Minerals in COVID-19

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Introduction

- Since the onset of the COVID-19 outbreak, fear and panic have traveled globally.

- This virus plays with an individual’s immunity, i.e., the severity of the infection depends on one’s immuno-competence.

- Every individual has a different kind of immune system, with their daily activity significantly impacting the immune system’s strength.

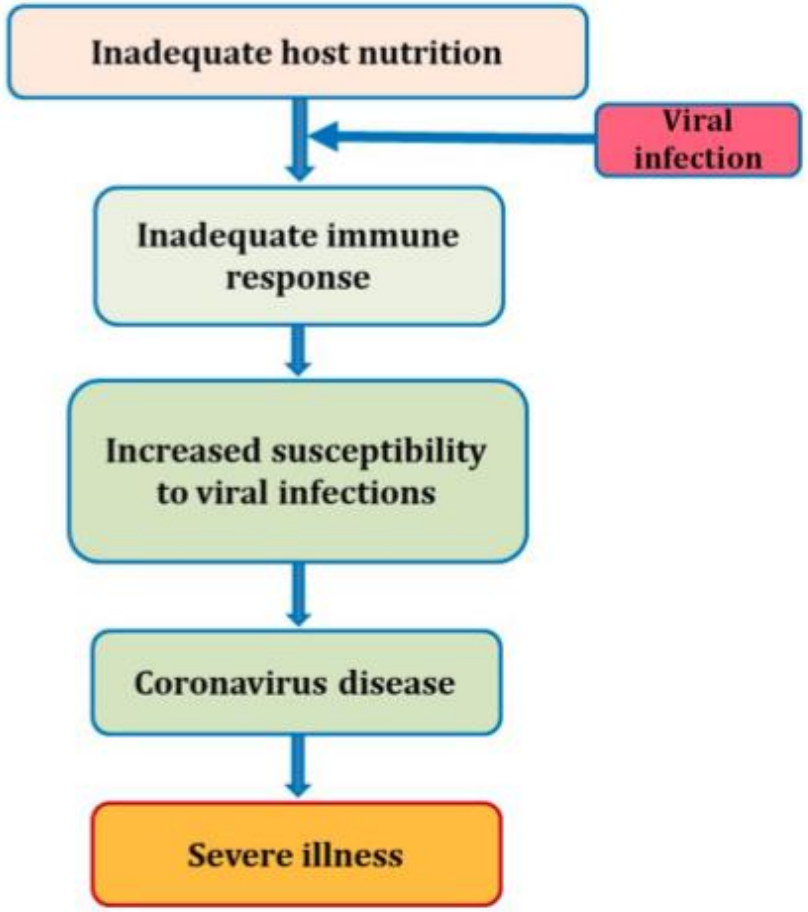

Fig. 1 Schematic representation of role of nutrition in immunity against viral infections

- In early COVID-19 studies, some data have been given that show how the presence and absence of minerals in the body are considered essential in regulating the expression of angiotensin-converting enzyme-2 (ACE2) in boosting the immune system.

- ACE-2 receptors are the coronavirus' main targets for its entry into the respiratory system and badly affect this system.

- Also, an animal study showed that mineral deficiency could increase the expression of ACE2.

- Therefore, we could consider that the long-term mineral deficiency may increase the level of ACE2 in lower respiratory tract cells, which would increase the sensitivity and pathogenicity of SARS-CoV-2 infection.

- A cross-sectional observational study showed that an insufficient Se and/or Zn status upon hospital admission was associated with a higher mortality rate and a more severe disease course in the entire study group, especially in the senior population.

Trace elements mediate vital biochemical functions by

- Acting as cofactors for many enzymes such as glutathione peroxidise (GPx), superoxide dismutase (SOD), RNA polymerase

- Act as centres for stabilizing structures of many enzymes and receptor proteins like Toll-like receptor-4 and transcription factors like Nf-kB

Table 1 Recommended dietary allowances of essential trace elements to promote immune functions

S. no	Trace elements	Supplementation quantity for adult male/day	Supplementation quantity for adult female/day
1	Zinc	11 mg	8 mg
2	Selenium	55 µg	55 µg
3	Iron	8 mg	18 mg
4	Copper	900 µg	900 µg
5	Magnesium	400 mg	310 mg

Table 2 Status of trace elements in various viral diseases along with their reference intervals in healthy adult individuals

