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Comparison of trace element (selenium, iron), electrolyte (calcium, sodium), and physical activity levels in COVID-19 patients before and after the treatment[☆]

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A R T I C L E I N F O

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A B S T R A C T

Objective: Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), a worldwide health problem, is the cause of 2019 coronavirus disease. This study aimed to compare the trace element (selenium and iron), electrolyte (calcium and sodium), and physical activity levels of COVID-19 patients before and after COVID-19 treatment.
Method: This prospective study was conducted in patients diagnosed with COVID-19 (n = 15). Trace element (selenium and iron), electrolyte (calcium and sodium), and physical activity levels of the patients were compared before and after the treatment.
Result: Most of patients had selenium deficiency (86.7 %), iron deficiency (73.3 %), calcium deficiency (66.7 %) and sodium deficiency (46.7 %) before COVID-19 treatment. The most important improvements were seen in iron deficiency (from 73.3 % to 26.7 %) and sodium deficiency (from 46.7 % to 13.3 %) after the treatment. Selenium, iron, calcium, and sodium levels of the patients were significantly higher after the treatment ($p < 0.05$). The patients had low physical activity before and after COVID-19 treatment. In addition, no statistically significant difference was found in the comparison of physical activity levels ($p > 0.05$).
Conclusion: This study indicated that selenium, iron, calcium, and sodium levels and deficiencies might improve after treating patients with COVID-19. However, the results of this study showed that the physical activity levels of COVID-19 patients might remain stable and low throughout the treatment process.

☆ The manuscript was prospectively registered, and the clinical trial registration number is NCT04694703 (date of registration: January 3, 2021).

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1. Introduction

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), an evolving worldwide health problem, is the cause of coronavirus disease 2019 (COVID-19), first reported in Wuhan, China, in December 2019 [1]. After an average incubation period of about five days (range: 2–14 days) [2], most cases showed mild symptoms, mainly from the respiratory tract, while some resulted in viral pneumonia, acute respiratory distress syndrome (ARDS), multiple organ failure, or death.

The clinical picture of COVID-19 can be heterogeneous, ranging from asymptomatic to severe disease associated with a cytokine storm. The pathogenesis of COVID-19 has not been fully understood; however, it seems to be likely multifactorial and, in severe cases, with a systemic hyperinflammatory response and associated thromboembolic complications [3].

COVID-19 patients with any of the four conditions such as having any comorbidity, having radiological features consistent with pneumonia, aged > 50 years, and clinical characteristics such as respiratory distress, tachypnea, oxygen saturation (SpO2) < 93 %, and tachycardia are hospitalized, and routine COVID-19 treatments are administered according to the COVID-19 guidelines of Turkish Ministry of Health. COVID-19 patients who have not had a fever and have not needed oxygen in the last 48–72 h are discharged according to the same guidelines [4].

Despite the urgent need to find an effective antiviral treatment for COVID-19 through randomized controlled trials, specific agents are used worldwide, either based on in vitro or extrapolated evidence or observational studies. The most frequently used agents worldwide are chloroquine, hydroxychloroquine, lopinavir/ritonavir, favipiravir, and remdesivir [5]. SARS-CoV-2 has been highlighted to have a genome sequence 75–80 % identical to SARS-CoV, so the current treatment for SARS and Middle East Respiratory Syndrome (MERS) shows favipiravir may assist in the development of COVID-19 therapeutics [6]. Favipiravir, also known as T-705, was developed in 2002 as an inhibitor of influenza virus replication [7]. A systematic review and meta-analysis stated that favipiravir induces viral clearance within seven days in COVID-19 cases and contributes to clinical improvement within 14 days [8]. It might be crucial to ensure an efficient treatment, decrease mortality, and allow early discharge about COVID-19 [9]. On the other hand, hydroxychloroquine is an aminoquinoline that has been used to treat malaria and autoimmune diseases for over 50 years. The drug has immunomodulatory effects, treating autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis [10]. In addition, several researchers have suggested using hydroxychloroquine on SARS-CoV-2 [11].

