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ORIGINAL ARTICLE – OPEN ACCESS

Investigation of the Relationship Between Ischemic Stroke Disease and Serum Zinc Levels

Nevra Alkanlı[1], Arzu Ay[2], Sezgin Kehaya[3]

ABSTRACT

Objective: The purpose of this study was to investigate the relationship between the development of ischemic stroke disease and the serum zinc level.

Materials and Methods: A total of 22 ischemic stroke patients and 38 healthy controls were included in the study. Routine blood samples of both groups were centrifuged at 5000 rpm for 5 minutes and serum samples were separated from the blood. Distilled water was added to the serum samples to make a total volume of 4 mL. Vortexing was used to homogenize the total mixture and standard solutions were used to detect zinc with an atomic absorption spectrophotometer. A concentration calibration graph was created to illustrate the results.

Results: The serum zinc level was significantly higher in the patient group than in the control group ($p<0.05$). No statistically significant relationship was determined between the serum zinc level and parameters associated with ischemic stroke risk factors and patient complications ($p>0.05$). However, a strong positive significant correlation was detected between hemoglobin and hematocrit parameters ($r=0.936$; $p<0.001$), a moderately positive significant correlation between C-reactive protein and chlorine parameters ($r=0.445$; $p=0.038$), a moderately positive significant correlation between sodium and chlorine parameters ($r=0.522$; $p=0.013$), and a moderately positive significant correlation between ischemic stroke duration and potassium parameters ($r=0.483$; $p=0.023$).

Conclusion: The significant increase in the serum zinc level of ischemic stroke patients and the significant positive correlations in parameters associated with ischemic stroke risk factors and complications may indicate an effect on neuronal metabolism that contributes to the development of ischemic stroke.

Keywords: Atomic absorption spectrophotometer, ischemic stroke, neurodegenerative diseases, trace elements, zinc level

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[1]Department of Biophysics, Haliç University Faculty of Medicine, İstanbul, Turkey
[2]Department of Biophysics, Trakya University Faculty of Medicine, Edirne, Turkey
[3]Department of Neurology, Trakya University Faculty of Medicine, Edirne, Turkey

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Correspondence
Nevra Alkanlı,
Haliç University Faculty of Medicine, Department of Biophysics, İstanbul, Turkey
Phone: +90 212 924 24 44 /2114
e-mail:
nevraalkanli@halic.edu.tr

INTRODUCTION

Ischemic stroke is a neurological disease characterized by cell damage and local brain tissue fragmentation or destruction as a result of decreased cerebral blood flow. The pathogenesis of ischemic stroke is not fully known, but it is thought that environmental factors as well as genetic factors play an important role in the origin and development of ischemic stroke. Known risk factors include hypertension, hypercholesterolemia or dyslipidemia, diabetes mellitus, smoking, atherothrombosis, carotid artery stenosis, atrial fibrillation, malnutrition, oxidative stress, transient ischemic attack or ischemic stroke history, hypercoagulability, electrolyte imbalance, inflammation, cerebral edema, deep vein thrombosis, and pulmonary embolism. These factors have been associated with high mortality and morbidity in ischemic stroke (1–3).

Trace elements can protect neurons and prevent neuronal damage, and are therefore important environmental factors in the pathogenesis of ischemic stroke. They play a valuable role in improving blood flow to an ischemic area, increasing energy, and preventing hippocampal neuron necrosis. This role in maintaining the metabolism of neurons means that trace element levels are an important consideration in the diagnosis and treatment of stroke. Imbalances in the levels of trace element have been associated with an increased stroke risk (4).

Zinc is a cofactor necessary for the function of many enzymes and has an important function in synaptic transmission (5). It is a significant component of metalloenzymes in the human body; zinc plays a structural role in the ribosome and cell membrane and affects the synthesis and stabilization of protein as well as DNA and RNA. There is a notable concentration of zinc in the brain, largely found in the synaptic vesicles, which contributes to maintaining cellular functions and maturation of the brain (6). Zinc also plays an important role in cell metabolism, tissue repair, neurotransmitter production, antioxidant defense, arterial pressure regulation, and the pathogenesis of arterial hypertension (7).

