



# A Review on the Serum Electrolytes and Trace Elements Role in the Pathophysiology of COVID-19

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## Abstract

All the world is involved in the COVID-19 disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coronavirus is a positive-sense RNA and has an envelope. There is no specific drug for this disease and treatment methods are limited. Malnutrition and electrolyte imbalance can make dysfunction in the immune system and impairment of the immune system causes increasing the risk of infection. Understanding the aspects of biological features of the virus will help the development of diagnostic tests, pharmacological therapies, and vaccines. Here, we review and discuss increasing and decreasing some trace elements and imbalance of serum and plasma electrolytes involving in COVID-19.

**Keywords** Covid-19 · Electrolytes · Trace elements · Micronutrients

## Introduction

Coronavirus disease 2019 (COVID-19), also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is caused by a strain of coronavirus which is a member of the genus *Betacoronavirus* and has become a global health problem that affected the lives of billions of people worldwide [1]. Understanding the aspects of biological features of the virus will help the development of diagnostic tests, pharmacological therapies, and vaccines.

It has been suggested dietary management is considered a strategy to minimize the potential risk of COVID-19 infection [2]. The nutritional condition should control in COVID-19 patients, and its disorders must be managed especially in patients associated with poor outcomes, including elderly, impaired wound healing, higher rates of nosocomial infections, and all-cause mortality. When malnutrition occurred, the

immune response also is weakened [3]. Patients with insufficient nutrition status should receive nutrition as soon as possible.

Also, some pathological conditions cause loss of water and electrolytes in the body, especially in the gastrointestinal form of COVID-19 disease, which is associated with diarrhea, in which the body experiences hyponatremia and the first step in a treat is water supply and electrolyte are lost [4]. Because of anti-inflammatory and antioxidant attributes of some vitamins and nutrients, they may be beneficial for the infected patients with COVID-19 [5, 6]. Vitamins including A, B, C, D, E, and folate and trace elements including iron, zinc, magnesium, selenium, and copper have important roles in supporting the innate and adaptive immune systems [7].

The function of immune system is supported with most nutrients that have pleiotropic roles. Also, they play a role in keeping and developing physical barriers, generation and function of antimicrobial proteins, differentiation and movement and chemotaxis of innate cells, neutrophils and macrophages phagocytosis, and relief from inflammation. By dearth of nutrients, the number of lymphocytes may decrease; phagocytosis may damage; production of cytokines may change; antibody responses may decrease, and also wound healing may be weakened [8, 9].

## Method

The bibliographic search was performed on PubMed, Scopus, and Web of Science databases on July 27, 2020.

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Search keywords including ‘Calcium’ OR ‘Copper’ OR ‘Ferrous’ OR ‘Folate’ OR ‘Folic Acid’ OR ‘Iron’ OR ‘Magnesium’ OR ‘Potassium’ OR ‘Selenium’ OR ‘Sodium’ OR ‘Zinc’ OR ‘Minerals’ OR ‘Trace Elements’ AND ‘coronavirus 2019’ OR ‘COVID-19’ OR ‘SARS-CoV-2’ in all fields. Any language or date restrictions were not applied. Identified studies were screened by title, abstract, and full text. The reference list of identified studies was also evaluated to increment the sensitivity and choice of most literature which we could not identify in the database. Initiate with greatest sensitivity search found the number of 325 articles on external databases, and collected by a researcher using Endnote software. Then unifying the articles from all the cited databases and bringing out duplicate articles, the two researchers separately investigated all the articles and excluded the articles that were not related to the topic and the inclusion index criteria. Afterward, several articles after reviewing titles and abstracts were excluded. The extant articles were cautiously evaluated and the relevant study was selected. The data for the studies, based on the title, examined method, sample size, etc., were evaluated. Finally, after obtain related articles and limitations of search strategy 61 articles were analyzed. During the reviewed articles in 2020, if we identified a new article, we would include it in our study.