Trace elements such as selenium (Se) and iron (Fe) play an essential role in supporting both innate and adaptive immune systems [12]. For example, Se is a free radical cleaner and aids cellular immunity [13], and Fe is needed for some reactions and cellular functions such as RNA/DNA synthesis and repair [14]. In addition, there is evidence from COVID-19 studies that patients may have electrolyte disturbances, including calcium (Ca) and sodium (Na) abnormalities [15,16]. According to studies in literature, COVID-19 patients with hypocalcemia have a higher inflammatory response [17] because COVID-19 patients with hypocalcemia had higher C-reactive protein (CRP). Furthermore, studies have shown a negative correlation between serum Ca levels and CRP [18,19].

In literature, adverse changes in Fe status have been documented in people who exercise regularly [20]. Similarly, Baltaci et al. suggested that Se and physical performance have a strong relationship [21]. In addition, Na and Ca are essential for metabolic balance during physical activity [22]. For considering an adult to be physically active, the general recommendation is to achieve at least 150 min of moderate or 75 min of vigorous-intensity activity per week, or an equivalent combination of both [23]. As COVID-19 has spread worldwide, healthy people have been requested to stay at home for a long time. As a result, COVID-19 has radically altered the determinants of the behaviors (individual, interpersonal, environmental, regional, or national policies and global) [24]. Accordingly, it can be viewed those regular activities have decreased due to isolation and limitations. Especially in the first weeks of the pandemic, the population had limited chances to find alternatives to keep active even at home and reducing sedentary behavior during the lock-down posed a significant challenge. Individuals have changed their lifestyles, decreased their social participation, and been adversely affected physically and mentally because of the restrictions such as social isolation and home confinement implemented to prevent the spread of the disease in the COVID-19 pandemic [24]. Because of this situation, public health advocates strongly encourage physical activity in the home environment to prevent the potentially harmful effects of protective lifestyle regulations due to COVID-19 and prevent the restrictions from causing physical inactivity [25]. Especially with the decrease in physical activity during the COVID-19 pandemic, the risks of cardiovascular diseases such as obesity, hypertension, and diabetes have increased, and recommendations for improving physical activity throughout the pandemic process have become widespread [25,26].

This study aimed to compare the Se, Fe, Ca, and Na status and physical activity levels of the patients with COVID-19 before COVID-19 treatment with the levels after the treatment. In addition, the relationships between physical activity levels and trace elements/electrolytes were determined.

2. Method

Fifteen patients diagnosed with COVID-19 between 45 and 65 were hospitalized and planned to receive the routine COVID-19 treatment in a pandemic clinic of Izmir Bakircay University Cigli Training and Research Hospital, a tertiary hospital, were included in the study. Informed consent was obtained from the patients before the study.

The patients diagnosed with COVID-19 via Positive Polymerase Chain Reaction (PCR) test and computerized tomography (CT) were included in this study. Patients who (1) took trace element supplements for the past two weeks, (2) had a diagnosis of kidney failure and heart failure, (3) were pregnant, (4) needed intensive care (severe-COVID-19 patients), and (5) did not require hospitalization (mild-COVID-19 patients) were excluded from the study. Only moderate-COVID-19 patients diagnosed according to the COVID-19 guidelines of the Turkish Ministry of Health [5] were included in this study. The patients who did not require oxygen treatment, who had the symptoms such as fever, muscle/joint pains, cough, and sore throat, and having respiratory frequency < 30/minute and SpO2 > 90) were categorized as moderate-COVID-19 patients.

Before data collection, this study was approved by both the Ethics Committee of Izmir Bakircay University (2020–142) and the Turkish Ministry of Health (2020–12–17T11_14_49).

2.1. Outcome measures

Serum trace element (Se, Fe) and electrolyte (Ca, Na) status, and physical activity levels of the patients were determined at the beginning of the COVID-19 treatment and before the discharge. In addition, routine parameters such as ferritin and CRP levels were also analyzed. Venous blood samples were collected into gel-separated blood tubes, then centrifuged at 2000 x g for 10 min. Serum samples were aliquoted and stored at − 80 °C until the biochemical analysis.

