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Evaluation of the Serum Zinc Level in Patients Followed in Hospital with the Diagnosis of COVID-19 in Samsun Province, Türkiye

Türkiye’de Samsun İlinde COVID-19 Tanısı ile Hastanede Takip Edilen Hastalarda Serum Çinko Düzeyinin Değerlendirilmesi

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Abstract

The COVID-19 (Coronavirus Disease 2019) outbreak has not yet ended and poses a persistent hazard to individuals, communities, and healthcare systems globally. Similar to numerous other diseases, the immune system of the patient is intricately associated with the advancement and mortality rates of COVID-19. In general, the immune system plays a crucial role in protecting the host against infections and neoplastic cells, and a well-balanced diet can enhance the immune system's ability to effectively defend against infectious agents. There have been suggestions that the administration of zinc supplements may decrease the occurrence of lower respiratory tract infections in children who are deficient in zinc. This study will thus examine the potential of zinc as a preventive and therapeutic agent, either on its own or in conjunction with other techniques, as zinc fulfills all the requirements outlined above. The study cohort was stratified into three distinct groups, namely critical care patients, service patients, and a healthy control group; a total of 24 COVID-19 patients in critical care, 27 ward-treated COVID-19 patients, and 26 healthy individuals. The groups exhibited a notable disparity in age distribution ($p < 0.001$). A statistically significant difference was seen among the groups in relation to the survey results, presence of chronic disease, and length of hospital stay ($p < 0.001$, $p < 0.001$, and $p = 0.007$, respectively). COVID-19 patients ($n = 51$) exhibited markedly reduced zinc levels in comparison to a control group of healthy individuals ($n = 26$). It was observed that the average zinc level in patients diagnosed with COVID-19 was 89 µg/dl (range: 43-123 µg/dl). In comparison, the median zinc level in individuals without COVID-19 was found to be 99.5 µg/dl (range: 79-125 µg/dl). A statistically significant difference was observed between the groups ($p = 0.023$). The study revealed that a total of 13 individuals, accounting for 25.5% of the COVID-19 patients, exhibited a deficiency in zinc levels. The findings of our study

indicate that zinc potentially plays a significant role in the context of COVID-19. However, additional research is required to get a comprehensive understanding of the association between COVID-19 and zinc.

Keywords: COVID-19, COVID prognosis, SARS-CoV-2, Serum zinc level.

Özet

Henüz tam olarak sonlanmamış olan COVID-19 (*Coronavirus Disease 2019*) salgını bireyler, topluluklar ve sağlık sistemleri için küresel ölçekte kalıcı bir tehlike oluşturmaktadır. Pek çok hastalıkta olduğu gibi hastanın bağışıklık sistemi COVID-19'un ilerlemesi ve ölüm oranlarıyla karmaşık bir şekilde ilişkilidir. Genel olarak bağışıklık sistemi, konakçıyı enfeksiyonlara ve neoplastik hücrelere karşı korumada çok önemli bir rol oynar ve iyi dengelenmiş bir beslenme, bağışıklık sisteminin enfeksiyöz etkenlere karşı etkili savunma yeteneğini artırabilir. Çinko eksikliği olan çocuklarda çinko takviyesinin alt solunum yolu enfeksiyonlarının oluşumunu azaltabileceği yönünde önerilerde bulunulmuştur. Bu çalışmada, çinkonun yukarıda özetlenen tüm gereklilikleri yerine getirmesine dayanarak, çinkonun tek başına veya diğer tekniklerle birlikte önleyici ve tedavi edici bir etken olarak potansiyeli incelenecektir. Çalışma kohortu kritik bakım hastaları, servis hastaları ve sağlıklı kontrol grubu olmak üzere üç ayrı gruba ayrıldı; 24 yoğun bakım COVID-19 hastası, 27 serviste tedavi gören COVID-19 hastası ve 26 sağlıklı kişi. Gruplar yaş dağılımı açısından anlamlı derecede bir eşitsizlik sergiledi ($p < 0.001$). Karşılaştırmalı analizler, survey (mortalite) sonuçları, kronik hastalık varlığı ve hastanede kalış süresi açısından gruplar arasında istatistiksel olarak anlamlı farklılıklar olduğunu gösterdi (sırasıyla $p < 0.001$, $p < 0.001$ ve $p = 0.007$). COVID-19 hastaları ($n = 51$), sağlıklı bireylerden oluşan kontrol grubu ($n = 26$) ile karşılaştırıldığında belirgin şekilde düşük çinko seviyeleri sergiledi. COVID-19 tanısı alan hastalarda ortalama çinko seviyesinin $89 \mu\text{g/dl}$ (aralık: $43\text{-}123 \mu\text{g/dl}$) olduğu gözlemlendi. Buna karşın, COVID-19 olmayan bireylerde ortalama çinko düzeyi $99.5 \mu\text{g/dl}$ (aralık: $79\text{-}125 \mu\text{g/dl}$) olarak belirlendi. Gruplar arasında istatistiksel olarak anlamlı düzeyde farklılık olduğu gözlemlendi ($p = 0.023$). Çalışma, COVID-19 hastalarının %25.5'ini oluşturan toplam 13 kişinin çinko düzeylerinde eksiklik sergilediğini ortaya çıkardı. Çalışmamızın bulguları çinkonun potansiyel olarak COVID-19 bağlamında önemli bir rol oynadığına işaret etmektedir. Ancak, COVID-19 ile çinko arasındaki ilişkinin kapsamlı bir şekilde anlaşılması için ek araştırmalara ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, COVID prognozu, SARS-CoV-2, Serum çinko düzeyi.

