Epidemiology and Health System Journal
doi:10.34172/ehsj.26071 2024 Spring;11(2):62-67 http://ehsj.skums.ac.ir

Original Article

# Association of Serum Zinc and Selenium Levels with Infection in Patients With Stroke

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**Abstract**

**Background and aims:** Patients with acute stroke are vulnerable to infectious diseases due to low consciousness, aspiration, dysphagia, and underlying conditions. Zinc and selenium play critical roles in boosting the immune system. This study aimed to compare serum zinc and selenium levels in patients with stroke before and after infection.

**Methods:** The present prospective study was conducted on patients with stroke in Hamadan, west of Iran, from 2019 to 2020. Serum levels of zinc and selenium were measured before and after infection in patients with stroke. The calculated sample size for this study was 78 patients. A paired *t*-test was used to compare the mean zinc and selenium levels. The linear regression model was used to assess the association of clinical and para-clinical factors with the change in the serum level of selenium after infection. The level of statistical significance was 0.05.

**Results:** The mean (±SD) age of participants was 71.33±14.27 years, and 55.1% of the participants were female. The mean (±SD) serum zinc levels before and after infection were 80.4±7.6 µg/dL and 74.3±7.9 µg/dL, respectively, indicating a significant difference ($P<0.001$). These values for selenium were 118.1±42.8 µg/dL and 78.4±29.4 µg/dL, respectively ($P<0.001$). There was a significant association between sepsis and decreases in the levels of selenium (-28.86 µg/dL, 95% CI: -56.13, -1.59) and zinc (-9.84 µg/dL, 95% CI: -16.12, -3.56).

**Conclusion:** Based on our results, the levels of zinc and selenium in patients with stroke significantly decrease after infection compared to before infection.

**Keywords:** Stroke, Selenium, Zinc, Infections

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**Received:** October 10, 2023
**Accepted:** May 11, 2024
**ePublished:** June 15, 2024

## Introduction

Infectious diseases such as pneumonia and urinary tract infections are among the most common complications in patients with acute stroke.[1] Patients with stroke are vulnerable to contagious diseases due to low consciousness, aspiration, dysphagia, and underlying conditions.[2] In 2019, the number of incident cases of stroke and deaths due to stroke were 12.2 and 6.5 million, respectively.

From 1990 to 2019, the number of incident cases, prevalent cases, deaths, and disability-adjusted life years (DALYs) of stroke increased by 70%, 85%, 43%, and 32%, respectively. In 2019, although the age-standardized incidence rates were similar in males and females, the standardized death rates and DALY were higher in men compared to women.[3] The incidence rate of all types of stroke in Iran in 2019 ranged from 124.3 to 141.7 per 100 000 people.[3]

Essential nutrients such as iron, zinc, copper, magnesium, fluoride, and selenium account for a small portion of the overall body weight (less than 0.01%). Their presence plays a significant role in modulating inflammation and fighting infections. The exact reason behind these effects remains uncertain, with possibilities ranging from inadequate dietary intake to disruptions in the inflammatory response system of the body controlled by cytokines.[4]

Zinc is a crucial micronutrient with different functions within the human body. It plays a pivotal role in the immune system.[5] The main effects of zinc on lymphocyte cells include T-cell activation, cell division, and antibody synthesis. Zinc deficiency causes immune dysfunction, thymus atrophy, and allergies, increasing fungal, bacterial, and viral infections.[6] Additionally, it leads to an imbalance of Th1 and Th2 and reduces the cytotoxic effect of killer T-cells.[6] Zinc is one of the main components of antioxidant enzymes, reducing the harmful effects of oxygen-free radicals.[7] Zinc is distributed

in acute phase responses in the liver and other organs, reducing zinc serum levels. This mechanism is triggered to restrict the access of microorganisms to zinc and other micronutrients.[8] The redistribution of zinc in infections might be due to the release of cytokines.[9] It is still unclear whether infection, inflammation, or sepsis lowers zinc levels in the serum or whether zinc deficiency increases vulnerability to infection or sepsis.[10]

