Journal of Urology and Renal Diseases
Putri R, et al. J Urol Ren Dis 09: 1396.
www.doi.org/10.29011/2575-7903.001396
www.gavinpublishers.com
Research Article

Serum Zinc Levels of Patients with COVID-19 Undergoing Hemodialysis

Takayasu Taira[1*], Atsushi Sugita[2], Makoto Hasegawa[1], Go Oda[1], Ryuuki Okuyama[3], Mitsuru Kurata[3], Yuichi Hisa[1], Koichi Azuma[1], Tetsuo Chiba[1], Ashio Yoshimura[1]

[1]Department of Nephrology, Yokohama Dai-ichi Hospital, Yokohama, Japan

[2]Department of Urology, Kitasato University School of Medicine, Sagamihara, Japan

[3]Department of Clinical Inspection, Prime Health Partners, Zenjinkai Group, Yokohama, Japan

[*]**Corresponding Author:** Takayasu Taira, M.D., Ph.D., Department of Nephrology, Yokohama Daiichi Hospital, 2-5-15 Takashima, Nishi-ku, Yokohama, Kanagawa 227-0011, Japan

Citation: Taira T, Sugita A, Hasegawa M, Oda G, Okuyama R, et al. (2024) Serum Zinc Levels of Patients with COVID-19 Undergoing Hemodialysis. J Urol Ren Dis 09: 13946. https://doi.org/10.29011/2575-7903.001396

Received Date: 22 August 2024; **Accepted Date:** 27 August 2024; **Published Date:** 31 August 2024

Abstract

Purpose: Strategies to minimize Coronavirus Disease (COVID-19) transmission in patients undergoing hemodialysis have been implemented worldwide. Chronic kidney disease is a risk factor for COVID-19 and zinc could exert antiviral effects by suppressing viral replication and enhancing immune responses. Therefore, this study investigated the serum zinc levels of patients with COVID-19 undergoing hemodialysis.

Method: This multicenter retrospective observational study included outpatients undergoing hemodialysis. We measured the serum zinc levels of patients with and without COVID-19 undergoing hemodialysis and compared the levels with those of adults with normal renal function.

Results: Of 91 patients undergoing hemodialysis, 24 (26.4%) tested positive for severe acute respiratory syndrome coronavirus-2 and 67 (73.6%) did not. All 24 patients with COVID-19 had hypozincemia (mean serum zinc level: 58.9±7.5 μg/dL): 9 (37.5%) had mild hypozincemia (zinc: <80 μg/dL) and 15 (62.5%) had severe hypozincemia (zinc: <60 μg/dL). Among patients undergoing hemodialysis, the mean serum zinc level in those with COVID-19 was significantly lower than that in patients without COVID-19 (58.9±7.5 vs. 63.3±11.4 μg/dL; p=0.03436). The mean serum zinc level of patients with COVID-19 undergoing HD was significantly lower than that in adults with normal renal function (58.9±7.5 vs. 78.0±8.3 μg/dL; p=0.00042).

Conclusion: Japanese patients with COVID-19 undergoing hemodialysis had low serum zinc levels. Most patients undergoing hemodialysis had hypozincemia. Hypozincemia therefore may be a risk factor for COVID-19 in patients undergoing hemodialysis.

Keywords: Chronic Kidney Disease; COVID-19; Hemodialysis; Serum Zinc Level

Introduction

The coronavirus disease (COVID-19) pandemic was caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Methods to reduce the risk of COVID-19 for patients undergoing hemodialysis have been rapidly implemented worldwide [1]. In a study involving approximately 1,300 dialysis facilities across the United States, the analysis of plasma levels of total antibodies against the spike protein receptor-binding domain in 28,503 adult patients on dialysis revealed that the seroprevalence of SARS-CoV-2 antibodies was 8.3% [2]. SARS-CoV-2 has four major structural proteins: spike (S), membrane, envelope, and nucleocapsid proteins. The S protein comprises an S1 subunit that mediates cell surface binding via the receptor-binding domain, and an S2 subunit that induces viral host cell membrane fusion. Antibodies to the highly immunogenic receptor-binding domain account for approximately 90% of neutralizing SARS-CoV-2-specific antibodies, whereas few studies have reported neutralizing