## Results

### Zinc

Zinc is an important trace element that has critical roles in the body. Proliferation and function of NK cells, macrophages, neutrophils, T and B cells, and also the production of cytokines can be controlled by zinc [10]. Also, zinc can protect cells from the effect of reactive oxygen species [11]. Zinc is involved in the controls of common cold due to its inhibitory mechanism in viral replication [12] and attachment to the nasopharyngeal mucous, and there is any evidence that it decreases the duration of common cold about 1.65 days. Also, zinc alleviates gastrointestinal and lower respiratory symptoms [13]. Although it depends on age, zinc dose, and salt form. In vitro studies showed that some respiratory pathogens like rhinovirus, respiratory syncytial virus, and SARS-CoV pathogenesis were modified by zinc [14]. Development and maintenance of both innate and adaptive immune systems need zinc and its deficiency causes dysfunction in the activation, and maturation of lymphocytes, impairment in cellular communication by cytokines and reduce innate immunity [9, 15, 16]. Chloroquine (CQ) and hydroxychloroquine agents (HCQ) both stack up in endosomes, lysosomes, or Golgi vesicles and increase intracellular PH. Since the new 2019 coronavirus is acidophile, so increasing in intracellular PH might

be the cause of treatment of SARS-CoV-2. It has shown that CQ is a zinc ionophore and transmits extracellular zinc into the cells [17]. Zinc has shown that it has an antiviral activity against several viruses. It has been understood that zinc inhibits the activity of RNA-dependent RNA polymerase (RdRp) of coronavirus [18]. Because of the antiviral effect of zinc and function of CQ/HCQ as a zinc ionophore compound, co-administration of them for the synergistic effect seems to be useful for COVID-19 treatment [19]. Indeed increasing the intracellular  $Zn^{2+}$  through CQ can be against SARS-CoV-2 [20]. Pyriithione also is a zinc ionophore, so using zinc with a low amount of pyriithione inhibits the SARS coronavirus replication [6]. Some antiviral drugs can be more efficient by using zinc, and their abdominal discomfort will decrease [11]. Using a combination of CQ, zinc, and azithromycin as eye drops or spray/aerosol for eyelids and the ocular surface can prevent binding of SARS-CoV-2 to the eyes as one of the major pathways of importing the virus into the body [21]. Zinc ions in the structure of viral proteins also can be targeted, and some drugs like disulfiram have shown that it can release  $Zn^{2+}$  from proteins of MERS-CoV and SARS-CoV and impair the proteins. So these Zn-ejector drugs are potential for the treatment of SARS-Cov-2 [20]. Zinc also enhances cytokines response and also causes an increase in the generation of  $CD4^+$  naive T cells [22, 23].

### Selenium

Selenium in the structure of some enzymes and as well as vitamin E prohibits producing free radicals [24]. Cellular immunity gets better by using selenium in people with a low concentration of plasma selenium and also a mutation in the viral genome decreased [9]. Deficiency in selenium unmakes the immune system of the host and also causes oxidative stress that increases the risk of mutation in the viral genome and changes it to a more dangerous virus [25, 26]. It has shown that using selenium with ginseng stem-leaf saponins in chickens causes the response of the immune system to a live bivalent vaccine of coronavirus [6, 27]. Mutation in the virus has been seen after passaging a virus in animals with selenium deficiency. All of these data lead us to assume that there is an association between selenium condition and COVID-19. It has been observed that the death rate in low selenium is higher than in other cities. It has been reported that selenium deficiency causes an increase in viral replication and mutation and also more pathogenicity and mortality [28]. It has demonstrated that high selenium intake (50–100  $\mu\text{g}/\text{day}$ ) causes better and more immune responses in adults [29] especially cellular immune responses. Also, it has been observed that an increase in selenium intake causes more production of T cells and IL-8 and IL-10 cytokines [23, 30].

