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Research

The Effect of Serum Uric Acid Level on Stroke Severity

Serum Ürik Asit Düzeyinin İnme Şiddetine Etkisi

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ABSTRACT

Objective: Stroke remains a leading cause of disability and mortality globally, affecting millions annually. Recognizing and managing stroke risk factors is essential for reducing its prevalence and improving patient outcomes. Among the various risk factors, uric acid (UA) has garnered attention for its potential role in stroke pathophysiology. This study investigates the effect of serum UA level on stroke severity, aiming to enhance understanding and management of stroke.

Methods: A retrospective analysis was performed involving 110 patients diagnosed with acute ischemic stroke (Group 1) and 83 individuals in the healthy control group (Group 2) between August 2016 and August 2017. The average serum UA level was measured in two different groups and was analyzed together with other contributors to stroke risk. Stroke severity was evaluated in relation to serum UA levels, utilizing the National Institutes of Health Stroke Scale (NIHSS).

Results: In group 1, the average serum UA level was 5.5 mg/dL, while in Group 2, it was 4.8 mg/dL, with a statistically significant difference identified between the groups ($p<0.001$). A serum UA threshold of 5.6 mg/dL was determined ($p<0.001$), and exceeding this threshold alone was recognized as a predisposing factor for ischemic stroke, irrespective of other possible risk factors (odds ratio: 3.107; 95% confidence interval: 1.424, 6.781; $p=0.004$). There was no significant correlation between serum UA levels and NIHSS scores ($p=0.527$)

Conclusion: The findings of this study indicate that while elevated UA levels might contribute to the development of ischemic stroke, their influence on stroke severity remains uncertain. Further research is necessary to determine whether therapeutic lowering of serum UA could improve stroke outcomes.

Keywords: Ischemic stroke, uric acid, NIHSS score, stroke severity

ÖZ

Amaç: İnme, dünya çapında milyonlarca insanı etkileyen, engellilik ve ölüm oranlarında önde gelen bir neden olmaya devam etmektedir. İnme risk faktörlerinin tanınması ve yönetilmesi, inme prevalansını azaltmak ve hasta sonuçlarını iyileştirmek için esastır. Çeşitli risk faktörleri arasında ürik asit (ÜA), inme patofizyolojisindeki potansiyel rolü nedeniyle dikkat çekmiştir. Bu çalışma, serum ÜA düzeyinin inme şiddeti üzerindeki etkisini araştırarak inmenin anlaşılmasını ve yönetimini geliştirmeyi amaçlamaktadır.

Gereç ve Yöntem: Retrospektif olarak, Ağustos 2016 ve Ağustos 2017 tarihleri arasındaki 110 akut iskemik inme hastası (Grup 1) ve 83 sağlıklı kontrol (Grup 2) üzerinde değerlendirme yapıldı. İki farklı grupta ortalama serum ÜA düzeyi ölçüldü ve inme için diğer risk faktörleriyle birlikte analiz edildi. Serum ÜA düzeylerinin inme şiddetine etkisi Ulusal Sağlık Enstitüleri İnme Ölçeği (USEİÖ) skoru üzerinden değerlendirildi.

Bulgular: Grup 1'de ortalama serum ÜA seviyesi 5,5 mg/dL iken Grup 2'de 4,8 mg/dL idi ve gruplar arasında istatistiksel olarak anlamlı fark bulundu ($p<0,0019$). Serum ÜA için eşik değer 5,6 mg/dL olarak belirlendi ($p<0,001$) ve bu eşiğin aşılması tek başına, diğer potansiyel risk faktörlerinden bağımsız olarak iskemik inme gelişimi için bir risk faktörü olarak kabul edildi (olasılık oranı: 3,107; %95 güven aralığı: 1,424, 6,781; $p=0,004$). Serum ÜA düzeyleri ile USEİÖ skoru arasında herhangi bir korelasyon gözlenmedi ($p=0,527$).