antibodies to viral structural proteins, such as the nucleocapsid protein [3]. Speer et al. reported a reduced antibody response to the first and second doses of the mRNA vaccine BNT162b2 (BioNTech) in patients on hemodialysis treatment. Most patients undergoing hemodialysis HD (82%) developed neutralizing antibodies after the second dose, but healthy controls had lower levels [4]. Japanese patients undergoing hemodialysis have exhibited evidence of immunity to SARS-CoV-2 after BNT162b2 mRNA vaccination; the majority of these patients develop spike antibodies after the second dose. The mean SARS-CoV-2 spike antibody levels are significantly higher after the third BNT162b2 vaccine dose than after the second dose [5].

Zinc is an essential trace element that plays various important roles in the body to maintain immune function and block the invasion and proliferation of pathogenic viruses. Symptoms of hypozincemia include general fatigue, dysosmia, dysgeusia, loss of appetite, hair loss, anemia, and headache [6]. A link between SARS-CoV-2 infection and zinc has been suggested [7-9]. Razzaque reported that zinc exerts antiviral effects by suppressing viral replication and enhancing immune responses [10]. Rheingold et al. reported that zinc supplementation is associated with decreased mortality in those with COVID-19. This is promising as zinc is widely available and may be valuable as a cost-effective way to prevent poor outcomes for those with COVID-19 [11]. However, the serum zinc levels of patients on hemodialysis treatment with SARS-CoV-2 infection have not been investigated. Hence, we investigated the serum zinc levels of Japanese patients with COVID-19 undergoing hemodialysis.

Materials and Methods

Study design, population, and data sources

This was an observational cohort study.

Study 1

We quantitatively measured zinc levels in the serum of patients who underwent hemodialysis in the dialysis facilities of the Aobadai Jin Clinic, Takada Jin Clinic, and Yokohama Dai-ichi Hospital between August 1 and December 1, 2023.

We quantitatively measured SARS-CoV-2 spike antibodies in the serum of patients with COVID-19 who underwent HD in the dialysis facilities of the Aobadai Jin Clinic, Takada Jin Clinic, and Yokohama Dai-ichi Hospital between August 1 and December 1, 2023 (Table 1)

	Patients undergoing hemodialysis		Adults with normal renal function
	With COVID-19	Without COVID-19	
N (%)	N=24 (26.4%)	N=67 (73.6%)	N=9
Sex			
Female	6	15	5
Male	18	52	4
Age (years)	68.6±12.6	68.1±14.4	32.2±3.4
HD duration (years)	7.8±6.8	7.8±6.8	
Cause of ESKD			
DKD	8	20	
CGN	3	8	
IgA nephropathy	5	6	
RPGN	0	2	
Nephrosclerosis	5	11	
Malignant hypertension	0	3	
ADPKD	1	4	
Pregnancy kidney	0	1	
Unknown	2	12	

ADPKD: Autosomal Dominant Polycystic Kidney Disease; CGN: Chronic Glomerulonephritis; COVID-19: Coronavirus Disease; DKD: Diabetic Kidney Disease; ESKD: End-Stage Kidney Disease; HD: Hemodialysis; IgA: Immunoglobin A; RPGN: Rapidly Progressive Glomerulonephritis

Table 1: Baseline demographics and characteristics (n=100).

Study 2

We measured zinc levels in the serum of nine adults with normal renal function (four males and five females) in the department of Clinical Inspection, Prime Health Partners, Zenjinkai Group between July 1 and August 31, 2023.

