fluid and sputum). The findings show changes in selenium and mercury concentrations in biological samples (serum, scalp, blood, nasal fluid, and sputum) from male smokers and nonsmokers in COVID-19 patients. The selenium concentration in scalp hair, blood, serum, sputum, saliva, and nasal fluid samples from male nonsmoking and smoking patients with COVID-19 was found to be lower in the 95 % confidence interval ([CI: 0.98–1.06] µg/L, [120–130] µL/L, [Cl 50.2–56.5] µg/L, [2.79–3.09] µg/L, [1.85–2.04] µg/L and [2.18–2.49] µg/L) and ([CI: 0.85–0.92] µg/g, [97.9–105] µg/g, [Cl 43.7–48.0] µg/L, [CI 1.70–1.99] µg/L, [1.30–1.45] µg/L, and [CI 1.64–1.82] µg/L), respectively, compared to Se levels in scalp hair, blood, serum, sputum, saliva, and nasal fluid samples of male nonsmoker and smoker referents ([CI: 1.80–2.12] µg/L, [Cl 2.25–2.39] µg/L, [Cl 99.6–110] µg/L, ([CI: 6.39–6.68] µg/L, [CI: 3.60–3.85] µg/L, and [Cl: 4.69–4.98] µg/L) and ([CI: 1.59–1.80] µg/g, [CI: 203–215] µg/L, [Cl 8.12–8.93] µg/L, [Cl: 4.13–4.55] µg/L, [Cl: 3.20–3.39] µg/L, and [Cl 3.68–4.05] µg/L), respectively (Table 5). Hg concentrations in biological samples from male smokers and nonsmoking patients with COVID-19 were significantly higher at 95 % C.I. ([Cl: 1.79–2.00] µg/L, [Cl: 1.60–1.89] µg/L, [Cl: 0.84–0.92] µg/L, [Cl: 1.09–1.20] µg/L, [Cl: 0.82–0.87] µg/L and [Cl: 0.91–0.99] µg/L) and ([Cl: 2.03–2.34] µg/L, [Cl: 1.80–2.15] µg/L, [Cl: 0.85–0.97] µg/L, [Cl: 1.21–1.40] µg/L, [Cl: 0.95–1.00] µg/L, and [Cl: 0.99–1.12] µg/L) compared with those in healthy male nonsmokers and smokers (p < 0.01). An independent Student’s t test was used to compare the mean values of COVID-19 smokers and nonsmokers and reference participants.

4. Discussion

The first corona case in Pakistan was reported on February 26, 2020. COVID-19 is currently a global pandemic. The objective of this study was to determine the levels of essential trace (Se) and toxic elements (Hg) in biological samples from patients with COVID-19 and controls in metropolitan Sindh, Pakistan (Hyderabad), with smoking and nonsmoking habits. Although it is uncertain whether the decrease in serum HDL cholesterol in COVID-19 infection follows the same path as HIV-1 infection, HDL particles and cholesterol have been linked to virus
sumption affects a high percentage of the global population in numerous
common in hospitalized patients and selenium deficiency can be quite
infection. In vitro investigations revealed that cholesterol in lipid rafts is
-
-
-
in vivo investigations revealed that cholesterol in lipid rafts is
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
-
higher levels of mercury and lead in their blood [68]. Exhaled nitric oxide levels were also associated with blood Hg levels, which is believed to be a sign of airway inflammation [69]. It is also worth noting that a high maternal Hg content was linked to an increased risk of lower respiratory infections among infants but not upper respiratory infections [70]. Through the development of oxidative stress and apoptosis, both methylmercury (CH₃Hg) [71] and HgCl₂ [72] have been proven to be harmful to A549 cells. The latter could be caused by Hg-induced changes in Bax, p53, and Bcl 2 expression [73]. In alveolar type II epithelial cells exposed to mercury, a similar impact was observed (Lu et al., 2010). Similarly, exposure to Hg was found to cause oxidative stress and the production of the heat shock protein 70 (Hsp 70) [74]. Endoplasmic reticulum stress (ER stress) could possibly be a contributing factor to Hg poisoning in the lungs [75]. It is also worth noting that inhalation of elemental mercury vapor greatly increased the expression of proinflammatory cytokines in lung tissue [76]. Although there is a lack of direct evidence that Hg affects airway epithelial permeability, exposure to Hg has been shown to change the expression of tight junction proteins in colonic epithelial cells [77].