As an essential micronutrient, selenium has antioxidant properties and enhances immunity. Selenoproteins are enzymes that have selenium at their active site.[11] Glutathione peroxidase 3 (GPx-3) is a selenium-dependent enzyme playing a role in detoxifying reactive oxidative species, preventing oxidative cellular damage. Due to antioxidant and anti-inflammatory activities, selenium is vital in treating patients, especially patients with sepsis or those admitted to intensive care units.[12] Studies show that selenium deficiency is associated with various diseases, including hypersensitivity, infection, and sepsis.[13]

Based on the results of studies, there is an association between selenium and zinc deficiency and the severity of infectious diseases,[14] and low levels of these micronutrients are common among patients with HIV.[15] In addition, low levels of zinc and selenium in patients with sepsis are related to oxidative damage and inflammation.[16] However, due to the prevalence of infectious diseases in patients with stroke, it is not well understood so far whether low micronutrient levels in the infection process existed before the onset of infection or decreased due to the acute phase of the infectious disease in patients with stroke. Therefore, this study aimed to compare the level of selenium and zinc in patients with stroke before and after infection.

## Materials and Methods

### *Type of Study*

This prospective study was conducted from 2019 to 2020 in Sina Hospital in Hamadan Province, West of Iran. It was a before-and-after study that followed patients with stroke after infection.

### *Study Population*

Patients with stroke in Sina Hospital in Hamadan province were included in this study. A neurologist confirmed the diagnosis of stroke according to the definition of the World Health Organization[17] and based on clinical and CT scan findings. The eligibility criteria for participation in the study were as follows: (1) having hemorrhagic or ischemic stroke with any signs and symptoms of infectious diseases on admission to the hospital and (2) not taking zinc and selenium supplements during the past month.

### *Sample Size*

The required sample size was calculated based on the study by Ehsanipour et al.[18] They reported that the mean serum zinc levels were 369 ± 180.1 and 428.5 ± 159.5 μg/dL in patients with pneumonia and control groups, respectively. The value for type 1 error (α) and power was considered to be 0.05 and 80%, respectively. The calculated sample size was 130 participants; however, we increased the sample size to 78 subjects because of the limited population of patients.

### *Sampling Method*

In this study, we used consecutive sampling.

### *Data Collection Method*

A researcher-made checklist was used to record patients' basic and clinical characteristics, including age, gender, history of an underlying disease, and type of stroke. Based on clinical and preclinical findings, an infectious disease specialist diagnosed infection and sepsis.

### *Laboratory Tools or Methods*

A 3-mL blood sample was taken aseptically from patients with hemorrhagic or ischemic stroke. The samples were transferred to the laboratory, and their separated sera were stored at -30 °C. Patients were monitored, and the second blood sample was taken from those with a hospital-acquired infection. Patients who were discharged from the hospital without infection and patients who died were excluded from the study. Those who provided two blood samples (before and after infection) were included in the study.

After taking the second sample and separating the sera, we measured the serum levels of zinc and selenium. For this purpose, 200 μL of sample, 200 μL water, and 200 μL of diluted 1000 μg selenium (Chem lab solution) were added into a cup. The atomic absorption was measured by a spectrophotometer under standard conditions according to the manufacturer's instructions.

Greiner kits were also used to measure serum zinc levels (with a reference range of 72.6 to 127 for males and 70 to 114 for females). Based on laboratory conditions and standard kits, serum zinc and selenium levels were classified as deficient, normal, and elevated.

### *Data Analysis*

Data were expressed using descriptive statistics such as mean and standard deviation (SD) for quantitative variables and ratio and percentage for qualitative variables. The change in the level of selenium and zinc was calculated by subtracting the level of each micronutrient after infection from its level before infection. A paired *t* test was used to compare the mean levels of zinc and selenium before and after infection. The multivariable linear regression model was used to evaluate the association of clinical and para-clinical factors with the change in the serum levels of selenium and zinc before and after infection. The backward stepwise approach was used to identify the factors associated with the change in serum levels of selenium and zinc. The significance levels for removal and addition to the model were considered to be 0.2 and 0.1, respectively. A *P* value of less than 0.05 was considered statistically significant. Stata software version

14.2 (StataCorp, TX, US) was used to analyze the data.