Inductively coupled plasma mass spectrometry (ICP-MS) (Thermo Scientific™ iCAP™ RQ ICP-MS, Waltham, MA USA) was used to determine serum Se levels. The serum autosampler was diluted to 10 in 1 % supra pure Nitric acid in a clean autosampler tube. The calibration standards 50, 100, 150, 200, 250 ppb were also prepared by diluting the stock Se standard in the same diluent. After adding the diluent, all the samples were vortexed. The prepared samples were aspirated into ICP-MS to determine Se levels. Helium was used as collision gas. The method was linear over the concentration 13.5 – 200 μg/L (r (2) =

0.999) with a Limit of Detection (LOD) and Limit of Quantitation (LOQ) of 0.06 and 0.1 13.5 – 200 μg/L, respectively. The accuracy of the method was between 97 % and 101 %. Seronorm™ Trace Elements Serum L-1 (LOT-1801802) and L-2 (LOT-1309416) materials with levels 95 μg/L and 138 μg/L were used as internal quality control samples (IQCs).

The colorimetric (700/570 nm) and the photometric (376/340 nm) methods were used for analyzing Fe and Ca levels, respectively. Na levels were measured by using Ion-Selective Electrode (ISE) method. The Immunoturbidimetric (570/800 nm) method was used for determining ferritin levels. Fe, Ca, Na, and ferritin levels were studied on Roche Diagnostic Cobas 8000 Modular Analyzer Series device, C702 module.

The reference data of Izmir Bakircay University Cigli Training and Research Hospital Biochemistry Laboratory were used for the reference ranges of trace elements, electrolytes, ferritin, and CRP levels.

The short form of the International Physical Activity Questionnaire (IPAQ-SF) containing questions for "the last seven days" was used to determine the physical activity level. This 7-question form provides information on sitting, walking, and moderate or vigorous activities. IPAQ-SF includes questions about physical activity performed at least 10 min in the last week. The total duration (minutes) and frequency (days) were included in calculating the walking, moderate and vigorous activity score. A score is obtained as "Metabolic equivalent (MET)-minute/week" in the calculations by multiplying the minute, day, and MET value. According to the scores, physical activity levels were categorized as low, moderate, and high [27].

2.2. Statistical analysis

IBM SPSS Statistics software (version 14.01; SPSS, Inc., Chicago, IL) was used to perform statistical analyses. The sample size and power calculations were carried out using the G*Power software version 3.1 (Düsseldorf University, Germany). The effect size was determined as 1.204 by using data of a previous study and the total sample size was calculated as minimum 12 [28]. Post hoc power calculations showed that our sample size (n = 15) had 0.964 power and 1.074 effect size at the level of α error probability was 0.05. The Kolmogorov–Smirnov test was performed to determine whether the data were normally distributed. Wilcoxon test was used for comparing the changing of all the parameters between before and after the treatment. The correlations between physical activity and trace element/electrolyte levels were analyzed via the Spearman test. Spearman's rho value was recorded as the correlation coefficient. The results were reported as median ± 95 % confidence interval (CI), number (n), and percentage (%). A value of $p < 0.05$ was considered statistically significant.

3. Results

The demographic and disease-related data are presented in Table 1. The mean age of the patients was 58.93 ± 6.70 years. According to the results of BMI, the patients were in the overweight category. The most common coexisting symptoms of the patients diagnosed with COVID-19 were cough (46.7 %), weakness (33.3 %), shortness of breath (26.7 %), and muscle pain (26.7 %). Hypertension (26.7 %) was the most common comorbidity among the patients.

It was determined that all the patients received Favipravir 200 mg tablet (2 ×1600 mg for loading dose, 2 ×600 mg for maintenance dose up to 5–10 days) and Hydroxychloroquine 200 mg tablet (2 ×400 mg for loading dose and 2 ×200 mg for maintenance dose up to 5–10 days). In addition, 93.3 % of the patients (n: 14) received enoxaparin sodium (1×40mg for 10 days), 60 % of the patients (n: 9) infused isotonic solution of sodium chloride (saline) (0.9 g per 100 ml), 40 % of the patients (n: 6) received dexamethasone (6 mg per a day up to 10 days) and 20 % of the patients (n: 3) received both saline (0.9 g per 100 ml) and dexamethasone (6 mg per a day up to 10 days).