Blood sampling and measurement of serum zinc

Serum zinc levels were measured several times during blood sampling at the start of hemodialysis. Serum zinc concentrations were analyzed using the Accuras Auto Zn kit (Shino-Test Corporation, Tokyo, Japan), which was developed to measure serum zinc levels, with an automatic analyzer at the clinical laboratory in our hospital. Serum zinc levels were classified per the Japanese Society of Clinical Nutrition, as follows: 80-130 μg/dL, normal; 60-80 μg/dL, subclinical zinc deficiency; and <60 μg/dL, clinical zinc deficiency [12]. In Harrison's Principles of Internal Medicine, an international standard indicator, clinical zinc deficiency is defined as serum zinc levels of <70 μg/dL [13]. Serum zinc levels tend to be affected by sex, age, and the time at which blood is sampled. We defined serum zinc concentrations of <80 and <60 μg/dL as mild and severe hypozincemia, respectively.

Antibody detection

We quantified the SARS-CoV-2 spike antibodies in human plasma. SARS-CoV-2 spike antibodies levels were evaluated with a fully automated Cobas e801 analyzer (Roche Diagnostics, Santa Clara, California, USA), using an Elecsys® anti-SARS-CoV-2 electrochemiluminescence immunoassay (Roche Diagnostics), which has 100% sensitivity and 99.81% specificity (Roche Diagnostics) to qualitatively detect SARS-CoV-2 spike antibodies in human plasma [14]. A semiquantitative index of <0.8 U/mL was classified as negative, and one of ≧0.8 U/mL was classified as positive.

Statistical analysis

Data are expressed as mean ± standard deviation or median (interquartile range) for continuous variables and as frequency (percentage) for categorical variables. The Wilcoxon signed–rank test was used for proportional assessments. Statistical significance was set at $p<0.05$, and all statistical analyses were performed using SAS Statistics software (version 9.4; SAS Institute, Cary, North Carolina, USA).

Ethics statement

The study was approved by the ethics committee of the Zenjinkai Group (approval number: 0001008422) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before the study.

Results

Data from 91 patients undergoing hemodialysis and 9 adults with normal renal function were analyzed in this study.

Study 1

The background characteristics of patients undergoing hemodialysis with and without COVID-19 are shown in Table1. Overall, 24 (26.4%) patients undergoing hemodialysis tested positive for SARS-CoV-2 on polymerase chain reaction testing, whereas 67 (73.6%) patients tested negative. Serum zinc concentrations in the patients on hemodialysis treatment are shown in Table 2. All 24 patients with COVID-19 had hypozincemia, of whom 9 (37.5%) had mild hypozincemia, and 15 (62.5%) had severe hypozincemia. The mean titer of SARS-CoV-2 spike antibodies was 10,032±4,695 U/mL. The mean serum zinc level in patients with COVID-19 undergoing hemodialysis was significantly lower than that in patients without COVID-19 (58.9±7.5 vs. 63.3±11.4 μg/dL; p=0.03436).

	With COVID-19	Without COVID-19	*p-Value*
Number of patients	24	67	
Serum zinc concentration (μg/dL)	58.9±7.5	63.3±11.4	0.03436
Mild hypozincemia (zinc: <80 μg/dL)	9 (37.5%)	35 (52.2%)	
Severe hypozincemia (zinc: <60 μg/dL)	15 (62.5%)	27 (40.3%)	
Normozincemia	0	5 (7.5%)	
COVID-19: Coronavirus Disease			

Table 2: Serum zinc concentration of patients on hemodialysis treatment.

Study 2

The daily variations in serum zinc concentration in adults with normal renal function are shown in Table 3. In Japanese adults (mean age: 32.2±3.4 years; 4 females, 5 males) with normal renal function, the mean serum zinc concentrations were 78.0±8.3, 74.7±13.6, and 75.6±11.2 μg/dL at 10 am, 2 pm, and 4 pm, respectively, indicating that the daily variations in serum zinc levels were minor. The mean serum zinc concentration in patients with COVID-19 undergoing hemodialysis was significantly lower than that in adults with normal renal function (58.9±7.5 vs. 78.0±8.3 μg/dL; p=0.00042). The mean serum zinc concentration in patients without COVID-19 undergoing hemodialysis was significantly lower than that in adults with normal renal function (63.3±11.4 μg/dL vs. 78.0±8.3 μg/dL; p=0.00049).