## Results

A total of 78 eligible patients with stroke were enrolled in the study. Participants' mean (±SD) age was 71.33±14.27 years. Based on the results, 55.1% of the patients were female. Additionally, 85.9% and 14.1% of the patients suffered from ischemic and hemorrhagic stroke, respectively. Other essential, clinical, and preclinical characteristics of participants are shown in Table 1. The mean (±SD) duration of follow-up between the first and second samplings was 4.02±5.24 days.

There was no significant relationship between the serum zinc and selenium levels of the first sample (before infection) and the gender, age, place of residence, and type of stroke. There were only six patients (7.7%) with lower zinc levels (<70 µg/dL) before infection, which increased to 24 (30.8) after infection. The serum level of selenium before infection was reported to be below 92 µg/dL in 21 (26.9%) patients, which increased to 55 (70.5%) after infection; the difference between pre- and post-infection was significant for both micronutrients.

The mean (±SD) serum zinc level before and after infection was 80.4±7.6 and 74.3±7.9, respectively. The level of serum zinc significantly decreased after infection in patients with stroke ($P<0.001$). Additionally, the mean (±SD) level of serum selenium before and after infection was determined to be 118.1±42.8 and 78.4±29.2, respectively. The mean level of selenium significantly decreased after infection in these patients ($P<0.001$) (Table 2).

Based on the results of the multivariable linear regression model, sepsis was significantly associated with a decrease in selenium level (-28.86 µg/dL) after infection ($P=0.038$). In addition, systolic blood pressure, C-reactive protein (CRP), and bedsore were significantly associated with decreased selenium levels after infection ($P=0.001$). Body temperature, diastolic blood pressure, and respiratory rate were associated with increased selenium levels after infection (Table 3).

Sepsis was significantly associated with decreased zinc level (-9.84 µg/dL) after infection ($P=0.003$). Moreover, erythrocyte sedimentation rate and creatinine were statistically associated with reduced zinc levels after infection. Pulmonary manifestations were significantly associated with an increase in zinc level (9.96 µg/dL) after infection ($P=0.010$) (Table 3).

**Table 1.** Baseline and Clinical Characteristics of Participants

| Variable | Number | Percent |
|---|---|---|
| **Categorical Variables** | | |
| Gender | | |
| Male | 35 | 44.9 |
| Female | 43 | 55.1 |
| Type of residence | | |
| Urban | 42 | 53.8 |
| Rural | 36 | 46.2 |
| Stroke | | |
| Ischemic | 67 | 85.9 |
| Hemorrhagic | 11 | 14.1 |
| Underlying diseases | | |
| Diabetes mellitus | 21 | 26.9 |
| Hypertension | 47 | 60.3 |
| COPD | 3 | 3.9 |
| Chronic renal failure | 2 | 2.6 |
| Cardiovascular disease | 18 | 23.1 |
| Diagnosis | | |
| Urinary tract infection | 32 | 41 |
| Pneumonia | 34 | 43.6 |
| Bed sore | 12 | 15.4 |
| Sepsis | 15 | 19.23 |
| **Continuous Variables** | | |
| Variable | Mean | SD |
| Age | 71.33 | 14.27 |
| Diastolic blood pressure | 79.19 | 11.50 |
| Systolic blood pressure | 125.77 | 19.84 |
| RR | 18.63 | 3.28 |
| PR | 82.04 | 9.77 |
| Temperature | 37.65 | 0.74 |
| BUN | 23.36 | 14.12 |
| Creatinine | 1.25 | 0.56 |
| Na | 139.97 | 4.67 |
| K | 4.05 | 0.52 |
| ESR | 25.23 | 17.59 |
| CRP | 6.04 | 7.10 |
| Zn before infection | 80.42 | 7.65 |
| Se before infection | 118.06 | 42.79 |

Abbreviations: COPD, chronic obstructive pulmonary disease; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RR, respiratory rate; PR, pulse rate; BUN, blood urea nitrogen