Table 1
Demographic and disease related data of the COVID-19 patients.

	Patients (n = 15)
Age (years), mean ± SD	58.93 ± 6.70
BMI, mean ± SD	26.95 ± 3.42
Gender (M/F)	12/3
Diagnostic tool, n (%)	
PCR test	1 (6.64)
CT	14 (93.3)
Time between onset of the symptoms and hospitalization (days), mean ± SD	2.33 ± 2.35
Length of stay in hospital (days), mean ± SD	9.87 ± 7.99
Presenting symptoms, n (%)*	
Cough	7 (46.7)
Weakness	5 (33.3)
Shortness of breath	4 (26.7)
Muscle pain	4 (26.7)
Sore throat	3 (20)
Fever	3 (20)
Dizziness	1 (6.7)
Headache	1 (6.7)
Loss of appetite	1 (6.7)
Joint pain	1 (6.7)
Loss of taste	1 (6.7)
Nausea	1 (6.7)
Chills	1 (6.7)
Diarrhea	1 (6.7)
No symptom	1 (6.7)
Comorbidities, n (%)	
Hypertension	4 (26.7)
Coronary arterial disease	1 (6.7)
Benign prostate hyperplasia	1 (6.7)
Psychosis	1 (6.7)

BMI: Body mass index (<18.5: Underweight, 18.5–24.9: Normal weight, 25.0–29.9: Pre-obesity, 30.0–34.9: Obesity class I, 35.0–39.9: Obesity class II, Above 40: Obesity class III), SD: Standard deviation, M: Male, F: Female, PCR: Polymerase chain reaction, CT: Computerized tomography, *Total numbers and percentages may differ from the number of cases, because patients may have more than one presenting symptoms.

According to the trace element deficiencies, 86.7 % of the patients had hyposeleniumia, and 73.3 % had hyposideremia before COVID-19 treatment; however, only 26.7 % of the patients had hyposideremia after the treatment (Table 2). Similarly, hypocalcemia and hyponatremia were seen in 66.7 % and 46.7 % of the patients before the treatment, respectively. However, only 13.3 % of the patients had

Table 2
Clinical data of the COVID-19 patients.

	Before the treatment n (%)	After the treatment n (%)
Hyperferritinemia	9 (60 %)	9 (60 %)
Trace element deficiencies*		
Se deficiency/ Hyposeleniumia	13 (86.7 %)	11 (73.3 %)
Fe deficiency/Hyposideremia	11 (73.3 %)	4 (26.7 %)
Electrolyte deficiencies*		
Ca deficiency/Hypocalcemia	10 (66.7 %)	7 (46.7 %)
Na deficiency/Hyponatremia	7 (46.7 %)	2 (13.3 %)
Physical activity levels (IPAQ-SF)		
Low	15 (100 %)	15 (100 %)
Moderate	–	–
High	–	–

Se: Selenium, Fe: Iron, Ca: Calcium, Na: Sodium, Hyperferritinemia: Ferritin levels > 400 μg/dL, Hyposeleniumia: Selenium levels < 95 μg/L, Hyposideremia: Iron levels < 45 μg/dL, Hypocalcemia: Calcium levels < 8.9 mg/dL, Hyponatremia: Sodium levels < 136 mmol/L, IPAQ-SF: International Physical Activity Questionnaire – Short Form, *Total numbers and percentages may differ from the number of cases, because patients may have more than one deficiency.

hyponatremia after the treatment. The comparisons of CRP levels, trace elements and electrolytes according to the classification of dexamethasone are shown in Table 3. There were statistically significant differences in trace elements and electrolytes in patients not received dexamethasone. In addition, significant difference was determined in CRP levels in patients received dexamethasone.