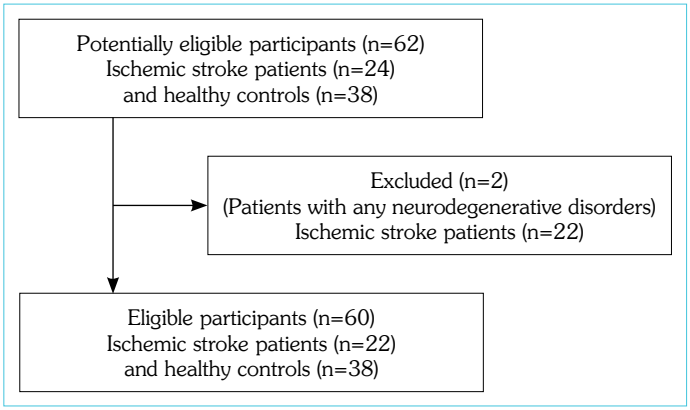

Figure 1. Flow diagram of the selection of the ischemic stroke patient group and the healthy control group

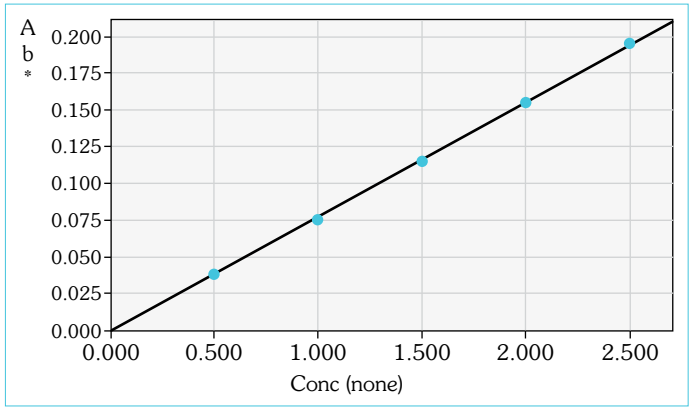

Figure 2. Concentration-calibration graph of the serum zinc level using standard solutions

The levels of trace elements, such as zinc, affect the origin and development of various neurodegenerative diseases, including ischemic stroke. Imbalance in the serum zinc level may cause neuronal damage. The development of ischemic stroke may trigger additional neuronal zinc release. Therefore, zinc homeostasis may be an important factor in the treatment of nervous system diseases (6).

Zinc can have both neurotoxic and neuroprotective effects and may be an independent risk factor for ischemic stroke. Determining the precise role of zinc and other trace elements that may impact the development of ischemic stroke could provide important information about the diagnosis, prognosis, progression, and treatment of disease (4). In addition, various hematological and biochemical parameters that may be associated with oxidative stress, hypercoagulability, electrolyte imbalance, and inflammation that have been reported to be risk factors for ischemic stroke may be associated with the prognosis of the disease (2). The purpose of this study was to investigate the role of the serum zinc level in the development of ischemic stroke disease.

MATERIALS and METHODS

Study Place and Design

This study was carried out in the Biophysics and Neurology departments of Trakya University Health Research and Application Center using peripheral venous blood serum samples. The research was approved by the Trakya University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (protocol code: TÜTF-BAEK 2018/251). All of the patients and controls provided written, informed consent.

Patients and Data Collection

The study group comprised 22 ischemic stroke patients and 38 healthy controls from the Thracian region. Serum samples were separated from blood samples collected from all of the participants. The patient group consisted of adults diagnosed with ischemic stroke based on a neurological examination, cerebral magnetic resonance imaging, computed tomography imaging, and other data. The healthy control group consisted of male and female volunteers aged ≥19 years without a cerebrovascular disease history. Patients and controls <19 years of age, those diagnosed with malignancy, and pregnant or breastfeeding women were excluded from the study. In addition, no patients with any other neurodegenerative disease related to the central nervous system were included. A flow diagram of the selection of the groups is presented in Figure 1.