## Discussion

The results of the current study revealed that the mean levels of selenium and zinc in the blood after infection were lower compared to before the infection. Furthermore, sepsis was found to be linked with a reduction in selenium and zinc levels following infection. Various studies have presented conflicting findings regarding the connection between serum zinc and selenium levels and the likelihood of infection.[19,20] Both zinc and selenium have significant antioxidant activities, and their sufficient serum levels may be related to a reduced risk of infection.[21] On the other hand, the prevalence of infection after stroke is higher compared to other clinical conditions among patients with stroke, and its impact on morbidity and mortality is considerable.[22] In addition, infection is a risk factor for poor functional outcomes and in-hospital mortality among patients with stroke.[23] Pneumonia and urinary tract infections were reported to be linked with the

**Table 2.** Comparison of Zinc and Selenium before and after Infection in Patients with Stroke

| Variables | Before infection Mean (±SD) | After infection Mean (±SD) | Difference Mean (±SD) | *P* Value |
|---|---|---|---|---|
| Zinc | 80.42±7.65 | 74.29±7.88 | 6.12±10.36 | <0.001 |
| Selenium | 118.06±42.76 | 78.40±29.38 | 39.67±40.75 | <0.001 |

duration of hospitalization and an increase in mortality among patients with stroke.[24]

Numerous research studies have shown that patients with infectious diseases tend to have low serum levels of essential micronutrients like zinc and selenium, making them more susceptible to infections. A study found that among 124 patients with HIV, 58% were deficient in zinc, and 8% were deficient in selenium.[25] In a comparative study, the prevalence of zinc deficiency was higher in patients with postoperative sepsis than in controls, which was associated with an increase in mortality.[26] In a study conducted in Finland, out of 551 patients with acute respiratory failure, 95.8% had zinc deficiency. In addition, serum zinc levels were significantly lower in sepsis and septic shock patients than in healthy individuals.[27] Another study reported that serum zinc levels were significantly lower in children with pneumonia than in controls.[18] According to Taghavi Ardakani et al, the lower mean serum zinc level in subjects with acute watery diarrhea was significantly correlated to the length of hospital stay and diarrhea duration of more than three days ($P=0.023$ and $P=0.004$, respectively).[28] However, Eini et al reported that although serum copper and zinc levels were lower in patients with brucellosis than controls, no significant difference was observed. In addition, no significant changes were found in the serum level of these minerals at the end of treatment.[29]

The reason for the lower level of micronutrients in infectious diseases has yet to be understood. Some studies noted the phenomenon of redistribution, in which with the onset of infection and secretion of cytokines, micronutrients shift from the peripheral bloodstream to internal organs, such as muscles and liver, which reduces their serum levels.[9,30] Another reason may be the increased excretion of micronutrients in the urine or involvement in synthesizing oxidative proteins containing micronutrients.[31] It may also be due to decreased serum albumin or micronutrient transporters after the onset of infection.[30] Unlike most studies, considering serum micronutrient deficiency as a predisposing factor for the development of infection, the results of the present study highlighted decreased post-infection serum levels of micronutrients compared to those of pre-infection. The decrease is mainly affected by the inflammatory process rather than the reduction before infection.

Some studies reported a relationship between decreased serum micronutrient levels[9,30,32] and SOFA score in sepsis patients; in other words, the higher the SOFA score, the greater the micronutrient decrease. In the study by Visalakshy et al, no significant association was observed between serum zinc levels and SOFA score on admission to the hospital, but it had a direct relationship with patients' prognosis.[33]

**Table 3.** The Adjusted Association of Clinical and Para-clinical Factors with the Change of Selenium and Zinc Levels before and after Infection Using Multivariable Linear Regression