Both trace element (Se, Fe) and electrolyte levels (Ca, Na) of the patients were significantly higher after the treatment ($p < 0.05$) (Table 4). Table 4 also showed that CRP levels had statistically significant differences between before and after the treatment; however, there were no differences in the results of ferritin levels.

The physical activity levels showed that all the patients had a low level of physical activity both before and after the treatment evaluations (Table 2). There was no statistically significant difference in the comparisons of physical activity levels before and after treatment ($p > 0.05$) (Table 4). In addition, there were no correlations between physical activity and trace/electrolyte levels (Table 5).

4. Discussion

To our knowledge, this is the first study to investigate the changing of trace elements, electrolytes, and physical activity levels of COVID-19 patients between baseline and discharge processes. This prospective study showed that patients diagnosed with COVID-19 had high rates of Se (86.7 %), Fe (73.3 %), Ca (66.7 %), and Na (46.7 %) deficiencies before the treatment. The serum Fe and Na levels of the patients after treatment approached the normal reference ranges relatively more closely than the Se and Ca levels. Although Se, Fe, Ca, and Na levels increased significantly after the treatment, some patients were still outside of the normal reference ranges. Especially most patients still had serum Se levels below the normal reference range. In addition, Ca deficiencies were still relevantly high in COVID-19 patients after the treatment. One of the most dramatic results of this study was that all the patients had a low level of physical activity both before and after the treatment.

Pre-infection signs of inflammation, such as high values for CRP, represent a common aggravating factor in COVID-19 [29]. A decrease in CRP levels is an early indicator for COVID-19 patients who received corticosteroid treatment [30]. The results of this current study, decreasing CRP level in COVID-19 patients who received corticosteroid including dexamethasone after the treatment, supports the literature.

Corticosteroids may affect serum trace element and electrolyte levels. It has been reported that corticosteroids increase [31] or decrease [32] or do not alter serum Se concentrations [33] in human subjects. The type of corticosteroids, dose and duration of steroid therapy, and patients' disease varied in these studies and may have contributed to the differing outcomes. Yamashita et al. stated that serum concentration of Fe was increased following dexamethasone treatment in an experimental study [34]. In another experimental study, serum Ca levels were increased in 5-day dexamethasone-treated mice [35]. It was explained that the release of bone Ca could contribute to the induction of serum Ca levels [36]. Glucocorticoids also affect salt and water balance in the human body. For example, cortisol treatment in Na replete volunteers caused Na retention and increased plasma and extracellular volume [37]. In our study, there were no statistically significant differences in Se, Fe, Na, and Ca levels between the groups based on dexamethasone treatment in our sample. These results may be due to the low number of cases in subgroup analyzes.

Adequate Se is essential for adequate immunodeficiency, which to some extent may prevent an inflammatory aggravation [38]. It is known that Se is an important trace element required for any human cell to carry out normal cellular functions [39]. In addition, Se seems to play a crucial role in protecting the respiratory system in various infectious diseases, especially against viral infections [40]. It has been suggested that hyposeleniumia may play an essential role in the occurrence of SARS-CoV [41]. Recently, Moghaddam et al. [42] showed that non-surviving COVID-19 patients had a marked deficiency in total serum Se concentrations compared to surviving patients. However, to our knowledge, the number of studies investigating the effect of drugs used in COVID treatment on Se levels is deficient. This current study showed that most of the patients (86.7 %) had hyposeleniumia before the treatment. Although there was a statistically significant increase in Se level after the treatment, 70 % of the patients still had hyposeleniumia. The mechanism of the partial increase in Se levels in our

Table 4
Comparisons of blood serum parameters and physical activity levels before and after the treatment.

