# Zinc Deficiency May Contribute to the Severity of Acute Stroke in Elderly Patients: Results of Preliminary Study and Literature Review

TWMUJ 5: 64-71, 2021

**Original**

# Zinc Deficiency May Contribute to the Severity of Acute Stroke in Elderly Patients: Results of Preliminary Study and Literature Review

**Amit Kumar, Yuichi Kubota, Mikhail Chernov,** and **Hidetoshi Kasuya**

Department of Neurosurgery, Tokyo Women's Medical University Medical Center East, Tokyo, Japan

(Accepted February 8, 2021)

(Advance Publication by J-STAGE April 2, 2021)

**Background:** Zinc (Zn) is highly important for metabolism in humans and its deficiency is associated with various diseases. The present retrospective study has assessed the serum Zn level in cases of acute stroke.

**Methods:** Study cohort included 47 patients (mean age, 73 years) with minor (N = 27), moderate (N = 13), and severe (N = 7) stroke. The National Institutes of Health Stroke Scale (NIHSS) score at admission varied from 1 to 40 (median, 3).

**Results:** Serum Zn level ranged from 23 to 102 μg/dL (mean, 68.4 μg/dL). It inversely correlated with the NIHSS score (P = 0.0340), was associated with the stroke severity (P = 0.0133), was significantly lower in patients with thrombotic stroke (P = 0.0434), and inversely correlated with the age of patient (P = 0.0220). In those aged >74 years (N = 23), but not in younger individuals, serum Zn level inversely correlated with the NIHSS score (P = 0.0155) and was associated with the stroke severity (P = 0.0117).

**Conclusions:** In patients with acute stroke the serum Zn level is frequently decreased. It is associated with the stroke severity, thrombotic type, and older age, and may contribute to more severe clinical course of the disease among the elderly.

**Keywords**: acute stroke, elderly population, serum zinc concentration, stroke severity, thrombotic stroke

## Introduction

Zinc (Zn) is an important component of metabolism in humans, and is involved in the multiple physiological processes playing multifaceted structural, catalytic, and regulatory roles, such as the formation of cellular components, the proper functioning of multiple proteins, the activation of enzymes, and the modulation of anti-oxidative, anti-inflammatory, and immune responses.[1-5] In particular, Zn is the most abundant trace metal in the central nervous system, where it takes part in the process of neurogenesis, neuronal migration and differentiation, and neurotransmission.[6,7] Zn is critically important for cell growth, proliferation, and apoptosis under both normal and pathological conditions, and its deficiency may result in the variety of diseases, including cataract, depression, gonadal hypofunction, abnormal pregnancy, ischemic heart disease, and cancer,[1,8] whereas some reports indicate that it may also contribute to the development of cerebrovascular accidents (CVA).[9-11]

The objective of the present study was assessment of the serum Zn level in patients with acute stroke and

Corresponding Author: Yuichi Kubota, Department of Neurosurgery, Tokyo Women's Medical University Medical Center East, 2-1-10 Nishiogu, Arakawa-ku, Tokyo 116-8567, Japan. kubota.yuichi@twmu.ac.jp

doi: 10.24488/twmuj.2020013

evaluation of its possible association with the symptoms severity and other relevant clinical and laboratory parameters.

## Patients and Methods

A single-center retrospective observational study was conducted in the Department of Neurosurgery, Tokyo Women's Medical University Medical Center East upon approval of the Institutional Review Board (Approval No. 5581; issued on May 1, 2020).

Patients with acute stroke admitted between November 2019 and March 2020 were considered eligible for the analysis. Cases of strokes related to brain injury, intracranial tumor, coagulation disorders, intracranial aneurysms, and arteriovenous malformations were excluded. Patients with major cardiovascular diseases, renal failure, and liver failure were also excluded, since these pathological conditions may significantly affect serum Zn level. All clinical and laboratory data were extracted from the computer-based medical records.

### Study cohort

Forty-seven patients (22 women and 25 men) were deemed eligible for the inclusion into study cohort. Their age varied from 44 to 93 years (mean, 73 ± 11; median, 74 years). The diagnosis was based on the clinical history, neurological examination, computed tomography (CT), perfusion CT, structural magnetic resonance imaging (MRI), diffusion-weighted imaging (DWI), and magnetic resonance angiography (MRA).

