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RESEARCH ARTICLE

An investigation of the role of trace elements and biochemical parameters in patients with COVID-19

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ABSTRACT

Aim: The COVID-19 pandemic is an emergent viral respiratory disease characterized by high fever and shortness of breath, and it was declared a pandemic by the World Health Organization in March 2020. Early assessment of patients' biochemical tests is important for accelerating diagnosis, allowing effective treatment, and controlling the further spread of the disease. The present study aimed to investigate the association between the disease, trace elements -including copper (Cu), zinc (Zn), selenium (Se), manganese (Mn), and cobalt (Co) vitamin D, Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) biochemical levels, and the correlation between the parameters tested in patients with COVID-19.

Methods: In our study, 40 patients (case group) who were hospitalized with a diagnosis of COVID-19 based on chest X-ray images and RT-PCR results evaluated by an infectious diseases specialist were included, along with 40 healthy individuals (control group) over the age of 18 who had no prior symptoms of COVID-19, no visits to a medical doctor for COVID-19, and no history of hospitalization due to the disease. Beckman Coulter AU5800 (Beckman Coulter, Brea, CA, USA) autoanalyzer was used for spectrophotometric analyses of clinical biochemistry tests, and vitamin D levels were examined using the HPLC method with the Shimadzu SIL-20A HT autosampler. Levels of trace elements-including Cu, Zn, Se, Mn, and Co-were measured by inductively coupled plasma mass spectrometry (ICP-MS) on an ICP-MS Bruker Aurora M90 analytical complex. The normal distribution hypothesis for the variables in question was tested using the Kolmogorov–Smirnov test. Student's t-test was used for intergroup comparisons of variables meeting the normal distribution hypothesis, whereas Mann–Whitney U test was used for variables that did not meet the hypothesis.

Results: Vitamin D levels were much lower in the case group (12.05 ng/mL ± 6.27) compared to the control group (23.54 ng/mL ± 10.54), and the difference was statistically significant ($p < 0.001$). Serum Cu, Zn, Se, Mn, and Co levels in the

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control group were higher compared to the COVID-19 group, yet only the differences in Zn, Se, and Mn levels were statistically significant ($p < 0.05$, $p < 0.001$, $p < 0.05$, respectively).

Conclusion: Decreased levels of vitamin D and trace elements (Se, Zn, Mg and Cu) are associated with the development of viral pathogens, including COVID-19, as well as increased ALT and AST parameters. It was concluded that a diet rich in vitamins and trace elements would strengthen the immune system, reduce the rate of virus spread, and slow down the disease aggravation.

Keywords: Clinical chemistry tests, COVID-19, vitamin D, trace elements

INTRODUCTION

The disease, which has caused severe mortality and morbidity rates across the world due to SARS-CoV-2-a member of the betacoronavirus family with an enveloped, positive single-stranded RNA genome-was named COVID-19 by the WHO (1). COVID-19 infection, a global pandemic that has caused more than one million deaths, is characterized by a wide range of symptoms, from asymptomatic to fatal (2,3). The disease is either asymptomatic or presents with symptoms such as fatigue, headache, joint and muscle pain, loss of smell, nasal congestion, nausea and vomiting, anorexia and diarrhea. These symptoms are present in more than 80% of patients diagnosed with COVID-19, while the remainder may present with more severe or critical symptoms (1,4-6). Furthermore, actively circulating macrophages can attack vital organs, including the lungs, liver, and brain, leading to ARDS (Acute Respiratory Distress Syndrome) and death (7). In general, a range of viral and bacterial infections induce cytokine production, inflammation, an increase in free radicals, and a depletion of antioxidants upon triggering oxidative stress (5,6,8). Lipid peroxides and free oxygen radicals, formed through the oxidation of unsaturated fatty acids or other lipids, may lead to cell membrane damage and loss of function. Consequently, this may cause cell mutations, weaken the immune system, and even necrosis by damaging DNA (9-11).