Introduction

The COVID-19 (Coronavirus Disease 2019) outbreak has not yet ended and poses a persistent threat to individuals, communities, and healthcare systems on a global scale. Similar to several other diseases, the immune system of the host exhibits a significant association with the advancement and mortality rates of COVID-19 [1]. The host's immune system plays a crucial role in protecting against infections and neoplastic cells, and a well-balanced diet can enhance the immune system's ability to effectively defend against infectious agents [2-4]. Zinc (Zn), a mineral known for its anti-inflammatory and antioxidant properties, has been identified as having a significant impact on immune function, particularly in relation to antiviral immunity [5,6]. Zinc, the second most prevalent trace metal in the human body following iron, plays a crucial role in various cellular processes, including immune mechanisms [7]. Zinc has been found to exhibit enhanced efficacy

in modulating T cells inside the immune system. The synthesis of serum thymulin, a crucial factor in the development of T lymphocytes, is reliant on zinc. In the event of a potential shortfall in zinc, the quantity of serum thymulin drops, leading to the suppression of T lymphocyte maturation. Additionally, a decrease in the production of cytokines, particularly IL-6, has been documented [8]. Zinc serves a dual role in biological systems, acting as both an anti-inflammatory molecule and an antioxidant that aids in the stabilization of cellular membranes [9].

According to a study conducted by Lassi et al. there is some evidence to suggest that zinc supplementation may decrease the occurrence of lower respiratory tract infections in children who have a shortage in zinc [10]. Furthermore, Singh and Das have proposed that the administration of zinc supplements may decrease the occurrence of lower respiratory tract infections in children who exhibit zinc deficiency [11].

In vitro investigations have demonstrated that a reduction in zinc levels facilitates the interaction between angiotensin converting enzyme 2 (ACE-2) and the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [12]. Conversely, elevated zinc levels impede ACE-2 expression, leading to a decrease in viral presence.

The objective of this study is to assess and compare the serum zinc levels among COVID-19 patients receiving care in both the general service and intensive care unit at our hospital. Additionally, the study aims to examine the correlation between serum zinc levels and the disease prognosis, while also comparing these levels with those of healthy individuals.

Material and Method

The study was conducted after obtaining ethical approval from "University of Health Sciences (UHS), Samsun Training and Research Hospital Non-interventional Clinical Research Ethics Committee", date: 12.03.2021, decision no: 2021/5/15. The study was carried out in accordance with the tenets of the Declaration of Helsinki.

The demographic information of the patients, the duration of hospital stay for COVID-19 prognosis, and the CO-RADS (*COVID-19 Reporting and Data System*) Score were subjected to statistical analysis using the SPSS software (IBM Corp., Armonk, NY). Individuals with underlying secondary diseases were defined as "presence of chronic disease". Such chronic diseases include hypertension, severe obesity, chronic obstructive pulmonary disease, asthma, diabetes, cardiovascular disease, chronic kidney, and chronic liver disease. Patients under the age of 18 were not included in the study.

During the period of March 15, 2020 to June 15, 2020, serum samples of COVID-19 patients who were monitored in both the general service and critical care unit were collected for analysis of zinc levels at our laboratory, in addition to other testing. A total volume of 5 milliliters of venous blood samples obtained from patients using a gel separator tube (BD Vacutainer, UK) and

afterwards stored at a temperature of -20°C. The zinc concentration was assessed in a total of 77 serum samples that had been kept. The colorimetric approach employed in this study utilized an automated Indiko Plus analyzer (Thermo Scientific, US). The reference range plasma concentration employed for zinc was 70-110 µg/dl. In order to assess the validity of the approach, a two-level random control was examined. The Randox chemistry control samples used were Human Test Control-2 LOT-1369 UN and Human Control-3 LOT- 1066 UE.