Data with normal reference ranges	Before the treatment (Median [95% CI])	After the treatment (Median [95% CI])	p
CRP (0 – 5 mg/L)	53.75 [30.56 – 92.50]	13.46 [8.36 – 26.42]	0.011*
Trace elements			
Se (95 – 165 μg/L)	71.51 [65.08 – 86.69]	88.14 [79.08 – 109.85]	0.005*
Fe (45 – 182 μg/dL)	34.00 [29.01 – 47.75]	63.00 [48.39 – 85.46]	0.010*
Ferritin (30 – 400 μg/dL)	677.00 [387.39 – 962.24]	527.00 [314.41 – 802.36]	0.730
Electrolytes			
Ca (8.9 – 10.3 mg/dL)	8.50 [8.30 – 8.71]	8.90 [8.56 – 9.16]	0.015*
Na (136 – 144 mmol/L)	135.00 [133.31 – 137.92]	137.77 [135.97 – 139.57]	0.023*
Physical Activity (IPAQ-SF) (0 – 600 METs = low) (600 – 3000 METs = moderate) (>3000 METs = high)	0 [0 – 102.65]	0 [0 – 189.80]	0.812

CRP: C-reactive protein, Se: Selenium, Fe: Iron, Ca: Calcium, Na: Sodium, IPAQ-SF: International Physical Activity Questionnaire – Short Form, MET: Metabolic equivalent, Wilcoxon test, *$p < 0.05$.

Table 3
Comparisons of CRP, serum trace elements and electrolytes according to the using of dexamethasone.

Data with normal reference ranges	Patients received dexamethasone (n: 6)			Patients not received dexamethasone (n: 9)		
	Before the treatment (Median [95% CI])	After the treatment (Median [95% CI])	p	Before the treatment (Median [95% CI])	After the treatment (Median [95% CI])	p
CRP (0 – 5 mg/L)	67.90 [20.69 – 127.57]	17.86 [4.69 – 36.63]	0.028*	20.07 [4.36 – 79.80]	6.30 [0 – 65.08]	0.110
Trace elements						
Se (95 – 165 μg/L)	81.05 [67.93 – 107.18]	88.41 [66.72 – 137.57]	0.116	70.15 [56.85 – 74.92]	88.07 [73.64 – 102.13]	0.008*
Fe (45 – 182 μg/dL)	45.00 [30.70 – 63.30]	63.50 [36.24 – 96.76]	0.116	26.00 [19.98 – 42.02]	63.00 [35.40 – 99.17]	0.043*
Electrolytes						
Ca (8.9 – 10.3 mg/dL)	8.55 [8.14 – 8.84]	8.62 [8.08 – 9.31]	0.276	8.50 [8.20 – 8.52]	8.90 [8.70 – 9.34]	0.032*
Na (136 – 144 mmol/L)	134.00 [130.11 – 137.22]	136.50 [133.52 – 138.48]	0.344	138 [134.01 – 140.56]	139 [136.80 – 141.77]	0.017*

Se: Selenium, Fe: Iron, Ca: Calcium, Na: Sodium, Wilcoxon test, *$p < 0.05$.

Table 5
Relationships between physical activity and trace/electrolyte levels.

		Se level differences (Δ)	Fe level differences (Δ)	Ca level differences (Δ)	Na level differences (Δ)
Baseline physical activity (IPAQ-SF, MET value)	rho	0.377	-0.057	0.180	0.051
	p	0.166	0.853	0.520	0.856
Physical activity differences (Δ, MET value)	rho	0.039	-0.016	0.147	-0.359
	p	0.891	0.960	0.601	0.189

Se: Selenium, Fe: Iron, Ca: Calcium, Na: Sodium, IPAQ-SF: International Physical Activity Questionnaire – Short Form, MET: Metabolic equivalent, Δ: The differences of the values between before and after treatment, Spearman test, *$p < 0.05$.

patients is unknown. A reasonable explanation might be the pharmacological stimulant effects of favipiravir and hydroxychloroquine on selenoproteins to suppress inflammation. In literature, Zhang et al. [43] hypothesized that selenium may be a choice for the treatment of COVID-19 and also plays a crucial role in the emergence and spread of SARS-CoV-2. In the light of the literature, it can be speculated that supplementation of Se during the treatment of COVID-19, especially in the patients with low serum selenium levels, can improve and strengthen the immune response against the virus. Keeping serum selenium levels high in patients via selenium supplementation can lead to an essential breakthrough in the treatment of COVID-19, since the serum selenium level may be still low after discharge.