In cases of infection, particularly COVID-19, nutritional support should include supplementation with vitamins, trace elements; copper (Cu), zinc (Zn), selenium (Se), manganese (Mn), iron (Fe), and magnesium (Mg) as well as carotenoids and polyphenols, with the aim of strengthening the immune system and reducing inflammation (1,5,12). Cu, Zn, Se, and Mg are the most important trace elements due to their immunomodulatory and antiviral properties (1,6,10,12). Many reactive oxygen species are produced during viral infections, and important antioxidant enzymes are used to reduce them as a part of the free radical defense mechanism. Cu and Zn are cofactors of one of these enzymes, i.e., superoxide dismutase (SOD), and Se acts as a cofactor for the GSH-Px enzyme (10,13). Zn is considered the second most important trace element in the cell after iron and it is an anti-inflammatory agent that reduces the production of oxidative stress biomarkers (10,14). Deficiency of Zn may lead to immunodeficiency by promoting mechanisms such as lymphopenia and increased apoptosis of lymphocytes. (10,14). Cu is associated with immunity to viral infections and the function of Natural Killer cells (NK) and T helper (Th) cells, and its deficiency is associated with decreased interleukin-2 (IL-2) levels (13). A decrease in serum Zn levels has been reported to correlate with increased severity of COVID-19, along with an increase in the Cu/Zn ratio (15). Se is a component of selenoproteins, which are important for the immune and antioxidant systems, and also contain selenocysteine amino acid in their active sites (12,16). Se plays an immunoregulatory role and is involved both structurally and as a cofactor in the regulation of endocrine functions during inflammatory processes. It is an important cofactor of GSH-Px, which suppresses oxidative stress in the systemic inflammatory response. Furthermore, Se increases phagocyte and NK cell activity, T cell proliferation, and immunoglobulin synthesis (17). Selenium deficiency is a known risk factor for viral infections and has also been reported as a contributing factor to mortality in severe conditions such as sepsis and polytraumatic injuries (12). Vitamin D regulates both the innate and acquired immune systems by affecting the proliferation and phenotype of T cells (18,19).

An investigation of trace elements, vitamins, and biochemical parameters in patients with COVID-19 could contribute to more robust and comprehensive interventions in the fight against this disease and other viral infections. The present study aimed to investigate the association between the disease and trace elements (including Cu, Zn, Se, Mn, and Co), vitamin D, Alanin Aminotransferaz (ALT) and Aspartat Aminotransferaz (AST) levels, and the correlation between the parameters tested in patients with COVID-19.

MATERIALS AND METHODS

The study included 40 patients (case group) who presented to Dicle University Faculty of Medicine Hospital with COVID-19 symptoms, were diagnosed with COVID-19 based on the *Public Health Surveillance for COVID-19: interim guidance* by WHO, and were hospitalized by an infectious diseases specialist as a result of positive RT-PCR test on the samples collected by nasopharyngeal swab and lung X-ray images. The study also included 40 healthy individuals (control group) over the age of 18 who had no COVID-19 symptoms, had not visited a doctor, or had no history of hospitalization due to COVID-19. The study was approved by the Ministry of Health of the Republic of Turkey (2021-03-30T19_52_07) and the Ethics Committee of Dicle University Faculty of Medicine (No: 20/08/2021-372). Patients who were diagnosed with SARS-CoV-2 infection, but had no viral RNA as indicated by the RT-PCR test results were excluded from the study. Patients under the age of 18, as well as those with chronic diseases (e.g., diabetes mellitus, hypertension, coronary heart disease, chronic kidney disease, chronic lung disease, neoplasia), and pregnant or breastfeeding women were excluded from the study.

Spectrophotometric analyses of clinical biochemistry tests were performed, hemogram measurements were conducted using a SYSMEX XN-1000 (Sysmex, Kobe, Japan) hematology analyzer, and vitamin D levels were determined by HPLC using a Shimadzu SIL-20A HT autosampler. For the Cu, Zn, Se, Mn, Co, ALT, and AST tests, blood samples were collected into standard clinical biochemistry test tubes, centrifuged at 1500 g for 20 minutes, and the resulting sera were then separated and stored at –80°C.

After the sera were brought to room temperature and thawed on the day of analysis, serum levels of trace elements Cu, Zn, Se, Mn, and Co were measured by ICP-MS on ICP-MS Bruker Aurora M90 analytical complex. ICP-MS (Agilent, Thermo Scientific, Perkin Elmer, Bruker Daltonics, Germany), Solutions; Merck, Israel.