Additionally, COVID-19 patients were categorized based on their serum zinc levels for the Randox Immunoassay Control. A zinc level below 70 µg/dl was classified as 'zinc deficient'.

Statistical analyses

The variables were subjected to a descriptive statistical analysis using IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, US). This analysis included the calculation of the mean, standard deviation, percent, median, and interquartile range (IQR; 25-75%). Chi-square and Fisher's exact test were used to compare the ratios and relationships among the attributes of the research groups. The Mann-Whitney U-test and t-test were employed to assess the differences in continuous variables across the various research groups. The researchers conducted a univariate logistic regression analysis in order to calculate the odds ratio (OR) and 95% confidence intervals (95% CI). Statistical significance was attributed to the results when the p value was less than 0.05.

Results

The study cohort was stratified into three distinct groups: A total of 24 COVID-19 patients in critical care, 27 service patients (ward-treated COVID-19 patients), and a control group consist of 26 healthy individuals. There existed a notable disparity in age distribution between the groups, with a statistical significance at the $p < 0.001$ level. A statistically significant difference was seen between the groups in relation to the survey results (mortality rate), presence of chronic disease, and length of hospital stay ($p < 0.001$, $p < 0.001$, and $p = 0.007$, respectively) (Table 1).

Table 1. Demographic and clinical characteristics of the study groups.

		Intensive care (n=24)	Service (n=27)	Healthy (n=26)	p
Age (year) [†]		67.54±13.32	50.67±12.05	50.15±16.02	<0.001
Sex [‡]	Female	14 (58.3%)	20 (74.1%)	16 (%61.5)	0.454**
	Male	10 (41.7%)	7 (25.9%)	10 (%38.5)	
Survey [‡]	Living	5 (20.8%)	25 (92.6%)	26 (%100)	<0.001**
	Exitus	19 (79.2%)	2 (7.4%)	0 (%0.0)	
Presence of chronic disease [‡]		16 (66.7%)	3 (11.1%)		<0.001**
Length of stay in hospital [†]		14.3±10.29	7.22±3.92		0.007***

[†]; mean ± standard deviation. [‡]; n (%). *: Kruskal Wallis Test. **: Pearson Chi-Square or Fisher's Exact test. *** Independent samples t-test.

A notable decrease in zinc concentrations was seen in individuals diagnosed with COVID-19 (n=51) in comparison to a control group of healthy individuals (n=26). The median zinc level in individuals diagnosed with COVID-19 was 89 µg/dl, with a range of 43 to 123 µg/dl. In contrast, the median zinc level in individuals without COVID-19 was found to be 99.5 µg/dl, with a range of 79 to 125 µg/dl. The observed discrepancy exhibited statistical significance (p=0.023). A total of 13 individuals, accounting for 25.5% of the COVID-19 patients, exhibited a deficiency in zinc levels. A zinc shortage was observed in one of the participants classified as healthy. There was a statistically significant difference seen between the groups in relation to zinc insufficiency (p=0.030).

The Spearman correlation study revealed a negative association between zinc levels and CO-RADS score (r=-0.248, p=0.031) (Figure 1).

Table 2 indicates that there was no statistically significant correlation observed between zinc levels and both age and hospitalization days.

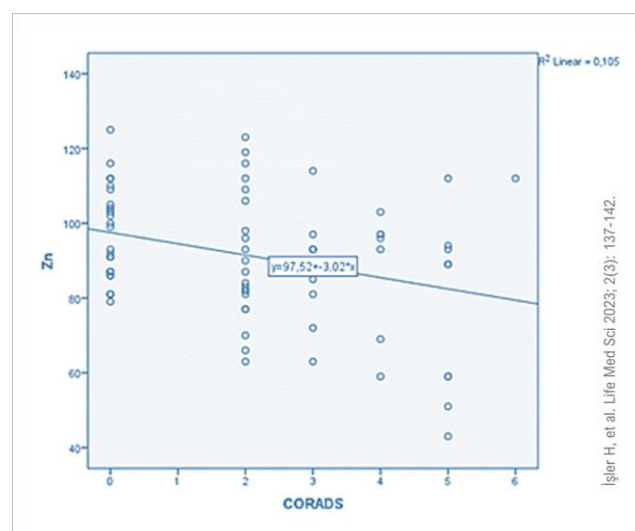


Figure 1. Correlation graph between zinc level and CO-RADS scores.

Table 2. Correlation between numerical parameters and the zinc levels.

Parameters		Spearman's rho*	p
Zinc levels	Age	-0.085	0.465
	Length of stay in hospital	-0.141	0.223

*Spearman's Rho; correlation coefficient.

The possible correlation between serum zinc concentration and the need for intensive care was evaluated and a negative correlation (r=-0.260, p=0.023) was found between the serum zinc levels and the likelihood of hospitalization in the critical care unit.