There were 7 cases of hemorrhagic stroke and 40 cases of ischemic stroke, including 19 thrombotic and 21 embolic. The National Institutes of Health Stroke Scale (NIHSS) score[12] at admission varied from 1 to 40 (median, 3). Minor, moderate, moderate-to-severe, and severe stroke were considered if the range of NIHSS score was, respectively 1-4, 5-15, 16-20, 21-42.[13] Medical history included chronic hypertension (32 cases; 68%), diabetes (21 case; 45%), continuing smoking (14 cases; 30%), and alcohol abuse (17 cases; 36%). At the time of admission systolic blood pressure (BP) varied from 110 to 210 mmHg (mean, 159 ± 28; median, 160 mmHg) and in 31 patients (66%) it was ≥140 mmHg. Dyslipidemia was revealed in 7 patients (15%). Glycated hemoglobin (HbA1c) level varied from 5.0 to 11.9% (mean, 6.3 ± 1.3; median, 5.8%); its prediabetic (5.7-6.4%) and diabetic (≥ 6.5%) levels were noted in 13 (28%) and 18 (38%) patients, respectively. Serum uric acid level varied from 2.8 to 9.3 mg/dL (mean, 5.4 ± 1.3; median, 5.4 mg/dL) and was increased above the upper limit of normal range (≥ 6 mg/dL) in 15 patients (32%). All blood samples were obtained within 24 hours of clinical stroke onset.

### Statistical analysis

Non-parametric statistical tests, namely, Spearman correlation (Rs), Kruskal-Wallis test, chi-square test, and Fisher exact test were used as appropriate for data analysis. Statistically significant difference was defined if two-tailed P-value was $< 0.05$.

## Results

Minor stroke was noted in 27 cases (2 hemorrhagic, 7 thrombotic, and 18 embolic), moderate in 13 (2 hemorrhagic, 8 thrombotic, and 3 embolic), and severe in 7 (3 hemorrhagic and 4 thrombotic). In the entire study cohort, serum Zn level ranged from 23 to 102 μg/dL (mean, 68.4 ± 15.3; median, 71 μg/dL). In 23 patients (49%) serum Zn level was decreased below the lower limit of normal range (70-150 μg/dL).[14]

### Serum Zn level and stroke severity

Serum Zn level demonstrated statistically significant inverse correlation with the NIHSS score ($Rs = -0.312$; $P = 0.0340$) and association with the stroke severity ($P = 0.0133$), as shown in **Figure 1** and **Table 1**. In the entire study cohort, patients with decreased Zn level below the normal range had non-significantly increased probability of moderate stroke (odds ratio [OR], 3.20; 95% confidence interval [CI]: 0.81-12.65; $P = 0.0972$) and significantly increased probability of severe stroke (OR, 12.00; 95% CI: 1.25-115.37; $P = 0.0314$).

### Serum Zn level and type of stroke

Overall, there was no statistically significant difference of the serum Zn level in cases of hemorrhagic and ischemic stroke (mean, 68.9 ± 24.9 vs. 68.3 ± 13.4 μg/dL; $P = 0.7114$). However, it was significantly lower in cases of thrombotic stroke in comparison with embolic one