ALT and AST levels were analyzed using the Beckman AU5800 ISE analyzer (20). The selected AU5800 features single or dual ISE flow cells in clinical chemistry module configurations (21). Vitamin D analysis was performed using an HPLC device manufactured by Shimadzu (Kyoto, Japan) (22).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) for Windows was used for statistical analyses of the data obtained in the study. The study data were expressed in percentages (%), mean ± standard deviation (SD), mean, median, and correlation coefficient (r).

The normal distribution hypothesis was tested using the Kolmogorov–Smirnov test for the variables in question. Mean and SD were used for variables that met the normal distribution hypothesis. For the comparison between groups, Student's t-test was used for variables that met the assumption of normal distribution, while the Mann–Whitney U test was applied to those that did not. Chi-squared test was used to compare categorical variables, and the relationship between numerical variables was investigated by Spearman's correlation analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

The study group consisted of 40 patients (25 females and 15 males) with COVID-19. The mean age of the patients was 57.75 ± 19.85 years. The control group included 40 healthy individuals (28 females and 12

Table 1. Age, gender and biochemistry test results of groups				
		Control (N: 40)	**Patients (N: 40)**	**p**
Gender (n)	Female	28	25	0.001***
	Male	12	15	
Age (years) median (IQR)		33 (12.75)	55.5 (37.75)	0.001***
ALT U/L median (IQR)		21.78 (10.43)	28.60 (32.32)	0.137
AST U/L median (IQR)		23 (9.84)	29.6 (21.15)	0.017*
D Vit (ng/mL)		23.54±10.54	12.05±6.27	0.001***

Data are presented as mean ± SD or n (%), median, IQR. *p < 0.05 vs. controls. **p < 0.01 vs. controls. *** p < 0.001. Vit D: Vitamin D, P: Phosphorus, Mg: Magnesium, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, IQR: Interquartile Range.

Table 2. Serum trace element levels of groups			
	Control (N: 40)	**Patients (N: 40)**	**p**
Co median (IQR), (µg/L)	27.08 (16.38)	17.96 (19.19)	0.14
Cu median (IQR), (µg/L)	1328.10 (704.87)	1302.26 (751.80)	0,288
Zn median (IQR), (µg/L)	1675.25 (276.90)	1440.77 (508.84)	0.001***
Se (µg/L)	108.30±42,11	64.59±24.29	0.001***
Mn median (IQR), (µg/L)	18.81 (5.68)	11.32 (4.47)	0.001***
Cu/Zn median (IQR)	0.84 (0.37)	1.04 (0.63)	0.094

Data are presented as mean ± SD or n (%), median, IQR. *p < 0.05 vs. controls. **p < 0.01 vs. controls. *** p < 0.001. Co: Cobalt, Cu: Copper, Zn: Zinc, Se: Selenium, Mn: Manganese, IQR: Interquartile Range.

males) with a mean age of 35.02 ± 8.12 years. The patient group was composed of older individuals, and there was a statistically significant difference in age between the two groups (There were more female patients than male patients; p<0.001) (Table 1).

As presented in Table 1, serum vitamin D levels were significantly lower in the COVID-19 group (12.05 ± 6.27 ng/mL) compared to the control group (23.54 ± 10.54 ng/mL), with the difference being statistically significant (p < 0.001).

Serum Cu, Zn, Se, Mn, Co levels are presented in Table 2. Serum Cu, Zn, Se, Mn, and Co levels in the control group were higher compared to the COVID-19 group, yet only the differences in Zn, Se, and Mn levels were statistically significant (p < 0.05, p < 0.001, p < 0.05, respectively) (Table 2). No statistically significant difference was found between the patient and control groups in terms of ALT enzyme levels (p>0.05). A significant difference was found in terms of AST enzyme levels (p<0.05) (Table 1). Serum AST level was higher in patient group.