S. no	Trace elements	Reference ranges of healthy adult individuals	Trends of trace elements in viral diseases
1	Zinc	66–110 μg/dL [85]	Decreased [39]
2	Selenium	5.8–23.4 μg/dL [85]	Decreased [51]
3	Iron	12.5–26 mmol/L [86]	Decreased [59]
4	Copper	75–145 μg/dL [85]	Decreased [68]
5	Lithium	0.8–1.2 mmol/L [87]	Decreased [78]
6	Nickel	0.3–1.1 μg/L [88]	Decreased [80]
7	Manganese	4.7–18.3 μg/dL [85]	Decreased [89]
8	Chromium	2–3 nmol/L [90]	Decreased [91]
9	Fluoride	0.29–1.52 μmol/L [92]	Decreased [93]
10	Cobalt	1.9–7.6 nmol/L [90]	Decreased [94]
11	Iodine	40–80 μg/L [95]	Mechanism unclear [96]
12	Molybdenum	0.28–1.17 ng/mL [97]	Decreased [98]

Role of macro minerals in COVID-19

Sodium

- Sodium plays a significant role in the regulation of electrolytic balance and the expression of ACE2 in SARS-CoV-2.
- In a meta-analysis, it was found that sodium concentration significantly decreases in COVID-19 patients.
- Another study has also reported that sodium level decreases with the increase in severity of disease.
- Such hyponatremia may be associated with SARS-CoV-2 infection and may serve as a biomarker of such an infection.

- 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 down-regulation in ACE2 and by reduction of ACE2s, entry of coronavirus into cells also decreases.

- However, sodium deficiency may increase the risk of developing severe and virulent COVID-19 infection.

Potassium

- Hypokalemia can increase ARDS and acute cardiac injury risk, which is considered the most commonly occurring complication in COVID-19.

- Hypokalemia is a high prevalence condition (up to 62%) among COVID-19 patients.

- **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**.

- A pooled analysis reported that potassium concentration is significantly lower in severe COVID-19 patients than non-severe. **The severity of COVID-19 illness is relevant to the amount of potassium deficiency**.

- As with low sodium, reduced plasma potassium levels may be a marker of SARS-CoV-2 infection.

- Myocardial failure can be prevented by an adequate amount of plasma K^+.

Calcium

- A joint analysis reported a **lower calcium concentration in critical COVID-19 patients** than those with less severe disease and concludes that serum calcium level in patients is inversely proportional to the severity of the disease.

- As with low sodium and potassium, hypocalcemia may serve as a marker of the severity of a SARS-CoV-2 infection.

Phosphorus

- A retrospective study suggests:

❑**hypophosphatemia is directly proportional to the severity of COVID-19**

❑ monitoring the serum phosphorus level in COVID-19's severe/critical patients is proved to be beneficial for prognosis.

- This virus, when it enters the body through ACE-2 receptors, our body activates innate immune responses against the viral infection.

- During coronavirus entry into the body, **the decreased phosphorus level increases the risk of proneness to the infections**.

- The body cannot recover the damage to the cells and tissues, leading to disease progression.

Magnesium (Mg)

- Mg supplementation **plays a significant role in immune function** by regulating various functions such as:

❑ Immune cell adherence

❑ Immunoglobulin synthesis

❑Antibody-dependent cytolysis

❑Macrophage response towards lymphokines

- In Singapore, a cohort study reported that the combination of vitamin D, magnesium, and vitamin B12 (DMB) **could reduce the progression rate in older patients with COVID-19.**

- Vitamin B12 (1000 IU) and magnesium (150 mg) have a protective effect against respiratory tract infection and reduce pro-inflammatory cytokines.

Role of micro minerals in COVID-19

- Trace elements are the essential micronutrients having a significant role in immunity.

- Apart from immune-modulatory action, trace elements such as **copper**, **zinc**, **manganese**, **selenium**, etc., show antiviral activity by inhibiting virus replication in host cells.

- The antioxidant properties of trace elements improvise the immune response and make alterations in the viral genome.

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Serum trace elements levels and clinical outcomes among Iranian COVID-19 patients

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ABSTRACT

Objectives: The relationship between immunity and trace elements levels is well known. We aimed to estimate the association of serum trace elements with severity and outcomes in the Coronavirus Disease-2019 (COVID-19) patients.