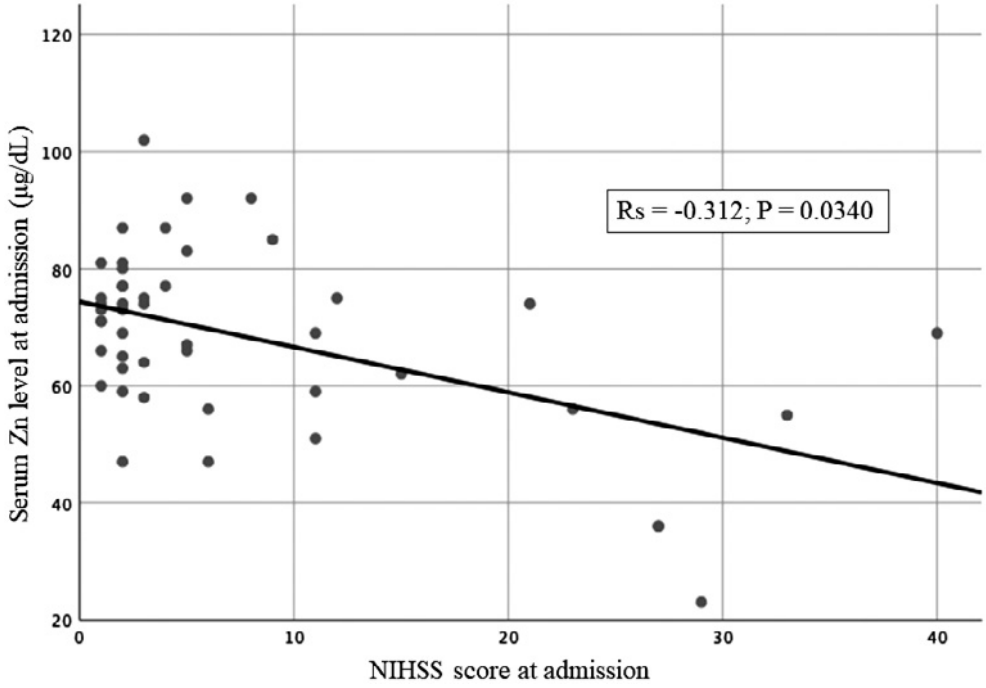


**Figure 1.** Regression line illustrating the inverse correlation between serum Zn level at admission and NIHSS score in patients with acute stroke.

**Table 1.** Association of serum Zn level at admission with the stroke severity.

| Stroke severity | Serum Zn level (µg/dL) | | | |
|---|---|---|---|---|
| | Mean ± SD | Median | Range | Decreased below the lower limit of normal range (i.e., < 70 µg/dL) |
| Mild (N = 27) | 72.6 ± 10.8 | 74 | 47 - 102 | 33% (9 cases) |
| Moderate (N = 13) | 69.5 ± 14.9 | 67 | 47 - 92 | 62% (8 cases) |
| Severe (N = 7) | 49.9 ± 18.8 | 55 | 23 - 74 | 86% (6 cases) |

According to Kruskal-Wallis test association between serum Zn level and stroke severity was statistically significant (P = 0.0133).
N, number of cases; SD, standard deviation.

(mean, 63.1 ± 14.0 vs. 73.0 ± 11.2 µg/dL; P = 0.0434). In addition, among the former subgroup the proportion of cases with decreased serum Zn level below the normal range was significantly greater (68 vs. 29%; P = 0.0117).

Serum Zn level did not demonstrate statistically significant correlation with the NIHSS score in subgroups of patients with hemorrhagic (Rs = −0.306; P = 0.4533), thrombotic (Rs = −0.380; P = 0.1074), and embolic (Rs = −0.022; P = 0.9203) stroke. Similarly, in the aforementioned subgroups there was no statistically significant association between serum Zn level and stroke severity (corresponding P-values, 0.1073, 0.1918, and 0.3657, respectively).

### Serum Zn level and age of patient

Serum Zn level demonstrated inverse correlation with the age of patient (Rs = −0.337; P = 0.0220). The age of patients with decreased serum Zn level (< 70 µg/dL) was significantly greater in comparison with those, who had it within the normal range (mean, 77.9 ± 7.5 vs. 68.9 ± 12.5 years; P = 0.0160).

Out of 23 patients aged >74 years, minor, moderate, and severe strokes were noted in 13, 6, and 4 cases, respectively. In this subgroup, the serum Zn level demonstrated statistically significant inverse correlation with the NIHSS score (Rs = −0.517; P = 0.0155) and association with the stroke severity (P = 0.0117). Out of 24 patients aged ≤74 years, minor, moderate, and severe

**Table 2.** Proportion of patients with decreased serum Zn level below the lower limit of normal range (i.e., < 70 μg/dL) with regard to type of stroke and age.

| Age group | Type of stroke | | |
|---|---|---|---|
| | Hemorrhagic | Thrombotic | Embolic |
| > 74 years (N = 23) | 100% (2 cases) | 80% (8 cases) | 45% (5 cases) |
| ≤ 74 years (N = 24) | 40% (2 cases) | 56% (5 cases) | 10% (1 case) |
| Entire cohort (N = 47) | 57% (4 cases) | 68% (13 cases) | 29% (6 cases) |

According to Fisher exact test the difference between 2 evaluated age groups was not statistically significant (P = 0.5946).
N, number of cases.

strokes were noted in 14, 7, and 3 cases, respectively. In this subgroup, the serum Zn level demonstrated neither statistically significant correlation with the NIHSS score (Rs = −0.158; P = 0.4473), nor association with the stroke severity (P = 0.3250).