| | Variables | Coefficient | 95% CI | *P* Value |
|---|---|---|---|---|
| Selenium | Systolic blood pressure | -1.09 | (-1.73, -0.46) | 0.001 |
| | CRP | -2.42 | (-3.69, -1.15) | <0.001 |
| | Body temperature | 20.57 | (5.46, 35.67) | 0.008 |
| | Na | 1.58 | (-0.18, 3.34) | 0.078 |
| | Sepsis | -28.86 | (-56.13, -1.59) | 0.038 |
| | CRF | 54.80 | (-2.05, 111.66) | 0.059 |
| | Creatinine | -10.74 | (-25.49, 4.01) | 0.151 |
| | Diastolic blood pressure | 1.49 | (0.39, 2.58) | 0.008 |
| | RR | 5.15 | (2.37, 7.92) | <0.001 |
| | Bedsore | -35.42 | (-60.92, -9.92) | 0.007 |
| | _cons | -1073.63 | (-1638.98, -508.29) | <0.001 |
| Zinc | Na | 0.35 | (-0.12, 0.81) | 0.144 |
| | PR | 0.20 | (-0.06, 0.45) | 0.126 |
| | Sepsis | -9.84 | (-16.12, -3.56) | 0.003 |
| | Diabetes | -3.62 | (-8.69, 1.46) | 0.159 |
| | ESR | -0.15 | (-0.28, -0.01) | 0.031 |
| | CRF | -10.97 | (-24.7, 2.76) | 0.115 |
| | Pulmonary manifestations | 6.96 | (1.71, 12.21) | 0.010 |
| | BUN | 0.17 | (-0.07, 0.40) | 0.159 |
| | Creatinine | -7.05 | (-12.93, -1.17) | 0.020 |
| | Bedsore | -6.15 | (-12.76, 0.45) | 0.067 |
| | _cons | -60.67 | (-126.4, 5.06) | 0.070 |

Abbreviations: CRF, chronic renal failure; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RR, Respiratory rate; PR, Pulse rate; BUN, blood urea nitrogen

Based on our adjusted results, sepsis was significantly associated with decreased selenium and zinc levels in patients with stroke. It may justify that the infection is associated with systemic manifestations such as fever, high respiration rate, positive CRP, and higher SOFA score. The more cytokines are released in the blood, the more micronutrients are shifted from the peripheral bloodstream to vital organs; in other words, the redistribution phenomenon occurs more strongly. Two studies have reported lower serum levels of selenium in critically ill patients with multi-organ involvement versus those without multi-organ involvement.[34,35] However, consistent with the present study, the study of Negm et al revealed that although serum selenium levels were lower in patients with sepsis than those without it, no significant relationship was found.[35] Although serum level of micronutrients might be underreported in patients with infectious diseases, therapeutic interventions by micronutrient supplementations, regardless of their serum levels, have been effective in some studies, including the

study by Fischer et al[36] on the role of zinc supplement in controlling diarrhea and pneumonia and also studies by Mahalanabis et al[37] and Yuan et al[38] on the effect of zinc therapy on the duration of fever and control of infection in patients with pneumonia. The results of a meta-analysis[39] indicate that the administration of single-dose selenium may significantly reduce the length of hospital stay and mortality in critically ill patients but does not affect the length of intensive care unit stay or the 28-day mortality. In the present study, decreased serum levels of micronutrients had no association with the infection site. However, Dizdar et al[40] reported higher serum selenium levels in patients with urinary tract infections than in those with soft tissue infections.

The strength of this study was the measurement of selenium and zinc before and after infection and follow-up of patients. However, in this study, we faced some limitations. First, we did not have a comparison group, and although we followed patients after infection, all participants were patients with stroke. Another limitation of our study was the small sample size. Because of the limited population of patients with stroke in the hospital, we could not include more patients, and we had to correct the calculated sample size. The study participants were selected from one hospital in Hamadan province. This issue and the small sample size of the study may affect the generalizability of the results; therefore, the results should be interpreted with more caution.

## Conclusion

The results of our study suggest that there is a significant decrease in the serum levels of zinc and selenium after infection compared to before infection in patients. In addition, sepsis was significantly associated with a decrease in both selenium and zinc levels. However, more studies are needed to assess the change in the serum levels of zinc and selenium after infectious diseases in patients with stroke.

### Acknowledgments

This article was derived from a research project approved by the Research and Technology Deputy of the Hamadan University of Medical Sciences (approval No. 9703221523). The researchers gratefully thank the patients who participated in this study.

### Authors' Contribution

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### Competing Interests

The authors declare that there is no conflict of interests.

### Ethical Approval

The study protocol was approved by the Research Ethics Committee of the Hamadan University of Medical Sciences (IR.UMSHA.REC.1397.147), and informed consent was received from all participants.

### Funding

Hamadan University of Medical Sciences supported this work.

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