Laboratory Investigations

Blood samples collected from the ischemic stroke patient and healthy control groups were centrifuged at 5000 rpm for 5 minutes and serum samples were separated from the blood. Distilled water was added to the serum samples to yield a total volume of 4 mL. The total mixture was vortexed and homogenized. Standard solutions (0.5, 1, 1.5, 2, 2.5 ppm [mg/L]) were prepared and used to assess the level of zinc with an atomic absorption spectrophotometer. A concentration-calibration graph of the results is provided in Figure 2.

Statistical Analysis

Independent sample and chi-squared testing were used to compare the clinical parameters of the ischemic stroke patient group and the healthy control group. The Mann-Whitney U test was used to examine the difference in the serum zinc level in the 2 groups, and a chi-squared test was used to compare the serum zinc level in terms of gender. Correlations between the serum zinc level and parameters associated with ischemic stroke were determined using Spearman correlation analysis. The arithmetic mean was determined if a parametric test was used to compare quantitative variables, and the median value was calculated for a nonparametric test. Results were expressed as number (percentage) or mean±SD. Statistical significance was accepted as $p<0.05$. The statistical analysis of the study data was performed using IBM SPSS Statistics for Windows, Version 20.0 software (IBM Corp., Armonk, NY, USA).

RESULTS

Our findings revealed a significant difference in the hypertension, diabetes mellitus, and cholesterol clinical parameters between the ischemic stroke patient group and the healthy control group ($p<0.05$) (Fig. 3). No significant difference was detected between the groups in the age, body mass index, gender, or smoking parameters ($p>0.05$) (Table 1). The serum zinc level was significantly higher in the patient group compared with that of the healthy control group ($p<0.05$) (Table 1) (Fig. 4). There was no significant difference between the patient and control groups in the serum zinc level based on gender ($p>0.05$) (Table 2) (Fig. 5). No statistically

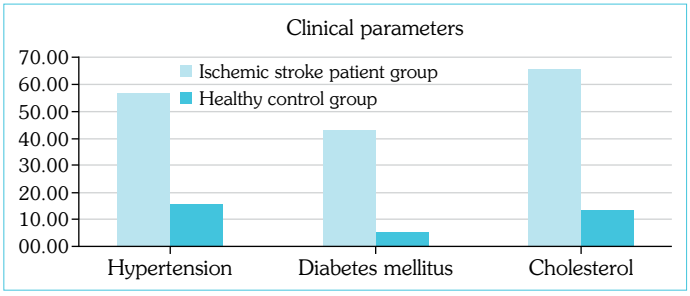

Figure 3. Comparison of the clinical parameters of the ischemic stroke patient and control groups

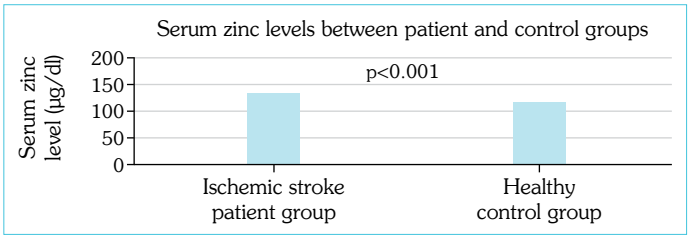

Figure 4. Comparison of the serum zinc level of the ischemic stroke patient and control groups

significant correlation was determined in a comparison of the serum zinc level and parameters associated with ischemic stroke risk factors (p>0.05) (Table 1). However, when comparing the parameters associated with the development of ischemic stroke, a strong positive correlation was determined between hemoglobin and hematocrit parameters (r=0.936; p<0.001). In addition, a moderately positive and statistically significant correlation was observed between C-reactive protein (CRP) and chlorine (r=0.445; p=0.038) as well as between the sodium and chlorine parameters (r=0.522; p=0.013). A moderately positive and statistically significant correlation was also determined between the duration of ischemic stroke and potassium in the patient group (r=0.483; p=0.023) (Table 3).