## Iron (Ferrous)

Many of host cellular functions need iron like enzymatic and non-enzymatic reactions, ATP generation, RNA/DNA synthesis, and repair and survival of ferroptosis of cells. Viral replication also needs iron. Proliferation and maturation of T cells and also the regulation of cytokines can do with the help of iron, and production of antibodies decreases when iron is deficient [10]. The activity of SARS-CoV and MERS-CoV helicases during replication needs ATP, and ATP synthesis needs iron. Iron homeostasis correlated with hepcidin and expression of hepcidin can influence by some cytokines like IL-6 and IL-1B. SARS-CoV-2 causes increasing in IL-1B, IFN- $\gamma$ , and IP10 levels and so these cytokines cause increasing of hepcidin and Iron storage in macrophages and hepatocytes will be enhanced. High iron storage in these cells will help viral replication [31]. CQ and HCQ may inhibit the release of IL-6, IL-1B, and TNF- $\alpha$  and so cause a decrease in hepcidin and inhibit viral replication [32]. Also, some drugs like tocilizumab suppress the synthesis of hepcidin [33]. Both host and pathogen need iron, and its deficiency impairs immunity in the host. Although excessive iron increases oxidative stress and risk of mutation in the viral genome [34]. It has been reported that iron leakage is a risk factor for the development of COVID-19 disease [35]. A high level of iron may increase viral infections. So iron chelators may inhibit viruses and can be used as antiviral materials against SARS-CoV-2. Iron has a role in viral replication, and lack of iron prevents replication of SARS-CoV-2, so iron chelators can be used as treatment. Also, the level of iron elevated in pulmonary fibrosis and iron chelators may inhibit pulmonary fibrosis [36]. On the other hand, it has been reported that COVID-19 patients with acute respiratory distress syndrome have low serum levels of Iron and intubation them [37]. The iron concentration 24 mcg/dl was reported in an 80-year-old patient with COVID-19 [38].

## Potassium

It has shown that COVID-19 patient's loss of potassium from urine so it causes hypokalemia in these patients. The entrance of the virus decreases the ACE2 and causes a reduction of angiotensin II decay, so the secretion of aldosterone increases, and it causes loss of potassium from urine [39, 40]. Hypokalemia is a high prevalence condition (up to 62%) among COVID-19 patients. About 108 of 175 patients had less than 3 mmol/L of  $K^+$  in plasma, and 10 people had 4 mmol/L plasma  $K^+$ . The recommended level of plasma  $K^+$  for myocardial patients is 4 mmol/L. The normal amount of plasma and serum potassium is 4 to 5.5 and 4.5 to 5.5. There are few reports about serum level of  $K^+$ , and only in one study reported 4.6 in the ICU patients and 4.1 in the non-ICU patients. The severity of COVID-19 illness is relevant to the

amount of potassium deficiency. Myocardial failure can be prevented by an adequate amount of plasma  $K^+$ . SARS-CoV-2 can hurt the heart through ACE2s, so it is good to control the potassium levels. Increasing gastrointestinal and urinary loss of  $K^+$  are both causes of hypokalemia in COVID-19 patients, but the gastrointestinal loss has less effect than urinary loss [41].

## Sodium

The most common impairments of electrolyte balance in patients are hyponatremia that mostly due to the syndrome of inappropriate antidiuresis (SIAD) [42]. The sodium in the serum of patients with pneumonia infected by SARS-CoV-2 is lower than non-pneumonia patients [43]. COVID-19 pathology is associated with IL-6, and this cytokine causes electrolyte disorder by inducing the vasopressin non-osmotic release. It has observed that IL-6 reversely correlates with  $[Na^+]$  and straightly associates with the  $PaO_2/FiO_2$  (P/F) ratio.  $[Na^+]$  and P/F ratios were significantly lower in patients with a higher level of IL-6 [42]. Sodium level was low at 123 mmol/l in a 77-year-old man with positive RT-PCR for COVID-19. There is not any other cause for hyponatremia in this case. Also, it has been reported that up to 12% of coronavirus patients have a low sodium level [44]. Expression of ACE2s in kidneys is higher than the lungs, and kidneys are a strong target for SARS-CoV-2. It has been reported that increases in sodium intake cause downregulation in ACE2 and by reduction of ACE2s, entry of coronavirus into cells also decreases. And sodium deficiency may increase the risk of developing severe and virulent COVID-19 infection [45, 46].