Methods: In this single-centered, prospective, observational study, we enrolled 114 patients admitted to severe intensive care units (ICUs) and corresponding 112 sex and aged-matched non-ICU ward patients. Demographic data, clinical characteristics, and outcomes were all collected. We analyzed serum levels of zinc (Zn), copper (Cu), selenium (Se), and manganese (Mn) in both severity groups.

Results: The serum levels of Cu, Se, and Mn in both groups were within the normal range while Zn serum levels were lower than normal values. Based on these findings, Zn, Cu, Se, and Mn serum levels were not associated with disease severity ($P > 0.05$), while we found Zn serum levels were strongly associated with patient outcomes ($P = 0.005$). Our results indicated lower Mn serum levels were associated with age more than 55 years ($P = 0.006$). Our results were not in favor of a causal relationship between serum trace elements levels and disease severity.

Conclusion: We found Zn level to be a strong indicator for patients' outcomes that can be considered for monitoring patient prognosis. Nutritional measures or supplementation can help reduce poor outcomes caused by low Zn levels in Iranian COVID-19 patients.

Table 2
Serum levels of Zn, Cu, Se, and Mn in patients with COVID-19 (severe and non-severe groups)

Elements	Normal range	Severity group All	ICU	Non-ICU	*P*-value
Cu	70-140 μg/dL	95.74 ± 1.25	94.58 ± 1.97	96.88 ± 1.57	0.362
Zn	Men: 72.6-127 Women: 77.0-114 μg/dL	67.87 ± 1.12	67.3 ± 1.79	68.42 ± 1.35	0.619
Se	70 to 150 μg/L	126.61 ± 2.05	130.19 ± 3.19	123.06 ± 2.58	0.084
Mn	0.6 to 4.3 μg/L	2.58 ± 0.069	2.68 ± 0.11	2.49 ± 0.08	0.167

P-values are for comparison between ICU and non-ICU ward groups. Cu: copper, Zn: zinc, Se: selenium, Mn: manganese.

Table 3
Serum trace elements levels by patients' outcomes (recovered vs. deceased)

Elements	Outcomes Recovered	Deceased	*P*-value
Cu	95.12 ± 1.43	97.64 ± 2.63	0.389
Zn	69.66 ± 1.34	62.43 ± 1.81	0.005
Se	125.77 ± 2.41	129.15 ± 3.91	0.481
Mn	2.59 ± 0.07	2.57 ± 0.14	0.900

Cu: copper, Zn: zinc, Se: selenium, Mn: manganese.

Table 4
Cu, Zn, Se, and Mn serum levels by age groups

Elements	Age (years) < 55 (n = 109)	≥ 55 (n = 117)	*P*-value
Zn	68.7 ± 16.18	67.1 ± 17.51	0.36
Cu	96.01 ± 21.55	95.5 ± 16.215	0.67
Mn	2.8047 ± 1.11801	2.38 ± 90	0.006
Se	128.92 ± 34.01	124.48 ± 27.37	0.23

Zn: zinc, Cu: copper, Mn: manganese, Se: selenium.

Table 5
Serum trace elements levels by sex

Elements	Age (years) Male (n = 114)	Female (n = 112)	*P*-value
Zn	71.36 ± 18.83	64.31 ± 13.80	0.002
Cu	97.77 ± 17.47	93.69 ± 20.19	0.106
Mn	2.44 ± 96	2.72 ± 1.07	0.047
Se	128.40 ± 31.29	124.80 ± 30.23	0.382

Zn: zinc, Cu: copper, Mn: manganese, Se: selenium.

Zinc (Zn)