Discussion

Zinc is classified as a trace element and possesses significant immunomodulatory and antiviral characteristics [13]. Several research have been conducted to investigate the serum zinc levels in adult individuals diagnosed with

COVID-19 [6]. In a study conducted by Jothimani et al., it was demonstrated that among a cohort of 47 adult patients who were hospitalized for COVID-19, 27 individuals (57.4%) exhibited low serum zinc levels [14]. According to another study conducted by Yasui et al. [15], among the 29 adult patients diagnosed with COVID-19 nine individuals, accounting for 31% of the cohort, exhibited low levels of serum zinc. A recent study conducted on a cohort of 33 adult patients diagnosed with COVID-19 revealed that low serum zinc levels in patients with COVID-19 might be a response to SARS-CoV-2 in the acute phase and the researchers suggested that intravenous zinc treatment can reverse this effect [16]. In our study, a notable distinction observed between the groups in terms of transitioning to the critical care unit. Also, notable disparities were observed among the groups with regards to the survey results (*mortality rates*), prevalence of chronic disease, and duration of hospitalization ($p < 0.001$, $p < 0.001$, and $p = 0.007$, respectively, [Table 1](#)).

In a research study involving children, it was shown that the rate of hospitalization among patients with low zinc levels was considerably greater compared to those with normal zinc levels [17]. Specifically, 5 of 11 patients (45.5%) in the low zinc group were hospitalized, whereas only 10 of 89 patients (11.2%) in the normal zinc group required hospitalization [17]. This difference was found to be statistically significant ($p = 0.011$). The study found that the median serum zinc level among individuals diagnosed with COVID-19 was 88.5 μdL , with an IQR of 77.2-100. This value was significantly lower compared to the median level of 98 μdL (IQR 84-111) observed in the control group. The statistical analysis revealed a p -value of 0.001, indicating a significant difference between the two groups. The study found no significant correlation between the severity of COVID-19 and the serum zinc levels in children [17]. In our investigation, we observed a notable decrease in zinc levels among individuals diagnosed with COVID-19 ($n = 51$) in comparison to a control group of healthy individuals ($n = 26$). We observed that the median zinc level among individuals diagnosed with COVID-19 was 89 $\mu\text{g/dl}$, with a range of 43 to 123 $\mu\text{g/dl}$. In contrast, the median zinc level among healthy individuals

was found to be 99.50 $\mu\text{g/dl}$, with a range of 79 to 125 $\mu\text{g/dl}$. The observed discrepancy exhibited statistical significance ($p = 0.023$).

In a recent study [14], a total of 47 COVID-19 patients were compared to a control group of 45 healthy individuals. The analysis revealed that the COVID-19 patients had considerably lower zinc levels compared to the healthy controls. The median zinc level in the COVID-19 group was 74.5 $\mu\text{g/dl}$, with an interquartile range of 53.4-94.6 $\mu\text{g/dl}$. In contrast, the healthy control group had a median zinc level of 105.8 $\mu\text{g/dl}$, with an interquartile range of 95.65-120.9 $\mu\text{g/dl}$. This difference was shown to be statistically significant, with a p -value of less than 0.001. The study also revealed that amongst the COVID-19 patients, 27 (57.4%) were exhibited a deficiency in zinc levels. These patients (*with zinc deficient*) had higher rates of complications ($p = 0.009$), a potential development of acute respiratory distress syndrome (18.5% vs. 0%, $p = 0.06$), utilization of corticosteroid therapy ($p = 0.02$), longer hospital stays ($p = 0.06$), and an elevated mortality rate (18.5% vs. 0%, $p = 0.06$). The observed odds ratio (OR) for the occurrence of problems among individuals diagnosed with COVID-19 and exhibiting zinc insufficiency was determined to be 5.54 [14]. Similarly, according to Patel et al. there exists a correlation between decreased levels of zinc in the serum and an elevated susceptibility to acute respiratory distress syndrome, heightened levels of proinflammatory mediators, prolonged durations of hospitalization, and increased mortality rates among adult patients [16].

Conclusion

In this study, a statistically significant inverse correlation was seen between serum zinc levels and intensive care hospitalization; when the concentration of zinc declined, there was a corresponding rise in the frequency of admissions to the intensive care unit. Also, a statistically significant decrease was found in zinc levels of COVID-19 patients. These findings indicate that zinc potentially plays a significant role in the context of COVID-19 course. However, additional research is required to well understanding of the association between COVID-19 and zinc.

Conflict of interest: The authors declare that there is no conflict of interest. The authors alone are responsible for the content and writing of the paper. **Financial disclosure:** There is no financial support for this study.

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