Tobacco-related illness results from repeated inhalation exposure to a variety of toxic substances, including hazardous elements in cigarette smoke that are created by pyrolysis or released during combustion. According to the World Health Organization (WHO), a person dies from tobacco use every ten seconds around the world [78]. Tobacco plant uptake of hazardous elements is influenced by their concentration in the soil, soil amendments with sewage sludge, and soil pH [79]. Cigarette manufactured from tobacco cultivated in different geographical regions or under different agricultural conditions are likely to contain variable quantities of heavy metals in the tobacco filler, resulting in different levels of heavy metals in the smoke [80,81]. Tobacco leaves naturally accumulate and concentrate relatively high levels of toxic heavy elements, making tobacco smoking an important source of exposure for smokers [80,81].

The chemical constitution of cigarette tobacco is heavily influenced by the country of origin and product type. One pack of cigarettes deposits 0–1.4 µg As, 2–4 µg Cd, 0.46–6.5 ng Hg, and 12–2 µg Pb into a smoker’s lungs, while some of the smoke travels into the air and is inhaled by both smokers and nonsmokers [39]. This result was also consistent with another study indicating that smokers have much higher body loads of As, Cd, Hg, and Pb than nonsmokers [80]. In recent years, more attention has been paid to interactions between toxic elements (TEs) and bio-elements that are important for life in the organism. Bio-elements including zinc (Zn), copper (Cu), iron (Fe), selenium (Se), calcium (Ca), and TEs like Cd, Pb, and Hg are involved in these complicated relationships [82]. The basis of Hg toxicity is its negative impact on cell enzymatic systems, which is caused by the substitution of other essential elemental ions (mainly Se) in selenoproteins, as well as its extremely strong affinity for biological structures with SH groups, such as proteins, enzymes, and nucleic acids [83]. The importance of As, Cd, Hg, Pb, Ni, Cu, and Fe–Zn and Se interactions should be examined in light of worldwide TE exposure [84] and global deficiency of essential trace elements, primarily due to dietary considerations [85,86].

5. Conclusion

Our findings revealed that patients with COVID-19 smokers and nonsmokers had higher concentrations of toxic Hg, and low concentrations of essential Se than those from healthy smokers and non-smokers, which might contribute to the recurrence of COVID-19 and other lung-related diseases. Here, we provide some recommendations for future research to determine the role and effect of underlying trace elements in patients with COVID-19.

CRediT authorship contribution statement

GQC, HIA, and AU: Formal analysis and revised the manuscript. FNT, HBK, NL, AG and QQM, collected the samples. GQC, HIA, FNT, ARC: Experiments. AU, HIA, GQC: wrote the original draft. AG, NU, and FNT, NI and ARC, RN modified the manuscript. All authors contributed to the article and approved the submitted version.

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.