There was no statistically significant difference (P = 0.5946) in the proportion of patients with decreased serum Zn level below the normal range with regard to the distribution of different types of stroke in 2 evaluated age groups (**Table 2**).

### Serum Zn level and other evaluated parameters

There was no association of serum Zn level with the patient's gender (P = 0.6171), history of chronic hypertension (P = 0.2150), diabetes (P = 0.5619), continuing smoking (P = 0.2501), alcohol abuse (P = 0.4715), as well as with systolic BP (P = 0.1499), dyslipidemia (P = 0.3628), HbA1c level (P = 0.3628), and serum uric acid level (P = 0.8259) evaluated at admission.

## Discussion

Existing data on association between Zn deficiency and cerebral ischemia are inconclusive. From one side, the comparison of blood samples in patients with ischemic stroke and age- and sex-matched healthy volunteers revealed significantly lower serum Zn levels in the former group, suggesting that it may represent an independent risk factor for the disease and possible target for its prevention.[10,11] In addition, in cases of ischemic stroke, in particular caused by the large artery atherosclerosis, some (although not all) studies revealed significantly increased serum level of copper (Cu),[11,15] which may reflect Zn deficiency even if its serum level is within normal range.[1] On the other hand, in a recent Chinese population-based large-scale epidemiological investigation of Wen et al.,[16] comparative analysis of 1,277 pairs of patients with newly diagnosed ischemic stroke and controls matched for age and sex did reveal lower Zn and higher Cu plasma concentrations in the former group, but the difference was not statistically significant (P = 0.235 and 0.615, respectively).

### Zn deficiency and stroke severity

The results of presented retrospective analysis have indicated that the serum Zn level is decreased below the lower limit of normal range (i.e., < 70 μg/dL) in 49% of patients with acute stroke. It is well corroborated with the previous report of Bhatt et al.,[9] who found that 57.6% of patients with ischemic stroke and 22% of those with transitory ischemic attack have low Zn level (≤ 65 μg/dL). Moreover, both aforementioned studies have revealed statistically significant inverse association between decreased serum Zn level and higher NIHSS score.

It is widely recognized that Zn deficiency may profoundly affect multiple interrelated physiological properties and may either predispose to, or augment the harmful effects of cerebral ischemia and subsequent reoxygenation on the neuronal tissue and brain vasculature amplifying their injury and leading to the more pronounced clinical manifestations of disease (**Figure 2**).[17] Within the brain Zn is found at the highest concentrations in the neuron-rich structures, such as hippocampus, amygdala, cerebral cortex, thalamus, and olfactory cortex.[18] In particular, it is highly concentrated in the synaptic vesicles of glutamatergic synapses, and during active neurotransmission under normal conditions is released along with glutamate into the synaptic cleft modulating both