DISCUSSION

Ischemic stroke is a complex vascular and metabolic process that may lead to the death of neuronal cells and ischemic tissue. The pathogenesis of ischemic stroke disease is not yet fully understood (1–3). The presence of diabetes mellitus is 1 factor that is known to increase the chances of ischemic stroke. The increase in blood glucose is associated with hypercoagulability, altered ischemic field volume, and poor functional status (8). The results of our study revealed a significant difference between the patient and control groups in the diabetes mellitus, hypertension, and cholesterol variables (p<0.05).

Serum trace element levels are accepted as an environmental factor in the pathogenesis of ischemic stroke. Since these elements can affect body homeostasis and various biological processes, imbalances contribute to the development of neurodegenerative diseases, such as ischemic stroke (9, 10).

Zinc is an important trace element in human health and plays a significant role in various metabolic and immunological processes, including intracellular and extracellular regulatory functions. An impaired zinc homeostasis has been associated with chronic diseases and infections (11, 12). A zinc imbalance has also been linked to

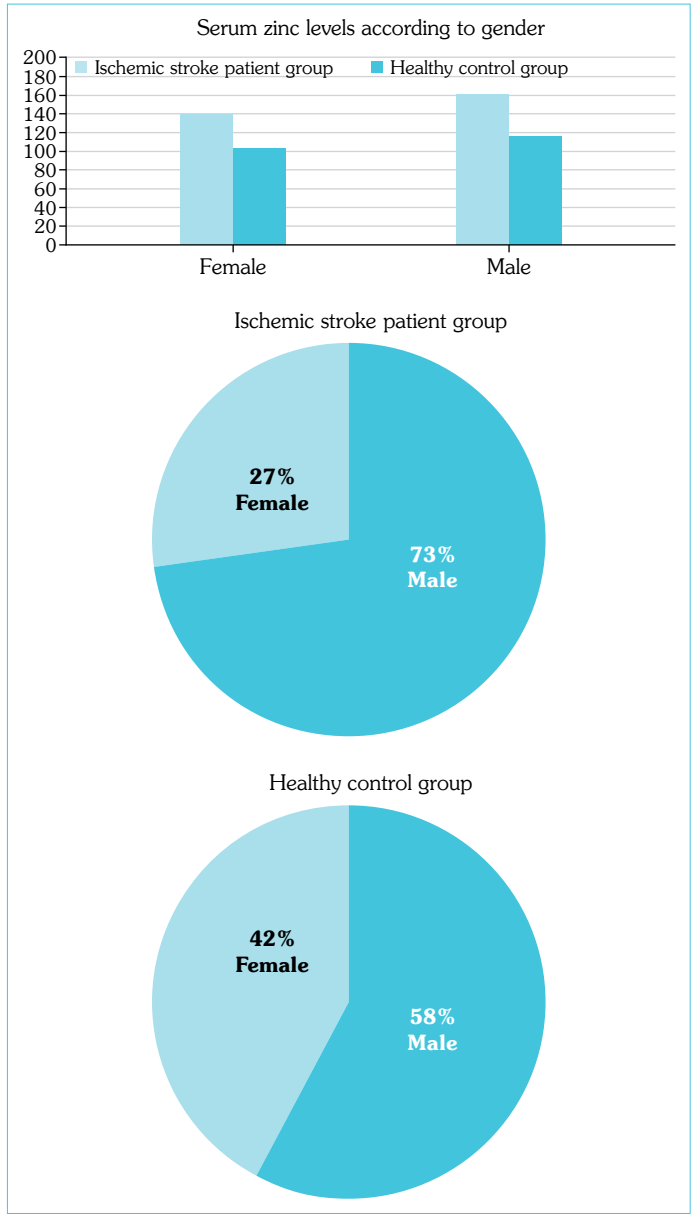

Figure 5. Comparison of the serum zinc level of the ischemic stroke patient and control groups according to gender

the development of neuronal damage (5). A low serum zinc level has been associated with development of acute cerebral infarction (4). A significant relationship was observed between zinc deficiency and cerebral infarction in a study of a Pakistani population (13).