## Calcium

Coronavirus membrane fusion is associated with extracellular conditions. It has been observed that cellular ion conditions involve in the entrance of the virus [47]. The fusion of SARS-CoV and MERS-CoV into cells was influenced by  $Ca^+$  [48], and it has demonstrated that their entry into some cell lines decreased when intracellular calcium is chelated [49]. SARS-CoV infection reduces more than MERS-CoV because SARS-CoV fusion peptide binds with two  $Ca^{2+}$  ions but MERS-CoV binds one [50].

## Magnesium

The role of magnesium in immune function is mediated by several mechanisms including immune cell adherence, antibody-dependent cytotoxicity, and immunoglobulin M (IgM) lymphocyte binding, exerting a significant effect on the immunoglobulin synthesis, macrophage response to lymphokines, and T helper-B cell adherence [23, 51].

## Folic Acid

A 3CL hydrolase (also called the main protease) has an important role in the coronavirus life cycle. It has shown that folic acid molecules create hydrogen bonds with this enzyme and inhibit its activity, so it can impair the viral life cycle. As folic acid has an inhibitory function, it might be useful for the treatment of new coronavirus [52].

## Copper

Copper is an essential trace element in the body and the need for protecting DNA from oxidative stress [53]. 7.8 mg/day intake of copper has been seen that causes increase ceruloplasmin activity, benzylamine oxidase, and superoxide dismutase compares to 1.6 mg/day. Although it has been seen that amount of neutrophil, serum IL-2R, and the antibody titer against the Beijing strain of influenza reduce by higher intake of copper (7.8 mg/day) [23, 54]. Impairment of the immune system and enhanced rate of infections has been associated with copper deficiency [55]. Chronic TNF- $\alpha$  induced inflammation of the lungs may cause by a lack of copper [56]. Although the excessive level of copper in serum has

adverse effects on human respiratory health [57]. There is no suggestion for the amount of copper intake against COVID-19, and also it is unknown that the changes due to copper are beneficial or not [13]. But it has reported that RNA replication of COVID-19 can be inhibited by copper, RDV (an analog of nucleotide for treatment of Ebola), and NO (nitric oxide) together [58]. It has been reported that the human immune system response is weak when Cu is deficient. The level of serum copper in COVID-19 patients is unknown. The entry of the virus and its replication is inhibited by  $\text{Cu}^+$  ions and Cu oxide nanoparticles. Also, they impair viral mRNA and capsid proteins. Therefore, Cu supplements may affect the host immune system and may be beneficial for patients with COVID-19 illness. It is evident that copper and zinc are competitively absorbed in the gastrointestinal tract. So zinc intake of high doses (> 150 mg/day) can result in Cu deficiency in healthy individuals. So people who are using zinc supplements regularly may be at risk of severing SARS-CoV-2 because of malabsorption of Cu from jejunum [59]. Also, high intake of copper may have some adverse effects including gastrointestinal symptoms (cramps, abdominal pain, nausea, diarrhea, and vomiting) and kidney and liver toxicity resulting to coma [58].