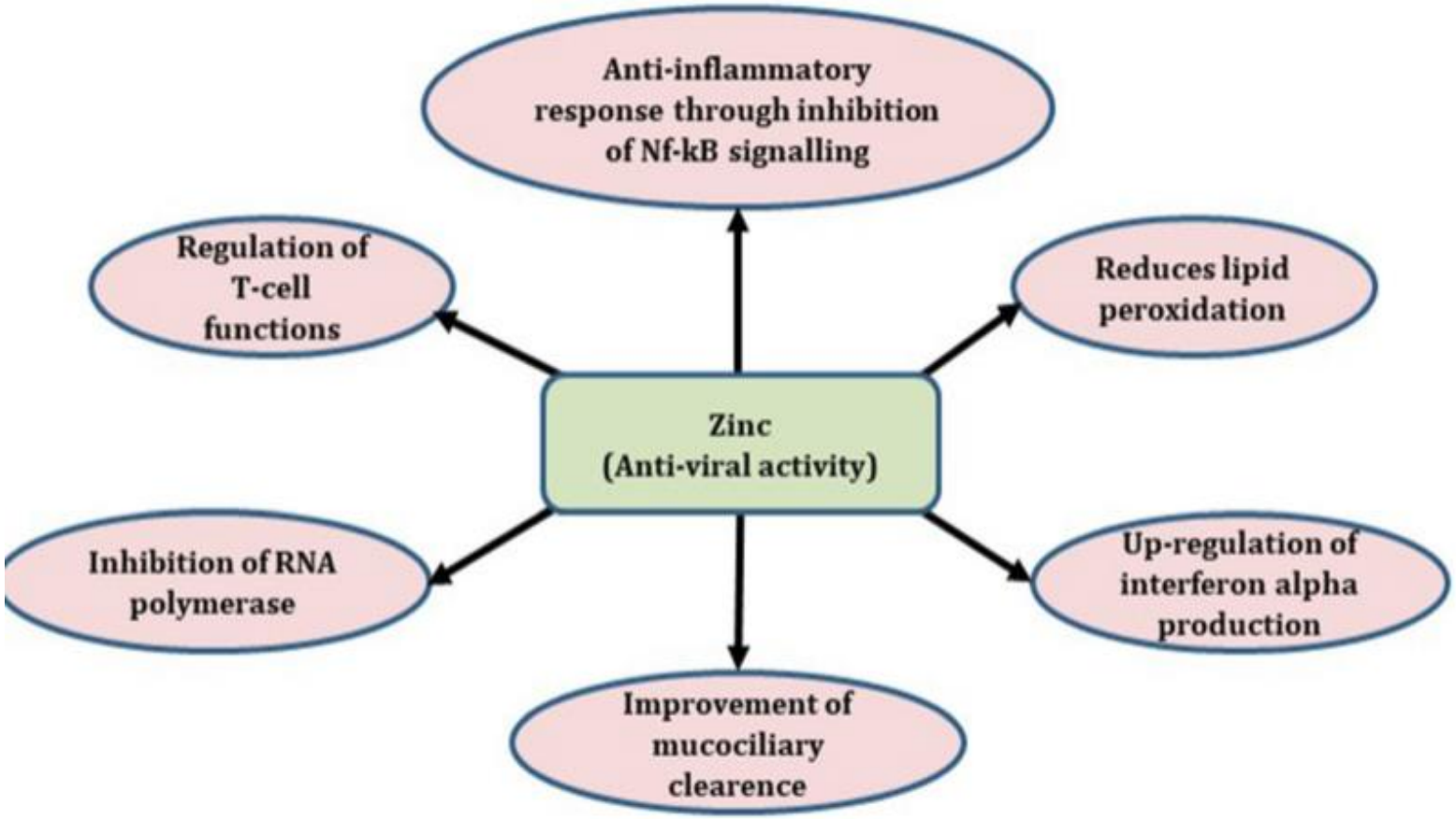
- Development and maintenance of both innate and adaptive immune systems need zinc and its deficiency causes:

❖Dysfunction in the activation, and maturation of lymphocytes

❖Impairment in cellular communication by cytokines

❖Reduce innate immunity

- Various pieces of evidence reveal that zinc shows antiviral property and plays an essential role in immunity. Zinc was reported as an active agent for immunity against H1N1 influenza.


Anti-inflammatory response through inhibition of Nf-kB signalling
Regulation of T-cell functions
Reduces lipid peroxidation
Zinc (Anti-viral activity)
Inhibition of RNA polymerase
Up-regulation of interferon alpha production
Improvement of mucociliary clearence

- Evidence reveals the decline in the activity of ACE2 in rat lungs after Zn^{2+} treatment.

- Furthermore, in vitro data demonstrate that Zn^{2+} cation allows the inhibition of SARS-coronavirus RNA polymerase by suppressing its replication, hence show anti-viral activity.

- It has shown that **CQ is a zinc ionophore** and transmits extracellular zinc into the cells.

- Because of the antiviral effect of zinc and function of CQ/HCQ as a zinc ionophore compound, co-adminstration of them for the synergistic effect seems to be useful for COVID-19 treatment.