DISCUSSION

This study demonstrates a significant association between COVID-19 and reduced serum levels of vitamin D, Zn, Se, and Mn. These micronutrients are known to play essential roles in immune regulation, antioxidant defense, and inflammatory responses. The observed deficiencies in the case group may contribute to increased vulnerability to SARS-CoV-2 infection or to the progression of the disease. Notably, the markedly lower levels of vitamin D in COVID-19 patients support previous findings suggesting its potential role in modulating respiratory infections and immune response. Trace elements, including Zn, Mn, Se, and Cu, help reinforce the immune system, support the immune system, and are also involved in the composition of various viral enzymes, proteases, and polymerases that help prevent viral infection

(23). Both Zn and Cu are trace elements with antiviral activity that activate the immune system. Al-Saleh et al. reported Zn deficiency (<0.693 µg/mL) in 25% of patients with COVID-19, whereas only 3% had Cu deficiency (<0.18 µg/mL), and 28% had elevated Cu levels (>1.401 µg/mL). Nevertheless, although a significant amount of patients in the aforementioned study had Zn deficiency, the authors did not identify a correlation between this deficiency and severity of COVID-19. Patients who died from COVID-19 had lower serum Zn levels (0.7 µg/mL) compared to the survivors (1.117 µg/mL), but the difference was merely on the borderline of statistical significance ($p = 0.065$) (1).

Muhammad et al. reported that serum Mn, Zn, Cu, and Se levels were significantly lower in COVID-19 patients compared to controls (23). Typically, the Cu/Zn ratio is close to 1:1 (24) and it has been suggested that Cu/Zn >2 indicated severe bacterial infection (25). Al-Saleh et al. reported a high Cu/Zn ratio (1.5 ± 0.63) in their study. They identified 128 patients (~83%) with a Cu/Zn ratio of >1 and 33 patients (21%) with a Cu/Zn ratio of >2, and suggested that an elevated Cu/Zn ratio may exacerbate inflammation in COVID-19 patients and might be associated with the severity of disease (1).

Skalny et al. categorized COVID-19 patients into mild, moderate, and severe groups, and reported that decreased levels of Zn, Mn, and Cu, as well as an increased Cu/Zn ratio, were particularly observed in the severe group. Especially in the moderate and severe groups, Zn values were significantly lower compared to the mild disease group and healthy controls. The Cu/Zn ratio gradually increased in COVID-19 patients (for mild, moderate, and severe disease cases: 18%, 39%, and 39%, respectively), and elevations in Cu levels and the Cu/Zn ratio were closely correlated with markers of disease severity (15). In the present study, only the difference in Zn levels was statistically significant despite the fact that both Cu and Zn levels were lower in the patient group compared to controls. The Cu/Zn ratio was >1 (1.04) in the patient group.

Selenium is reportedly important for the maturation and function of CD8+ T cells and NK cells, and it plays a prominent role in the production of antibodies (6,26,27). A German study found that the serum Se levels in surviving COVID-19 patients were significantly higher compared to the deceased patients (12). In China, it was reported that Se levels were significantly correlated with the recovery rate in patients with COVID-19, and patients with higher Se concentrations maintained a higher rate of recovery (26). Similarly, Im et al. identified Se deficiency in 42% of COVID-19 patients in their study conducted in Korea (28). In the study of Skalny et al., serum Se levels were lower in COVID-19 patients compared to healthy individuals (15). Consistent with the results of previous studies, the Se levels in the present study were lower in the COVID-19 group compared to healthy controls ($p<0.001$).

Mn has been reported to play an important role in innate immunity and antiviral defense, and that Mn, Fe, or Zn deficiency have been associated with increased incidence of infectious disease and higher mortality rates. A Chinese study by Zeng et al. reported decreased Mg and Mn levels in patients with COVID-19 through whole blood testing, and noted significant differences between severe disease and non-severe disease groups in this regard ($p < 0.05$) (29). A study by Muhammad et al. found that Mn levels were lower in patients with COVID-19, contrary to the elevated Mn levels reported by the study of Skalny et al. (15). Additionally, a study conducted in Kazakhstan observed a decrease in Mn concentrations ($p <0.001$) upon trace element analysis of hair strands of those who recovered from COVID-19 (30). In the present study, Mn levels were lower in the COVID-19 group ($p < 0.001$).