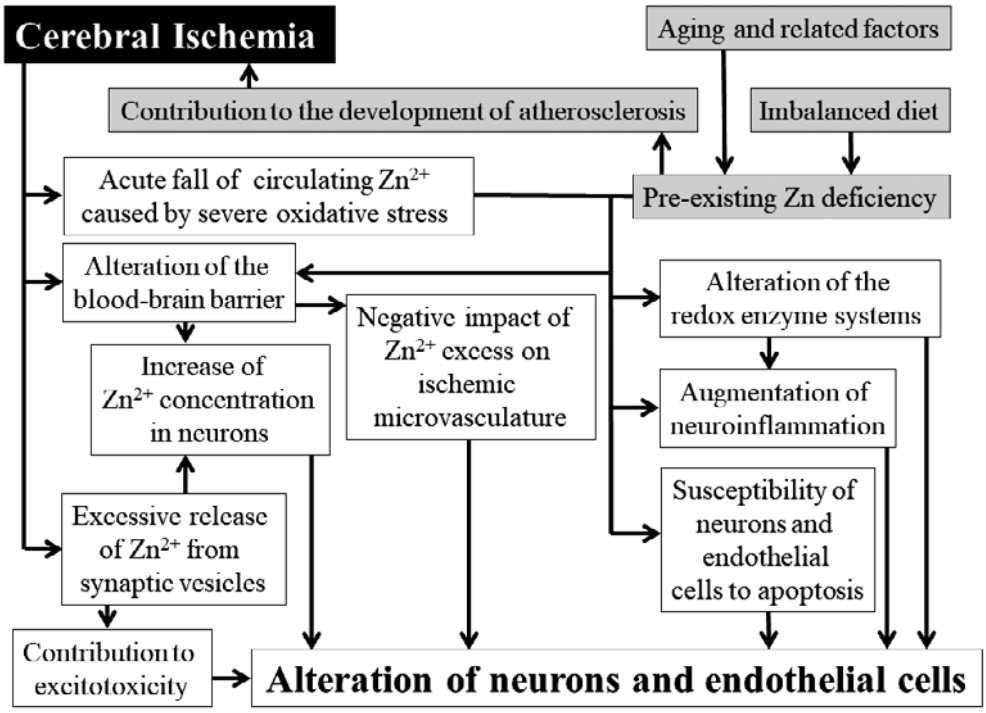


**Figure 2.** Possible involvement of Zn in the pathophysiological effects of cerebral ischemia. Factors predisposing to the development of stroke are marked by grey color.

ionotropic and metabotropic receptors, and negatively influencing post-synaptic calcium (Ca) mobilization.[18-20] Cerebral ischemia may trigger excessive release of $Zn^{2+}$ from synaptic vesicles and its subsequent translocation into vulnerable post-synaptic neurons.[21] On the other hand, Zn deficiency with its low release from the synaptic vesicles may contribute to excitotoxicity through increasing glutamate-induced intracellular $Ca^{2+}$ influx.[19-21]

Zn is playing a highly important role in the integrity and normal functioning of the blood-brain barrier (BBB), which alteration, in turn, causes Zn dyshomeostasis with increased passage from the blood resulting in the damage of the brain tissue microenvironment.[21-23] Even small changes in Zn homeostasis may disproportionally influence intracellular signaling through activation of dependent proteins.[8] It was shown, that intracellular accumulation of Zn is playing an important role in neuronal death following ischemia.[21, 22, 24] Animal experiments also demonstrated the direct negative impact of Zn on ischemic microvessels, which may be in part realized through functional modification of the metal transporters.[22, 23]

Zn is an essential and integral part of some critical redox enzyme systems, such as superoxide dismutase, metallothionein, glutathione, and catalase, which are involved in cleavage of reactive oxygen species (ROS) in response to the oxidative stress and lipid peroxidation.[5] Zn also reduces the activities of oxidative enzymes, including nitric oxide synthases (NOS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and inhibits the generation of lipid peroxidation products,[5, 8, 17] although opposite effects have been also reported.[24] All these physiological mechanisms may be affected in case of Zn deficiency.

Zn is highly important for regulation of the anti-inflammatory reaction,[5] thus crucial for the attenuation of brain inflammation, one of the main pathophysiological consequences of stroke.[25] In addition, low Zn level may reduce cell viability and increase neuronal and endothelial apoptotic cell death in response to oxidative stress through activation of the caspase-3 pathway.[8, 19, 26]

It should be noted however, that low serum Zn level in patients with severe stroke may be related not only to its pre-existing deficiency, but result from an acute fall owed to severe oxidative stress and correspondent mobilization of the circulating $Zn^{2+}$ into antioxidant defense of the affected brain tissue.[10] Such a metabolic response to acute injury has been recognized for a long time. In particular, Low and Ikram[27] revealed progressive decrease of

plasma Zn concentration during the first 3 days after myocardial infarction, which might have both diagnostic and prognostic implications, since greater fall was noted in patients with more severe clinical condition. Unfortunately, to the best of our knowledge, such dynamic studies with serial Zn concentration measurements were not performed in patients affected by CVA.

**Associations of Zn deficiency with type of stroke and age of patient**

Obviously, subgroup analysis of the presented study cohort was underpowered owed to the limited number of cases, but 2 important findings were clearly demonstrated.

First, 68% of patients with thrombotic stroke showed decreased serum Zn level below the normal range, which was significantly more frequent in comparison with the embolic stroke (29%). It may be related to the disease pathophysiology, in particular its close interrelationships with the presence of atherosclerosis. Zn exhibits a protective effect on the vascular endothelium as an anti-inflammatory agent, antioxidant, stabilizer of cell membranes, and modulator of the multiple signaling processes important to the maintenance of cell integrity.[8, 28] Zn deficiency may activate in cell-specific manner nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a key protein complex regulating transcription of DNA, gene expression, cytokine production, immune and inflammatory responses, cellular survival and apoptosis. In endothelial cells activation of NF-κB is considered as a key signaling process in the adhesion molecule gene upregulation.[8] On the other hand, development of atherosclerosis is closely related to changes in the nitric oxide production, whereas NOS expression is also dependent on NF-κB activation. Finally, Zn deficiency renders endothelial cells more susceptible to the effects of oxidative stress through activation of caspase enzymes leading to apoptosis.[8] All these factors significantly contribute to the process of atherogenesis.