Time	Serum zinc concentration (μg/dL)
10 am	78.0±8.3
2 pm	74.7±13.6
4 pm	75.6±11.2

Table 3: Daily variations in the serum zinc concentration of adults with normal renal function.

Discussion

Zinc is an essential mineral that plays various important roles in the body, such as maintaining immune function and blocking the invasion and proliferation of pathogenic viruses [6]. Brewer et al. reported that zinc may be effective against SARS-CoV-2 infection [7]. Serum zinc levels are low in severe cases, suggesting a link between COVID-19 infection and zinc levels [8, 9]. Tsuchiya et al. reported that serum zinc levels are significantly lower in SARS-CoV-2-infected patients with pneumonia than in those without pneumonia [15]. Vogal-González et al. reported that serum zinc levels of <50 μg/dL at admission are correlated with a worse clinical presentation, longer time to reach stability, and higher mortality [16]. *In vitro* results have indicated that low zinc levels favor viral expansion in SARS-CoV-2-infected cells [16]. Yasui et al. reported that prolonged hypozincemia is a risk factor for severe COVID-19 [17]. Matsuda et al. reported that the most frequent symptom in patients with long COVID with hypozincemia is general fatigue. Serum zinc levels should be measured in patients with long COVID with general fatigue [18].

Japanese patients with COVID-19 undergoing hemodialysis had low serum zinc levels. Hypozincemia was detected in most patients undergoing hemodialysis and may be a risk factor for COVID-19. Weiss et al. reported that patients undergoing hemodialysis have a higher risk of SARS-CoV-2 infection than the general population [19]. Prasad reported that zinc deficiency is related to smell dysfunction, taste abnormalities, delayed wound healing, skin changes, hair loss, and mental lethargy [20]. Therefore, patients with COVID-19 undergoing hemodialysis with hypozincemia may have more complaints, including dysgeusia, general fatigue, and hair loss, which are common complains among patients with COVID-19 undergoing hemodialysis. Fromonot et al. reported that hypozincemia is more frequently observed in patients with COVID-19 than in those without [21]. In the present study, hypozincemia was detected in most patients undergoing hemodialysis. Highly predictive clinical factors must be examined to forecast the outcome immediately after COVID-19. Yasui et al. reported that almost all severe cases show subclinical or clinical zinc deficiency and that prolonged hypozincemia is a risk factor for critical illness in COVID-19 [17]. Razzaque reported that zinc can exert antiviral effects by suppressing viral replication and enhancing immune responses [10]. Rheingold et al. reported that zinc supplementation is associated with decreased mortality in those with COVID-19 but does not change symptomatology. This is promising because zinc is widely available and may be valuable as a cost-effective way to prevent poor outcomes for those with COVID-19 [11]. Ota reported that acquired immunity against primary SARS-CoV-2 confers protection from re-infection [22]. Sethuraman et al. found that a SARS-CoV-2 infection can also be detected indirectly by measuring the host's immune response. Serological diagnosis is particularly important for patients with mild to moderate illness who may present late in the course of their infection, particularly more than 2 weeks after the onset of illness [23]. To et al. reported that enzyme-linked immunosorbent assay-based immunoglobin M and immunoglobin IgG antibody tests had a >95% specificity for the diagnosis of SARS-CoV-2. The receptor-binding domain of S is a host-attachment protein, and antibodies to RBD-S are more specific and are expected to be neutralizing [24].

We aimed to examine the relationship between serum zinc levels and COVID-19 in patients undergoing hemodialysis to evaluate whether hypozincemia could be a predictive factor for critical illness in patients with COVID-19 undergoing hemodialysis. Urinary epidermal growth factor levels have been associated with acute kidney injury [25]. Menez et al. reported that lower urinary epidermal growth factor levels are associated with poor prognosis in patients hospitalized with COVID-19. Urinary biomarkers are associated with adverse kidney outcomes in patients hospitalized with COVID-19 and provide valuable information to monitor kidney disease progression and recovery [26]. Further studies are needed to validate the association between urinary epidermal growth factor levels and serum zinc levels of patients undergoing hemodialysis with COVID-19.