It has been demonstrated that zinc accumulation occurs during cerebral ischemia, which can cause brain damage through neuronal apoptotic death. Therefore, zinc homeostasis is important to reducing ischemic brain damage. Appropriate zinc levels may have a neuroprotective effect, whereas excess zinc may cause cytotoxicity, neuroinflammation, cerebral dysfunction, and neuronal death. The zinc level has been associated with stroke severity and it has been proposed that zinc supplementation may reduce ischemic stroke risk. In research conducted with an Iranian study group, ischemic heart disease, elevated serum zinc levels, and hyperlipidemia were found to be related to the occurrence of stroke (4).

Table 1. The clinical findings, serum zinc level, and ischemic stroke-related parameters in the ischemic stroke patient group and the healthy control group

Clinical findings	Patient group (n=22)	Control group (n=38)	p
Serum zinc level, and ischemic stroke-related parameters			
Age (years)	62.636±15.1549	56.526±13.2558	0.108[a]
BMI (kg/m^2)	27.559±4.4631	27.519±5.0715	0.976[a]
Gender (male/female)	16 (72.7%)/6 (27.3%)	22 (57.9%)/16 (42.1%)	0.384[b]
Hypertension (+/-)	13 (59.1%)/9 (40.9%)	7 (18.4%)/31 (81.6%)	**0.003**[b*]
DM (+/-)	10 (45.5%)/12 (54.5%)	3 (7.9%)/35 (92.1%)	**0.002**[b*]
Cholesterol (+/-)	15 (68.2%)/7 (31.8%)	6 (15.8%)/32 (84.2%)	<**0.001**[b*]
Smoking (+/-)	4 (18.2%)/18 (81.8%)	11 (28.9%)/27 (71.1%)	0.536[b]
Serum Zn (µg/dL)	160.4 (124.7–471.5)	108.7 (45.2–198.2)	<**0.001**[c*]
Serum zinc level and ischemic stroke-related parameters in the ischemic stroke patient group (n=22)			
Na (mEq/L)	140.136±2.4552	-0.093	0.680[d]
K (mEq/L)	4.341±0.5333	0.105	0.641[d]
Cl (mmol/L)	104.045±2.6273	-0.227	0.309[d]
Hemoglobin (g/dL)	12.927±2.7558	-0.161	0.475[d]
Hematocrit (%)	39.241±4.7140	-0.037	0.869[d]
CRP (mg/L)	1.080±1.9391	-0.204	0.363[d]

Values presented as mean±SD or median (minimum–maximum). a: Independent sample test; b: Chi-squared test; c: Mann-Whitney U test; d: Correlation coefficient for serum zinc level (µg/dL); *: Significance (p<0.05); (+/-): Present/absent; BMI: Body Mass Index; Cl: Chlorine; CRP: C-reactive protein; DM: Diabetes mellitus; K: Potassium; Na: Sodium; Zn: Zinc

Table 2. Comparison of the serum zinc level in the ischemic stroke patient and control groups according to gender

Trace element	Groups according to gender Patient group (n=22) / Control group (n=38)		p
Serum Zn (µg/dL)	Patient male (n=16)	Control male (n=22)	1.000[a]
	Median: 174.3250	Median: 116.3700	
	Minimum: 124.75	Minimum: 45.20	
	Maximum: 471.50	Maximum: 198.20	
	Patient female (n=6)	Control female (n=16)	0.174[a]
	Median: 160.4350	Median: 101.7750	
	Minimum: 140.47	Minimum: 71.70	
	Maximum: 221.52	Maximum: 186.36	

a: Mann-Whitney U test. *: Significance (p<0.05); Zn: Zinc

In this study, there was a significant difference in the serum zinc level of the ischemic stroke patient group and the healthy control group: The patient group had a significantly higher zinc level (p<0.05).