Second, our study revealed statistically significant inverse correlation of the serum Zn level with the age of patient. Zn homeostasis is normally regulated over a wide range of the metal intake, but increasing age is usually associated with its deficiency.[1, 8] The Third National Health and Nutrition Examination Survey (NHANES III) of the U.S. population documented that people older than 70 years are at the greatest risk from inadequate Zn intake.[29] Beside imbalanced diet, Zn deficiency among the elderly is also influenced by some age-related factors, including intestinal malabsorption, changes of metabolism, presence of chronic diseases, and interactions with prescribed medications.[1, 30] Long-term deprivation of Zn intake or its excessive uncompensated losses renders an organism more susceptible to the injury induced by oxidative stress, including increased lipid, protein, and DNA oxidation.[31-33] In our patients aged >74 years, the serum Zn level demonstrated statistically significant inverse correlation with the NIHSS score and association with the stroke severity, which was not demonstrated in younger individuals. It suggests that effects of Zn deficiency on the clinical course of cerebral ischemia are particularly harmful among the elderly.

Of note, neither the present study, nor previous investigation of Bhatt et al.[9] revealed statistically significant associations of the serum Zn levels with the presence of established stroke risk factors, including history of chronic hypertension, diabetes, continuing smoking, and several relevant laboratory parameters (e.g., dyslipidemia), which indicate that this trace metal may be involved in the development of CVA through somewhat independent mechanisms, still largely remaining unknown.

**Possible use of Zn supplementation for treatment of stroke**

Some reports indicated that low serum Zn level in patients with ischemic stroke at admission is associated with the unfavorable functional outcomes.[9, 34, 35] It may suggest possible inclusion of Zn supplementation into the therapeutic protocols in such cases. Indeed, Zn may potentially protect the cerebral tissue through stabilization of the BBB reducing the risk of hemorrhagic transformation of ischemic stroke, brain edema, and local inflammation, which may also improve the cerebral blood flow (CBF) in ischemic region.[23] In addition, according to the current knowledge Zn may prevent neuronal injury due to downregulation of the inflammatory cytokines generation and free radical production, and stabilization of the macromolecules against radical-induced oxidation.

The results of animal experiments have been contra-

dictory and indicated both neuroprotective and neurotoxic effects of Zn administration.[21] Some studies showed that Zn chelation may increase neurotoxicity and enhance early development of infarction after temporary ischemia.[19] In particular, Zhao et al.[36] demonstrated neuroprotective effects of $Zn^{2+}$ *in vivo*. They compared pretreatment with equimolar doses of Zn protoporphyrin (antagonist of interleukin-1), Zn chloride, and protoporphyrin before temporary ischemia/reperfusion in rats. In comparison with the control, significant reduction of the infarct volume of comparable magnitude was noted in all 3 experimental groups. However, in difference with Zn protoporphyrin and protoporphyrin, Zn chloride reduced only infarct volume, but not brain edema formation, which suggests that $Zn^{2+}$ may provide neuroprotection by mechanisms other than reducing brain edema.[21, 36] Nevertheless, using the similar model Kadoya et al.[37] showed that only pretreatment with Zn protoporphyrin may reduce infarct size, brain edema formation, sodium accumulation, and potassium loss, whereas such effects are generally not observed if it is given after temporary or before permanent interruption of CBF. Moreover, Qi et al.[22] revealed that in ischemic rats Zn chelation could greatly attenuate BBB permeability as measured by Evans Blue extravasation, brain edema volume, and MRI. Zhao et al.[24] showed that synergistic interaction between Zn and ROS may amplify ischemic brain injury. In fact, as was shown by Kitamura et al.[19] variability of the Zn influence on neuronal viability under ischemic conditions may be explained by its biphasic pattern, with neuroprotective and neurotoxic effects in low and high concentrations of the metal, respectively.