Our observational cohort study was limited by its design, small number of patients on hemodialysis treatment, and timing of serological testing. Our preliminary data requires confirmation through further testing.

Conclusions

We revealed that Japanese patients with COVID-19 undergoing

hemodialysis had low serum zinc levels. Most patients undergoing hemodialysis had hypozincemia. Among patients undergoing hemodialysis, the mean serum zinc level in those with COVID-19 was significantly lower than that in patients without COVID-19. Hypozincemia therefore may be a risk factor for COVID-19 in patients undergoing hemodialysis.

Author Contributions: Data analysis: TT, MH, AS, GO, RO, MK, and YH; supervision/mentorship: KA, TC, and AY. Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work were appropriately investigated and resolved.

Acknowledgments: The authors thank the staff of the renal dialysis facilities of the Zenjinkai Group for their support and the patients for taking the time to complete the research protocol. The authors are also grateful for the support of Ms. Kaori Soneda, Hiroshi Yamamoto, Hiroshi Shinada, and Yuya Okazaki of the Division of Total Management System in the Yokohama Daiichi Hospital. We thank Editage (www. editage.com) for the English language editing.

Funding: None.

Institutional Review Board Statement: The study was approved by the ethics committee of the Zenjinkai Group (approval number: 0001008422) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement: Written informed consent was obtained from all patients before the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: None.