Changes in hematological parameters can affect cerebral metabolism and blood flow, and thereby impact the course of ischemic stroke. Poor initial hemoglobin and hematocrit levels have been associated with mortality after ischemic stroke (14). Hemoglobin is an important molecule responsible for oxygen transport in the blood and therefore has great influence on outcomes in the penumbral region and neurological function (15). It was reported in a study carried out with a male Korean population that there was a statistically significant relationship between the hemoglobin level and stroke development. Unfavorable hematocrit values are an independent risk factor for ischemic stroke. Increased blood viscosity with a high hematocrit volume may lead to peripheral resistance and decreased cerebral circulation (16–18). The pathogenesis of ischemic stroke includes reduced oxygen supply to the brain tissue, and reduced hemoglobin and hematocrit levels have been associated with poor outcomes (15, 19). A Chinese study found a significant relationship between high hematocrit levels and increased incidence of stroke. In a study performed with a Japanese population, there was a significant relationship between low hematocrit levels and increased incidence of ischemic stroke (16). Another study also noted that the hemoglobin and hematocrit levels of ischemic stroke patients were significantly different from those of healthy controls (2).

Table 3. Relationship of ischemic stroke-related parameters in patient group

Parameters	Correlation (p)	Duration of IS (month)	Na	K	Cl	Hb	Hct	CRP
Na (mEq/L)	Correlation coefficient	0.046	1.000	-0.272	0.522	0.137	0.121	0.341
	Significance (p)	0.840	–	0.220	**0.013***	0.543	0.591	0.120
K (mEq/L)	Correlation coefficient	0.483	-0.272	1.000	-0.026	0.023	0.099	-0.339
	Significance (p)	**0.023***	0.220	–	0.909	0.919	0.660	0.123
Cl (mmol/L)	Correlation coefficient	0.202	0.522	-0.026	1.000	-0.124	-0.141	0.445
	Significance (p)	0.368	**0.013***	0.909	–	0.583	0.530	**0.038***
Hemoglobin (g/dL)	Correlation coefficient	0.047	0.137	0.023	-0.124	1.000	0.936	-0.147
	Significance (p)	0.835	0.543	0.919	0.583	–	<**0.001***	0.514
Hematocrit (%)	Correlation coefficient	0.021	0.121	0.099	-0.141	0.936	1.000	-0.156
	Significance (p)	0.927	0.591	0.660	0.530	<**0.001***	–	0.487
CRP (mg/L)	Correlation coefficient	-0.351	0.341	-0339	0.445	-0.147	-0.156	1.000
	Significance (p)	0.110	0.120	0.123	**0.038***	0.514	0.487	–
Duration of IS (month)	Correlation coefficient	1.000	0.046	0.483	0.202	0.047	0.021	-0.351
	Significance (p)	–	0.840	**0.023***	0.368	0.835	0.927	0.110

Spearman Correlation Analysis. IS: Ischemic stroke; Na: Sodium; K: Potassium; Cl: Chlorine; CRP: C-Reactive protein; Hb: Hemoglobin; Hct: Hematokrit; *: Significance ($p<0.05$).

In our study, no statistically significant correlation was seen between the serum zinc level and the hemoglobin parameter in patients with ischemic stroke ($r=-0.161$; $p>0.05$). In addition, there was no significant correlation detected between the serum zinc level and the hematocrit parameter ($r=-0.037$; $p>0.05$). However, a strong positive and statistically significant correlation was observed between the hemoglobin and hematocrit parameters ($r=0.936$; $p<0.001$).

The anti-inflammatory and antioxidant effects of zinc act to protect vascular cells from inflammatory damage. Therefore, a sufficient zinc level has been associated with a reduction in inflammatory and oxidative damage (20). CRP may be an influential factor in the development of ischemic stroke due to its relationship to zinc concentration level (21). CRP is an indicator of inflammation and has an effect on neuronal damage caused by the activation of the immune response and cytokines, which can be associated with the course of ischemic stroke (14). Therefore, CRP is an important inflammation marker in the immunological process that can trigger vascular remodeling (21).