In their clinical study, Aquilani et al.[38] evaluated 26 patients with subacute stroke and low Zn intake, who were randomly allocated for treatment with and without Zn supplementation (dose, 10 mg $Zn^{2+}$ per day). After 30 days of therapy, the improvement of NIHSS score was significantly higher in those who received Zn supplementation, and there was the inverse correlation between NIHSS score and $Zn^{2+}$ intake.[38] Others, however, underlined possible neurotoxic effects of Zn in cases of cerebral ischemia, which may be particularly related to its role in activation of matrix metalloproteinases, and emphasized that the metal overload may be similarly harmful for brain tissue as its deficiency.[19, 21-23, 39]

Therefore, at present it remains unclear whether and under which conditions Zn supplementation exerts its neuroprotective and neurotoxic effects in cases of CVA.

## Conclusions

According to results presented herein, serum Zn level is decreased below the lower limit of normal range in approximately half of patients with acute stroke and associated with its severity, thrombotic subtype, and older age of patients. Thus, it may be suggested that low serum Zn level may predispose individuals to thrombotic stroke and may contribute to more severe clinical course of the disease, in particular among the elderly. Further investigations should clarify these preliminary findings.

**Funding**: None. The authors do not have any personal or institutional financial interests in drugs, materials, or devices described in this paper.

**Conflicts of Interest**: None.

**Author Contributions**: Amit Kumar: Concept, Study design, Data collection, Data evaluation, Paper writing.

Yuichi Kubota: Concept, Study design, Technical support, Study supervision, Paper review and editing.

Mikhail Chernov: Data evaluation, Statistical analysis, Paper writing, review, and editing.

Hidetoshi Kasuya: Material support, Study supervision, Paper review and editing.

### References

1. Yanagisawa H. Zinc deficiency and clinical practice. JMAJ. 2004;47:359−64.
2. Tudor R, Zalewski PD, Ratnaike RN. Zinc in health and chronic disease. J Nutr Health Aging. 2005;9:45−51.
3. Overbeck S, Rink L, Haase H. Modulating the immune response by oral zinc supplementation: a single approach for multiple diseases. Arch Immunol Ther Exp (Warsz). 2008;56:15−30.
4. Zastrow ML, Pecoraro VL. Designing hydrolytic zinc metalloenzymes. Biochemistry. 2014;53:957−78.
5. Olechnowicz J, Tinkov A, Skalny A, et al. Zinc status is associated with inflammation, oxidative stress, lipid, and glucose metabolism. J Physiol Sci. 2018;68:19−31.
6. Levenson CW, Morris D. Zinc and neurogenesis: making new neurons from development to adulthood. Adv Nutr. 2011;2:96−100.
7. McCord MC, Aizenman E. The role of intracellular zinc release in aging, oxidative stress, and Alzheimer's disease. Front Aging Neurosci. 2014;6:77.
8. Beattie JH, Kwun IS. Is zinc deficiency a risk factor for atherosclerosis? Br J Nutr. 2004;91:177−81.