References

[1] Jhu, C. (2020). Coronavirus 2019-nCoV global cases by Johns Hopkins CSSE., (n. d.).
[2] M.A. Shereen, S. Khan, A. Kazmi, N. Bashir, R. Siddique, COVID-19 infection: emergence, transmission, and characteristics of human coronaviruses, J. Adv. Res. 24 (2020) 91–98.
[3] A. Gami, T. Tippipattara, P.K. Majuwdiya, M. Penna, A. Menzel, M. Dadar, G. Bjerkland, Micronutrients as immunomodulatory tools for COVID-19 management, Clin. Immunol. 220 (2020), 108545.
[4] S. Akhtar, J.K. Das, T. Ismail, M. Wahid, W. Saeed, Z.A. Bhutta, Nutritional perspectives for the prevention and mitigation of COVID-19, Nutr. Rev. 79 (3) (2021) 289–300.
[5] M.K.-Molecules, undefined 2019, Selenium-fascinating microelement, properties and sources in food, MedChi. (n.d.). https://doi.org/10.3390/molecule20072989.
[6] S.J. Fairweather-Tait, Y. Bao, M.R. Broadley, R. Collings, D. Ford, J.E. Hesketh, R. Hurst, Selenium in human health and disease, Liebetype.Inc. (n.d.). https://www.liebertpub.com/doi/abs/10.1089/ars.2010.3275 (accessed April 9, 2022).
[7] U. Grober, M.F. Holick, The coronavirus disease (COVID-19) - a supportive approach with selected micronutrients, J. Int. De. Vitaminol. Et. De. Nutr. 92 (2022) 13–34, https://doi.org/10.1024/055-1500695.
[8] V.N. Gladyshev, E.S. Arner, M.J. Berry, R. Brigelius-Flohe, E.A. Braford, R.F. Burk, B.A. Carlson, S. Castellano, L. Chavatte, M. Conrad, P.R. Copeland, Selenoprotein gene nomenclature, J. Biol. Chem. 291 (2016) 24036–24040, https://doi.org/10.1074/JBCM116.756155.
[9] S.J. Fairweather-Tait, Y. Bao, M.R. Broadley, R. Collings, D. Ford, J.E. Hesketh, R. Hurst, Selenium in human health and disease, Antioxid. Redox Signal 14 (2011) 1337–1383.
[10] M.A. Beck, C.C. Matthews, Micronutrients and host resistance to viral infection, Proc. Nutr. Soc. 59 (2000) 581–585.
[11] J. Long, Y. Lui, X. Zhou, L. He, Dietary serine supplementation regulates selenoprotein transcription and selenozyme activity in pigs, Biol. Trace Elem. Res. 199 (2021) 148–153.
[12] J. Zhang, E.W. Taylor, K. Bennett, R. Saad, M.P. Rayman, Association between regional selenium status and reported outcome of COVID-19 cases in China, Am. J. Clin. Nutr. 111 (2020) 1297–1299.
[13] A. Moghaddam, R.A. Heller, Q. Sun, J. Seelig, A. Cherkezov, L. Seibert, J. Häcker, P. Seemann, J. Diegmann, M. Pflö, Selenium deficiency is associated with mortality risk from COVID-19, Nutrients 12 (2020) 2098.
[14] D.E. Gordon, G.M. Jiang, M. Bouhaddou, J. Xu, K. Obernier, K.M. White, J. M. O’Meara, V. v Rezelj, J.Z. Guo, D.L. Swaney, A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 583 (2020) 456–458.
[15] M.A. Beck, O.A. Lavender, J. Hardy, Selenium deficiency and viral infection, J. Nutr. 133 (2003) 14685–14679.
[16] O.M. Guilin, C. Vindry, T. Ohlmann, L. Chavatte, Selenium, selenoproteins and viral infection, Nutrients 11 (2019) 2101.
[17] H. Pearson, T. Clarke, A. Abbott, J. Kost, D. Cynarski, SARS: what have we learned? Nature 424 (2003) 121–126.
[18] M. Hartill, Micronutrient selenium deficiency influences evolution of some viral infectious diseases, Biol. Trace Elem. Res. 143 (2011) 1325–1326.
[19] O.M. Guilin, C. Vindry, T. Ohlmann, L. Chavatte, Selenium, selenoproteins and viral infection, Nutrients 11 (2019), https://doi.org/10.3390/NU110929101.
[20] M. Kieliszek, B. Lipinski, Selenium supplementation in the prevention of coronavirus infections (COVID-19), Med Hypotheses 143 (2020), https://doi.org/10.1016/J.MEHT.2020.108978.
[21] L. Hißler, B. Rakotoambinina, Selenium and RNA Virus Interactions: Potential Implications for SARS-CoV-2 Infection (COVID-19), Front. Nutr. 7 (2020) 164, https://doi.org/10.3389/FNUT.2020.00164/BIFTEX.
[22] M.C. Houston, Role of mercury toxicity in hypertension, cardiovascular disease, and stroke, J. Clin. Hypertens. (Greenwich) 13 (2011) 621–627, https://doi.org/10.1111/J.1751-7176.2011.01489.X.
[23] N. Sorensen, K. Murata, E. Buus-Jorgensen, P. Weise, P. Grandjean, Prenatal methylmercury exposure as a cardiovascular risk factor at seven years of age, Epidemiology (1999) 370–375.
[24] X.F. Hu, K. Singh, L.H.M. Chan, Mercury exposure, blood pressure, and hypertension: a systematic review and dose-response meta-analysis, Environ. Health Perspect. 126 (2018), https://doi.org/10.1289/EHP2863.
[25] M. Jaisankar, T. Tseten, N. Anbalagan, B.B. Mathew, K.N. Beeregowda, Toxicity, mechanism and health effects of some heavy metals, Interci. Toxicol. 7 (2014) 60–72, https://doi.org/10.2478/intox-2014-0009.
[82] M.M. Brzoska, J. Moniszko-Jakoniuk, M. Jurczuk, M. Chhaniuk, The influence of cadmium on bone tissue in rats, Pol. J. Environ. Stud. 6 (1997) 29–32.
[83] S.J. Stohs, D. Bagchi, Oxidative mechanisms in the toxicity of metal ions, Free Radic. Biol. Med. 18 (1995) 321–336.
[84] M.P. Waalkes, T.P. Coogan, R.A. Barter, Toxicological principles of metal carcinogenesis with special emphasis on cadmium, Crit. Rev. Toxicol. 22 (1992) 175–201.
[85] H.H. Sandstead, J.G. Penland, N.W. Alcock, H.H. Dayal, X.C. Chen, J.S. Li, F. Zhao, J.J. Yang, Effects of repletion with zinc and other micronutrients on neuropsychologic performance and growth of Chinese children, Am. J. Clin. Nutr. 68 (1998) 470S–475S.
[86] B. Lonnerdal, Dietary factors influencing zinc absorption, J. Nutr. 130 (2000) 1378S–1383S.