References

1. Ikizler TA, Kliger AS (2020) Minimizing the Risk of COVID-19 Among Patients on Dialysis. Nature Reviews Nephrology 16: 311–313.
2. Anand S, Montez-Rath M, Han J, Bozeman J, Kerschmann R, et al. (2020) Prevalence of SARS-CoV-2 Antibodies in a Large Nationwide Sample of Patients on Dialysis in the USA: A Cross-Sectional Study. Lancet (London, England) 396: 1335–1344.
3. Piccoli L, Park Y-J, Tortorici MA, Czudnochowski N, Walls AC, et al. (2020) Mapping Neutralizing and Immunodominant Sites on the SARS-CoV-2 Spike Receptor-Binding Domain by Structure-Guided High-Resolution Serology. Cell 183: 1024–1042.e21.
4. Speer C, Göth D, Benning L, Buylaert M, Schaier M, et al. (2021) Early Humoral Responses of Hemodialysis Patients after COVID-19 Vaccination with BNT162b2. Clinical Journal American Society of Nephrology. 16: 1073–1082.
5. Taira T, Oda G, Kurata M, Kobayashi A, Hisa Y, et al. (2023) SARS-CoV-2 Antibodies in Patients on Hemodialysis After the BNT162b2 mRNA Vaccination. Journal of Urology Renal Diseases 08: 1303.
6. Read SA, Obeid S, Ahlenstiel C, Ahlenstiel G (2019) The Role of Zinc in Antiviral Immunity. Advances Nutrition (Bethesda, MD) 10: 696–710.
7. Brewer J, Gomez Marti JL, Brufsky A (2021) Potential Interventions for SARS-CoV-2 Infections: Zinc Showing Promise. Journal of Medical Virology 93: 1201–1203.
8. Dubourg G, Lagier JC, Brouqui P, Casalta JP, Jacomo V, et al. (2021) Low Blood Zinc concentrations in Patients With Poor Clinical Outcome During SARS-CoV-2 Infection: Is There a Need to Supplement With Zinc COVID-19 Patients? Journal of Microbiology, Immunology, and Infection 54: 997–1000.
9. Skalny AV, Timashev PS, Aschner M, Aaseth J, Chernova LN, et al. (2021) Serum Zinc, Copper, and Other Biometals are Associated With COVID-19 Severity Markers. Metabolites 11: 244.
10. Razzaque MS (2020) COVID-19 Pandemic: Can Maintaining Optimal Zinc Balance Enhance Host Resistance? The Tohoku Journal Experimental Medicine 251: 175–181.
11. Rheingold SZ, Raval C, Gordon AM, Hardigan P (2023) Zinc Supplementation Associated With a Decrease in Mortality in COVID-19 Patients: A Meta-Analysis. Cureus 15: e40231.
12. Itakura H, Omori H, Sasaki M, Sando K, et al. (2016) Guideline for Treatment of Zinc Deficiency. Journal of the Japanese Society Clinical Nutrition 38: 104–148.
13. Suter PM and Russell RM (2018) Vitamin and Trace Mineral Deficiency and Excess (Chapter 326). Minerals. Zinc. In: Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 20th ed. New York: McGraw Hill; pp. 96e9-96e10.
14. Egger M, Bundschuh C, Wiesinger K, Gabriel C, Clodi M, et al. (2020) Comparison of the Elecsys® Anti-SARS-CoV-2 Immunoassay with the EDI™ Enzyme Linked Immunosorbent Assays for the Detection of SARS-CoV-2 Antibodies in Human Plasma. Clinica Chimica Acta 509: 18–21.
15. Tsuchiya T, Sato Y, Kudo A, Oikawa M, Iijima H. (2022) A Study on SARS-CoV-2 Infected Patients with Measured Serum Zinc Levels During Home Care. Metallomics Res 2: reg-1.
16. Vogal-González M, Talló-Parra M, Herrera-Fernández V, Pérez-Vilaró G, Chillón M, et al. (2021) Low Zinc Levels at Admission Associates with Poor Clinical Outcomes in SARS-CoV-2 Infection. Nutrients 13: 562.
17. Yasui Y, Yasui H, Suzuki K, Saitou T, Saitou T, Yamamoto Y, et al. (2020) Analysis of the Predictive Factors for a Critical Illness of COVID-19 During Treatment-Relationship Between Serum Zinc Level and Critical Illness of COVID-19. International Journal of Infectious Diseases 100: 230–236.
18. Matsuda Y, Tokumasu K, Otsuka Y, Sunada N, Honda H, et al. (2023) Symptomatic Characteristics of Hypozincemia Detected in Long COVID Patients. Journal of Clinical Medicine 12: 2062.
19. Weiss S, Bhat P, Del Pilar Fernandez M, Bhat JG, Coritsidis GN (2020) COVID-19 Infection in ESKD: Findings From a Prospective Disease Surveillance Program at Dialysis Facilities in New York City and Long Island. Journal of the American Society of Nephrology 31: 2517–2521.
20. Prasad AS. (1985) Clinical Manifestations of Zinc Deficiency. Annual Review of Nutrition 5: 341–363.

21. Fromonot J, Gette M, Ben Lassoued A, Guéant JL. Guéant-Rodriguez RM, et al. (2022) Hypozincemia in the Early Stage of COVID-19 is Associated with an Increased Risk of Severe COVID-19. Clinical Nutrition (Edinburgh, Scotland) 41: 3115–3119.

22. Ota M (2020) Will We See Protection or Reinfection in COVID-19?. Nature Reviews. Immunology 20: 351.

23. Sethuraman N, Jeremiah SS, Ryo A (2020) Interpreting Diagnostic Tests for SARS-CoV-2. JAMA 323: 2249–2251.

24. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, et al. (2020) Temporal Profiles of Viral Load in Posterior Oropharyngeal Saliva Samples and Serum Antibody Responses During Infection by SARS-CoV-2: An Observational Cohort Study. The Lancet. Infectious Diseases 20: 565–574.

25. Taira T, Yoshimura A, Iizuka K, Iwasaki S, Ideura T, et al. (1993) Urinary Epidermal Growth Factor Levels in Patients With Acute Renal Failure. American Journal of Kidney Diseases 22: 656–661.

26. Menez S, Moledina DG, Thiessen-Philbrook H, Wilson FP, Obeid W, et al. (2022) Prognostic Significance of Urinary Biomarkers in Patients Hospitalized With COVID-19. American Journal of Kidney Diseases 79: 257–267.