**Table 1** Summary of the electrolytes and trace element roles in the COVID-19

Element	Physiologic role	Role in COVID-19
Zinc	It has a role in both innate and adaptive immune systems and also has an antiviral activity [16]	Zinc inhibits the activity of RNA-dependent RNA polymerase (RdRp) of coronavirus [18], and compound both of zinc and CQ/HCQ is useful for COVID-19 treatment [19]
Selenium	Selenium is a free radical scavenger and helps cellular immunity [24]	High selenium intake (50–100 $\mu\text{g}/\text{day}$ ) causes better and more immune responses [29]
Iron	Iron is needed for some reactions and cellular functions like RNA/DNA synthesis and repairs [10]	High level of iron may increase viral infections [36], although it has reported that COVID-19 patients have low serum level of iron [37]
Potassium	It is important for cell functions and the need for membrane potential [61]	Hypokalemia is a high prevalence condition (up to 62%) among COVID-19 patients [41]
Sodium	Sodium can modulate immune cell activities [62]	The sodium in the serum of patients with pneumonia infected by SARS-CoV-2 is lower than non-pneumonia patients [43]
Calcium	Calcium has a role in the activation of lymphocytes [63]	It has been seen that SARS-CoV entry into some cell lines decreases when intracellular calcium decreases [49]
Magnesium	It has important roles in immune functions including immunoglobulin synthesis and immunoglobulin M (IgM) lymphocyte binding [51]	ND
Folic acid	Synthesis of purines and thymidylate that they are necessary for mitochondrial producing of ATP need folic acid [65]	Folic acid impairs the viral life cycle by creating hydrogen bonds with 3CL hydrolase. In severe patients, the level of folic acid is lower [52, 64]
Copper	It is an essential trace element in body and is needed for protecting DNA from oxidative stress [53]	It has been reported that the human immune system response was weak when Cu is deficient. The level of serum copper in COVID-19 patients is unknown [59]

## Discussion

A new widespread viral pneumonia is due to the new coronavirus (SARS-CoV2). There is not enough information about this virus and its disease. There is no special drug or vaccine for this virus yet. Many parameters and body conditions may affect the entrance and pathogenicity of coronavirus in the human body. Also, environmental circumstances may have affected the trace elements level in the body; for example, heavy metals and volcanic gases and trace elements present in the air pollution along with specific climate conditions and regional topography may be involved in the spread of COVID-19 pandemic [60].

One major parameter is electrolyte balance and sufficient intake of minerals and vitamins because they affect the immune system. Impairment in electrolyte balances and lack of trace elements or vitamins cause immune system dysfunction and increase the risk of severe infection [7]. Here, we studied all the researches about electrolyte changes in COVID-19 until now. We have understood that some electrolyte changes and increasing or decreasing some of them can affect on pathogenicity of SARS-CoV2. And also some changes in electrolytes or trace elements are due to SARS-CoV2. Some changes might have a good effect on patients and cause improvement in the disease. Increasing zinc is good because zinc has an antiviral effect and a combination of zinc and CQ/HCQ may have more effect due to ionophore function of CQ/HCQ for zinc [19, 20]. But increasing in iron may have a bad effect because of excessive iron increase oxidative stress and also iron has a role in the replication of SARS-CoV2. So decreasing iron by using iron chelators can be considered a treatment [34, 36]. Also, both hypokalemia and hyponatremia were reported in COVID-19 patients, and deficiency of both sodium and potassium is dangerous for the body [41, 43]. Selenium deficiency causes immune system dysfunction and increases the viral replication [28]; copper might be beneficial for COVID-19 patients due to inhibitory effects on entry and impairment of viral mRNA and capsid [59], calcium decreases the entrance of viruses [49], and folic acid may impair the viral life cycle [52]. Finally, we suggest controlling the level of electrolytes and the number of trace elements in the body and using supplements if needed to make treatments better and faster (All data were summarized in Table 1).

## Conclusion

In the present study, by reviewing the available articles on the level of serum electrolytes and micronutrients in patients with COVID-19, significant results were obtained, and it was found that the trace elements and electrolytes levels in the blood circulation have important roles to alleviate or increase the severity of the disease and thus the mortality rates of the

patients are affected. Therefore, personalized medicine via measuring the level of the trace elements and electrolytes in patients with COVID-19 and supporting the deficiencies as soon as possible to return the body to a physiologic condition to choose the accurate treatment, shorten hospitalization time, and faster recovery is suggested.

**Authors' Contributions** The conception and design of the study: F.N. and M.T. Acquisition of data, analysis, and interpretation of data: A.B. and F.N. Drafting the article: A.B. and F.N. Revising the article critically for important intellectual content: M.T., P.H., and F.N. Final approval of the version to be submitted: M.T. and F.N.

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**Data Availability** All data are available via the corresponding author.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Code Availability** Not applicable.

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