According to this current study, 60 % of the patients had hyperferritinemia before and after the treatment. It was stated that increased ferritin levels might indicate a robust inflammatory reaction in COVID-19 disease [44]. Ferritin stores Fe in a biologically available form for vital cellular processes while protecting proteins, lipids, and DNA from the potential toxicity of Fe [45,46]. For this reason, hyperferritinemia may be related to viral entry into the human body, considering the impact of hyperferritinemia on Fe metabolism [44,47]. Serum Fe level drops early after the infection but returns to normal ranges in the following week [48]. Hyposideremia is associated with reduced activity of immune cells and decreased cytokine production [49]. The results of this current study supported the literature considering 73.3 % of the patients had hyposideremia before the treatment, while only 26.7 % of the patients had hyposideremia after the treatment. In addition, the decrease in the Fe level of the patients after the treatment was statistically significant. Considering the effect of viral infections on the Fe mechanism, we think that the host cell is negatively affected because of the antiviral influence of the drugs used in the treatment. On the other hand, Ersoz and Yılmaz determined that serum Fe levels can provide information about the prognosis of COVID-19 disease [50]. Therefore, monitoring the level of Fe may have importance in the COVID-19 prognosis.

The Ca ion is required to fuse the coronavirus and its entry into host cells [51]. However, the role of hypocalcemia in COVID-19 infection is not fully known yet. It can be speculated that the "consumption" of circulating Ca for the virus to enter the host cells, as noted by Mikail and Mali [52], may contribute to hypocalcemia. Tezcan et al. reported that low basal Ca levels are associated with higher mortality rates, higher intensive care unit and mechanical ventilation requirements, and more extended hospital stay [53]. They found that 9.5 % of COVID-19 patients had hypocalcemia [53]. According to Zhou et al., COVID-19 patients had low blood Ca levels even in the early stages of the disease, and hypocalcemia worsened in severe cases [15]. Pal et al. stated that non-severe COVID-19 patients tend to have low serum total Ca levels at first presentation (before the treatment), implying hypocalcemia are likely disease-specific [54]. Although the disease severity of the COVID-19 patients in our study was moderate, hypocalcemia was found to be quite common. This finding was consistent with the studies in the literature. In addition, the decrease in hypocalcemia from 66.7 % to 46 % during the treatment process demonstrates that serum Ca levels of the patients improved after COVID-19 treatment. However, almost half of the patients had hypocalcemia even after the treatment. For this reason, as Yang et al. reported in the literature [55], monitoring blood calcium levels and initiating the therapy earlier in COVID-19 patients who have lower serum Ca levels may be critical for improving the prognosis. In addition, assuming that serum calcium levels may be low in COVID-19 patients at discharge, Ca supplements may be given to the patients.

It was reported that the most common electrolyte deficiency in COVID-19 patients is hyponatremia [53]. Duan et al. stated that Na levels have high predictive power for the progression of COVID-19 from mild to severe disease [56]. In another study, Lippi et al. reported that severe COVID-19 patients had significantly lower Na levels than non-severe patients [57]. Tezcan et al. stated that baseline electrolyte abnormalities, especially hyponatremia, are a sign of unfavorable prognosis in COVID-19. They also noted that even after hospitalization, baseline electrolyte evaluation would help assess the risk of severe COVID-19 [53]. In contrast to some reports in the literature, hyponatremia was not the most prominent electrolyte abnormality in this current study. Moreover, only 13.3 % of the patient had hyponatremia after the treatment in this current study. The improvement of Na level may be due to the fact that 60 % and 93.3 % of the patients received saline and enoxaparin Na during the COVID-19 treatment process, respectively.