9. Bhatt A, Farooq MU, Enduri S, et al. Clinical significance of serum zinc levels in cerebral ischemia. Stroke Res Treat. 2010;2010:245715.
10. Munshi A, Babu S, Kaul S, et al. Depletion of serum zinc in ischemic stroke patients. Methods Find Exp Clin Pharmacol. 2010;32:433−6.
11. Gönüllü H, Karadaş S, Milanlioğlu A, et al. Levels of serum trace elements in ischemic stroke patients. J Exp Clin Med. 2013;30:301−4.
12. Lyden P. Using the National Institutes of Health Stroke Scale: a cautionary tale. Stroke. 2017;48:513−9.
13. Ver Hage A. The NIH Stroke Scale: a window into neurological status. Nursing Spectrum. 2011;24(15):44−9.
14. Smith JC Jr, Butrimovitz GP, Purdy WC. Direct measurement of zinc in plasma by atomic absorption spectroscopy. Clin Chem. 1979;25:1487−91.
15. Xiao Y, Yuan Y, Liu Y, et al. Circulating multiple metals and incident stroke in Chinese adults: the Dongfeng-Tongji cohort. Stroke. 2019;50:1661−8.
16. Wen Y, Huang S, Zhang Y, et al. Associations of multiple plasma metals with the risk of ischemic stroke: a case-control study. Environ Int. 2019;125:125−34.
17. Marreiro DDN, Cruz KJC, Morais JBS, et al. Zinc and oxidative stress: current mechanisms. Antioxidants (Basel). 2017;6(2):E24.
18. Frederickson CJ, Suh SW, Silva D, et al. Importance of zinc in the central nervous system: the zinc-containing neuron. J Nutr. 2000;130(5 Suppl):1471S−83S.
19. Kitamura Y, Iida Y, Abe J, et al. Protective effect of zinc against ischemic neuronal injury in a middle cerebral artery occlusion model. J Pharmacol Sci. 2006;100:142−8.
20. Takeda A. Involvement of zinc in neuronal death in the hippocampus. Biomed Res Trace Elements. 2007;18:204−10.
21. Galasso SL, Dyck RH. The role of zinc in cerebral ischemia. Mol Med. 2007;13:380−7.
22. Qi Z, Liang J, Pan R, et al. Zinc contributes to acute cerebral ischemia-induced blood-brain barrier disruption. Neurobiol Dis. 2016;95:12−21.
23. Qi Z, Liu KJ. The interaction of zinc and the blood-brain barrier under physiological and ischemic conditions. Toxicol Appl Pharmacol. 2019;364:114−9.
24. Zhao Y, Yan F, Yin J, et al. Synergistic interaction between zinc and reactive oxygen species amplifies ischemic brain injury in rats. Stroke. 2018;49:2200−10.
25. Saleh A, Schroeter M, Ringelstein A, et al. Iron oxide particle-enhanced MRI suggests variability of brain inflammation at early stages after ischemic stroke. Stroke. 2007;38:2733−7.
26. Adamo AM, Zago MP, Mackenzie GG, et al. The role of zinc in the modulation of neuronal proliferation and apoptosis. Neurotox Res. 2010;17:1−14.
27. Low WI, Ikram H. Plasma zinc in acute myocardial infarction: diagnostic and prognostic implications. Br Heart J. 1976;38:1339−42.
28. Bao B, Prasad AS, Beck FWJ, et al. Zinc decreases C-reactive protein, lipid peroxidation, and inflammatory cytokines in elderly subjects: a potential implication of zinc as an atheroprotective agent. Am J Clin Nutr. 2010;91:1634−41.
29. Briefel RR, Bialostosky K, Kennedy-Stephenson J, et al. Zinc intake of the U.S. population: findings from the third national health and nutrition examination survey, 1988-1994. J Nutr. 2000;130(5 Suppl):1367S−73S.
30. Mocchegiani E, Romeo J, Malavolta M, et al. Zinc: dietary intake and impact of supplementation on immune function in elderly. Age (Dordr). 2013;35:839−60.
31. Herbein G, Varin A, Fulop T. NF-κB, AP-1, zinc-deficiency and aging. Biogerontology. 2006;7:409−19.
32. Vasto S, Mocchegiani E, Candore G, et al. Inflammation, genes and zinc in ageing and age-related diseases. Biogerontology. 2006;7:315−27.
33. Kumar V, Kumar A, Singh SK, et al. Zinc deficiency and its effect on the brain: an update. Int J Mol Genet and Gene Ther. 2016;1(1). doi: 10.16966/2471-4968.105.
34. Gower-Winter SD, Levenson CW. Zinc in the central nervous system: from molecules to behavior. Biofactors. 2012;38:186−93.
35. Rautaray SS, Sarkar PD. To study serum zinc levels in ischemic stroke patients. J Transl Sci. 2017;3(2):1−2. doi: 10.15761/JTS.1000178.
36. Zhao YJ, Yang GY, Domino EF. Zinc protoporphyrin, zinc ion, and protoporphyrin reduce focal cerebral ischemia. Stroke. 1996;27:2299−303.
37. Kadoya C, Domino EF, Yang GY, et al. Preischemic but not postischemic zinc protoporphyrin treatment reduces infarct size and edema accumulation after temporary focal cerebral ischemia in rats. Stroke. 1995;26:1035−8.
38. Aquilani R, Baiardi P, Scocchi M, et al. Normalization of zinc intake enhances neurological retrieval of patients suffering from ischemic strokes. Nutr Neurosci. 2009;12:219−25.
39. Tomas-Sanchez C, Blanco-Alvarez VM, Gonzalez-Barrios JA, et al. Prophylactic chronic zinc administration increases neuroinflammation in a hypoxia-ischemia model. J Immunol Res. 2016;2016:4039837.