It was reported in a British study that low-level inflammation detected with high-sensitivity CRP was an independent marker for cerebrovascular events, including recurrent ischemic stroke. In another meta-analysis, a high CRP level was found to be associated with the development of ischemic stroke. The CRP level, an important indicator of inflammation, may be useful to predict ischemic stroke (22).

Our findings revealed no significant correlation between the serum zinc level and the CRP parameter in patients with ischemic stroke ($r=-0.204$; $p>0.05$). However, a moderately positive and statistically significant correlation was detected between the CRP and chlorine parameters ($r=0.445$; $p<0.05$).

Electrolyte imbalance and metabolic disorder also play an important role in pathogenesis of ischemic stroke. Detection of an electrolyte imbalance caused by disturbances in sodium and potassium concentrations is an important factor in ischemic stroke evaluation and is significant to preventing mortality and morbidity. Serious complications can occur as a result of changes in electrolyte concentrations (3).

Sodium is the primary cation in the extracellular fluid and is important to the regulation of electrolyte balance and osmotic pressure. Disruptions in the water-electrolyte balance can lead to fluid change. Thus, a decrease in the blood flow to the brain occurs and blood vessels may rupture due to pressure changes. Excitotoxicity has been associated with uncontrolled cation entry to neural cells (23, 24). Zinc, sodium, and potassium affect neuronal excitability. Some of the zinc in the brain is located in the presynaptic vesicles of glutaminergic neurons. It also plays an important role in cortical communication released into the synaptic cleft after stimulation in the nerves (13).

In our study, there was no statistically significant correlation between the serum zinc level and the sodium parameter in patients with ischemic stroke ($r=-0.093$; $p>0.05$). Furthermore, no statistically significant correlation was determined between the serum zinc level and the potassium parameter ($r=0.105$; $p>0.05$). Similarly, no statistically significant correlation was seen between the serum zinc level and the chlorine parameter ($r=-0.227$; $p>0.05$). However, a moderately positive and statistically significant correlation was detected between the sodium and chlorine parameters in patients with ischemic stroke ($r=0.522$; $p<0.05$). In addition, a moderately positive and statistically significant correlation was observed between the duration of ischemic stroke and the potassium parameter of the ischemic stroke patients ($r=0.483$; $p<0.05$).

Some limitations of this study should be pointed out. First, this research was performed with a small sample. The limited statistical power of a small population may have contributed to the lack of a significant correlation between the serum zinc level and parameters

associated with ischemic stroke. The selection criteria used for the participants may also have affected the results. Larger and more comprehensive studies would help to confirm the effects of zinc and other parameters associated with the pathogenesis of ischemic stroke.

CONCLUSION

This study was conducted with a population from the Thracian region. The serum zinc level was significantly higher in the ischemic stroke patients in comparison with that of the controls, however, there was no significant correlation between the serum zinc level and parameters associated with ischemic stroke risk factors or complications seen in ischemic stroke patients. Statistically significant strong and moderately positive correlations were detected in parameters associated with ischemic stroke development in the patient group. Based on these findings, it appears that an evaluation of serum trace element levels such as zinc with parameters that may contribute to the ischemic stroke development may be important in terms of obtaining important biomarkers for ischemic stroke diagnosis, progression, and treatment.

Ethics Committee Approval: The Trakya University Non-Invasive Clinical Research Ethics Committee granted approval for this study (date: 02.07.2018, number: TÜTF-BAEK 2018/251).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – NA, AA; Design – NA, AA; Supervision – NA, AA; Resource – NA, AA; Materials – AA, SK; Data Collection and/or Processing – AA, SK; Analysis and/or Interpretation – NA, AA; Literature Search – NA, AA; Writing – NA; Critical Reviews – NA, AA.

Conflict of Interest: The authors have no conflict of interest to declare.

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