Physical activity plays a crucial role in strengthening the immune system [58]. It is known that the immune system function improves with regular physical activity and the incidence of various viral infections, symptoms, and mortality rates decreases [58,59]. With the emergence of COVID-19 disease, quarantine and social isolation rules have been applied worldwide, limiting people's access to other places where they can be active [60]. There has been a significant decrease in physical activity levels of individuals since the beginning of the pandemic [61–63]. Ammar et al. stated that the restrictions taken for social isolation in COVID-19 disease negatively affect the physical activity levels of individuals [61]. Duncan et al. stated that the COVID-19 pandemic affected physical activity and mental health, and those with low physical activity levels had high stress and anxiety levels [62]. Tavakol et al. showed that physical inactivity is associated with the severity of COVID-19 disease. In addition, they stated that the symptoms in patients with low physical activity were longer [64]. In this current study, the patients' physical activity levels were similar before and after the treatment. In both times, the patients showed a low level of physical activity. The quarantine and restrictions brought about by the COVID-19 pandemic may also be the reason for the decrease in physical activity level [61]. The low physical activity level of the patients after the treatment may be because they maintained their sedentary life before the treatment (last seven days). Considering the positive effects of physical activity on the immune system and other systems, it seems essential to provide physical activity counseling in addition to the medical treatment of COVID-19.

Adequate trace elements and electrolytes are essential for sports activities. Physical exercise creates additional needs depending on the nature, intensity, duration of exercise, training periods, and pre-competition recovery opportunities. However, only a few publications in the literature have addressed the relationship of trace elements and electrolytes with physical activity in healthy subjects [65]. To the best of our knowledge, there are no studies about the relationships between these parameters in COVID-19 patients. Regarding Ca, moderate exercise stimulates bone mineralization; however, very strenuous exercise may promote Ca loss [22]. Fe deficiency can impair aerobic physical performance because it is essential to maintain reserves of Fe to maintain physical activity performance [66]. For this reason, low physical activity may modify iron status but cannot explain low iron levels. Previous cross-sectional or interventional studies have produced conflicting results regarding the effect of physical activity on Se status [67,68]. In addition, the impact of physical exercise on serum Ca was studied in literature; the results were also controversial. Some authors observed a decrease in total Ca [69,70], while others found no change [71,72] or an increase [73,74]. These divergent results may be attributed to whether Ca was adjusted to hemoconcentration [74], the type of exercise, whether characteristics such as intensity and duration were evaluated [71], training level [75], and physical fitness [76]. Our results showed no relationship between either baseline physical activity or physical activity difference and trace/electrolyte levels. We think that the reason for the results of our study is that no patient had moderate and high physical activity levels; all the patients had low physical activity levels.

4.1. Limitation

This study has some limitations. First, only the moderate-COVID-19 patients were included in this study. Further studies could investigate the changing levels of trace elements, electrolytes, and physical activity in different stages of COVID-19 diseases. Second, the long-term results of these levels could also be evaluated. Third, we compared specific trace elements and electrolyte levels. Examination of other trace elements and electrolytes may evaluate future studies to guide the treatment process of COVID-19. Fourth, all the patients had only low physical activity levels before and after the treatment. In future studies, information about trace element and electrolyte levels can be obtained in individuals in different physical activity levels.

5. Conclusion

This study showed that trace elements including Se and Fe and electrolytes including Ca and Na levels improved after the COVID-19 treatment. However, some patients still had trace element and electrolyte deficiencies after the treatment. In addition, the patients had low physical activity before the treatment, and there was no change in physical activity levels after the treatment. Physical activity recommendations may be a key factor for the hospitalization of COVID-19 patients to support the treatment process and improve the immune system.

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Author contribution

All authors have read and approved the submission of this manuscript. KO, TKB, GK, and SK contributed to the study concept and design. OM, TS, IK, and MYY reached the patients. ES and OM were responsible for biochemical analysis. KO did the statistical analyses. KO, TKB, and GK drafted the manuscript and interpreted the data. ES, OM, MYY, and SK contributed to critical revisions of the manuscript for important intellectual content. All authors provided study supervision.

Ethics statement

The Ethics Committee of Izmir Bakircay University approved all procedures (2020–142).

Consent to participate

Not applicable.

Consent for publication

All authors gave their final approval and agreement to be accountable for all aspects of the work.

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.

Data Availability

Not applicable.

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