- It has also been reported that **COVID-19 patients had significantly lower zinc levels** compared with healthy individuals.

- This was associated with a greater than 5-fold increased likelihood of developing complications.

Iron (Fe)

- 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.
- 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.
- Recent evidence reveals that COVID-19 patients display a broader spectrum of hyper-inflammatory syndromes distinguished by cytokine release syndrome (CRS).
- Hyper-ferritinemia is the primary feature of these syndromes, which plays a significant role in inflammation.
- The findings support the theory that the acute phase of SARS-CoV-2 infection induces ferritin production associated with the rapid onset of inflammation.

- Iron has also a role in viral replication. Therefore, **iron chelation therapy** is considered an appropriate approach to **improve survival in COVID-19 patients.**

- **The activity of SARS-CoV helicase** during replication needs ATP, and ATP synthesis needs iron.

- SARS-CoV-2 causes increasing in IL-1B and IFN-γ. 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.

- On the other hand, it has been reported that COVID-19 patients with acute respiratory distress syndrome have low serum levels of Iron.

- Either iron deficiency or overload had unfavorable functional cost to the immune system.

- Only optimum concentration is required for the proper functioning of immune system against infectious agents.

Copper (Cu)

- Cu is involved in B cells' normal functioning, T helper cells, macrophages, and natural killer (NK) cells, also involved in cell-mediated immunity, and produce antibodies against the pathogen.

- Studies reveal that Cu's exposure to coronavirus damage the viral genome and impact viral morphology irreversibly.

- Impairment of the immune system and enhanced rate of infections has been **associated with copper deficiency**.

- The excessive level of copper in serum has adverse effects on human respiratory health.

- The entry of the virus and its replication inhibit by 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 mal-absorption of Cu from jejunum.

Selenium (Se)

- For multiple reasons, Se is considered the most reliable trace element due to its **antiviral and anti-inflammatory properties**.

- Distinct sets of **seleno-proteins** regulate the normal functioning of the immune system comprised of seleno-cysteine.

- **Deficiency of Se** established severe risk factors for viral infections.

- It has demonstrated that **high selenium intake** (50–100 µg/day) causes better and more immune responses in adults 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.

- Recently, it has been showed that non-survivor SARS-CoV-19 patients with neoplasm **have a pronounced deficit in total serum Se and SELENOP concentrations** compared to surviving patients.

- Antiviral mechanism of selenite is exhibited through oxidize thiol groups in viral proteins and renders penetration into host cell membrane.

- The **antiviral proprieties** of selenite (Se^{+4}) are related to antioxidant capacity of this trace element.

- **Selenium insufficiency** causes oxidative damage to viral RNA and consequently increases the mutation rate.

- Increased mutation in viral genome favors the generation of pathogenic aggressive new strains.

Manganese (Mn)

- In an emerging approach towards the treatment of COVID-19, various sherds of evidence reveal **Mn's immune-modulatory and antiviral action.**

- It acts as a potent antiviral agent.

- Evidence also suggests **impaired antibody production** as a response to Mn deficiency, highlighting its crucial role in promoting immunity.

Iodine (I)

- In in vivo systems, iodine plays an essential role as antiviral in respiratory mucosa, saliva, and airways.

- Evidence reveals the **augmentation of innate antiviral immunity** upon **iodine delivery to airway mucosa**.

- Furthermore, a **high dose of iodide supplement** reduces the risk of severity in the respiratory syncytial virus and improves mucosal oxidative defenses.

- Iodine's external and internal applications make it a feasible candidate to be used as supportive therapy in SARS-CoV-2 infection.

Cobalt (Co)

- Its high affinity towards RNA template inhibits the RNA translation and is responsible for therapeutic effects against several viral infections such as hepatitis virus, herpes simplex virus, and Epstein–Barr virus.

- Their therapeutic activities against a wide range of viral infections indicate its role as supportive therapy in COVID-19 treatment.

Sulfur (S)

- Evidence reveals that the sulfate-based compound like sodium thiosulfate possesses therapeutic efficacy for lungs and respiratory infection.

- Furthermore, clinical data demonstrate that sodium thiosulfate successfully ameliorates pneumonia and lung injury in adults and children.

- Based on multiple therapeutic roles and the respiratory system's involvement, sulfur might show a protective effect against COVID-19.

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 μg/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 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 binds 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]