Zinc induces regulatory T cells (TREGs) and suppresses proinflammatory TH17 and TH9 cell differentiation. Zinc supplementation was recommended as part of a potential solution to immunosuppression, since zinc deficiency is associated with impaired immune function and an increased risk of infection (31). Zinc inhibits the replication of various RNA viruses, including SARS-CoV-2. Considering the inhibitory effect of zinc on the replication of coronavirus, zinc would likely have similar effects on COVID-19 infection (32). In the present study, a significant difference in zinc trace element levels was detected between the patient group and control group, with zinc levels being significantly lower in the patient group ($p < 0.001$).

A study by Polat et al., reported that aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), laktat dehidrogenaz (LDH), Gama-glutamil transferaz (GGT), Alkalen fosfataz (ALP) levels, which are indicators of liver, and heart functions, were significantly higher in the COVID-19 group (33). In the present study, ALT and AST levels were higher in the COVID-19 group, consistent with the study by Polat et al. ($p < 0.05$).

Vitamin D contributes to the production of antimicrobial peptides against bacteria, viruses, and fungi by stimulating the immune system. Vitamin D has notable effects on the immune system along with one of its functions, i.e., regulating calcium and phosphorus homeostasis (26). An increasing number of studies suggest that vitamin D deficiency is associated with a higher risk of contracting various infectious diseases (including respiratory viruses) and with worse clinical outcomes due to the loss of its immunomodulatory effects (34). Povaliaeva et al. suggested that their study results were consistent with the overall low prevalence of vitamin D levels, noting that only 3% of patients with COVID-19 had adequate vitamin D levels, while the median 25OH-D3 level in patients with COVID-19 was only 10.8 ng/mL (18). A meta-analysis of the correlation between 25-hydroxyvitamin-D [25(OH) D] levels and the risk and outcomes of COVID-19 reported that the risk of COVID-19 was higher in cases of vitamin D deficiency, and that there was a significant relationship between vitamin D deficiency and the severity of disease and mortality (35). One study found that 68% of COVID-19 patients had vitamin D-3 deficiency. However, there was no significant difference in vitamin D-3 deficiency between patients with mild, moderate, and severe symptoms, and asymptomatic patients, because vitamin D deficiency was present in all subgroups. An Israeli study reported that 25(OH)D deficiency (≤20 ng/mL) approximately doubled the risk of hospitalization due to COVID-19 infection (36). In the present study, vitamin D levels were lower in patients with COVID-19, consistent with findings in other studies ($p < 0.001$).

The present study found that Cu, Zn, Mn, and Se levels, which had a well-established role in reinforcing the immune system, were lower in patients with COVID-19 compared to the control group. Oxidative stress appears to be elevated in patients with COVID-19, leading to increased antioxidant utilization and consequently reduced serum levels of trace elements. The main limitation to the present study is that it was designed as a single-center research and the sample size was relatively small. Therefore, the results cannot be generalized. Furthermore, most of the hospitalized patients were elderly individuals, and demographic data with adequate details pertaining to the patient and control groups could not be obtained because the epidemic period was very busy for hospital staff.

CONCLUSION

In light of the present study and previous reports, vitamin (vitamins A, C, D and E) and trace element (Se, Zn and Cu) deficiencies, which are associated with weakened immune system, may contribute to viral diseases, including COVID-19, and aggravate the disease by increasing ALT and AST levels, which are indicators of hepatocellular injury.

It was concluded that a diet rich in vitamins and trace elements may strengthen the immune system, reduce the rate of virus spread, and slow down the disease aggravation. We believe that the present study will guide physicians by showing the importance of nutrition in all viral diseases, especially COVID-19, and serve as a guide for future, more comprehensive studies.

Ethical approval

This study has been approved by the Dicle University Medical Faculty Ethics Committee For Non-Interventional Studies (approval date 20/08/2021, number 372). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: HT; Concept: İS, VU, RECE; Design: İS, VU, RECE; Data Collection or Processing: İS, VU, RECE; Analysis or Interpretation: İS, VU, RECE; Literature Search: EÖ, ÇM; Writing: İS, VU, RECE, EÖ, ÇM, HT. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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