Sonuç: Bu çalışma, yüksek ÜA seviyelerinin iskemik inme riskinin artmasıyla ilişkili olduğunu, ancak inme şiddetini tahmin etmede rollerinin belirsiz olduğunu göstermektedir. Serum ÜA seviyelerinin terapötik olarak düşürülmesinin inme sonuçlarını iyileştirip iyileştiremeyeceğini belirlemek için daha fazla araştırma gereklidir.

Anahtar Kelimeler: İskemik inme, ürik asit, USEİÖ skoru, inme şiddeti

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INTRODUCTION

Stroke is a significant medical condition that impacts public health worldwide, ranking as one of the top causes of disability and mortality, affecting millions of people each year (1). In such an important public health issue, identifying and managing stroke risk factors is crucial to reduce the prevalence and severity of stroke. Along with non-modifiable risk factors such as age and gender, there are numerous modifiable contributors to stroke such as hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), and abdominal obesity (2,3). The presence of many modifiable risk factors makes stroke a largely preventable neurological disease. Ongoing research is investigating emerging areas of stroke risk factors, focusing on identifying biomarkers that can predict stroke severity to improve patient outcomes.

Uric acid (UA) results from the metabolic breakdown of purines which originate from internal metabolic processes and dietary intake. Typically, UA dissolves in the blood and is excreted via the kidneys in urine (4). However, when UA levels surpass the blood's solubility threshold, urate crystals can form, leading to hyperuricemia. Hyperuricemia is primarily caused by increased production or reduced excretion of UA. Increased production can be caused by a purine-rich diet (e.g., red meat, seafood, and alcohol), increased cell turnover (e.g., cancers and chemotherapy) or genetic factors. The more common cause, reduced excretion, is usually due to renal dysfunction or certain medications such as diuretics that reduce the kidneys' ability to excrete UA.

Under physiological conditions, UA has antioxidant properties that can minimize oxidative stress by reducing the number of free radicals, thus protecting cells from damage (5). However, endogenous high serum UA levels traditionally lead to health problems such as gout and kidney stones (6). In more recent approaches, it is assumed that there is a connection between the serum UA level and vascular risk factors such as HT, DM, and coronary heart disease (CHD) (7,8). In this emerging approach, the next step requires a comprehensive investigation of the relationship between UA and stroke.

The interest in UA's role in stroke has been growing, with research exploring its potential as a biomarker for stroke risk and prognosis. Some studies indicate that high UA levels correlate with an increased risk of stroke and worse post-stroke outcomes (9-11). In contrast, others suggest that UA may have neuroprotective effects due to its antioxidant properties (12,13). Understanding the dual role of UA in the pathophysiology of ischemic cerebrovascular events is crucial for developing targeted therapies, enhancing preventive strategies, and ultimately improving clinical outcomes for patients. The purpose of this study is to investigate the influence of serum UA concentration on the severity of clinical outcomes in patients diagnosed with acute ischemic stroke.

METHODS

Study Design

A retrospective evaluation was carried out on 110 ischemic stroke patients (69 males and 41 females) who presented with acute stroke symptoms between August 2016 and August 2017 at the stroke clinic of our hospital (Group 1). The demographic data, clinical information, neuroimaging, and blood results of the subjects were obtained from our hospital's medical records. Patients were diagnosed with ischemic stroke based on neurological examination, computed tomography scans, and diffusion-weighted magnetic resonance imaging. Based on neurological examinations conducted upon patient admission, National Institutes of Health Stroke Scale (NIHSS) scores were calculated (14). The control group included 83 subjects who had no chronic neurological disease and were comparable to the patient group in both age and sex. Following their presentation to the neurology clinic with headaches, their clinical exams and neuroimaging results were normal (Group 2).

Predisposing factors for stroke were assessed in both the patient and control groups. HT was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or receiving antihypertensive medications (15). DM was specified as a fasting serum glucose level ≥126 mg/dL or the use of anti-diabetic therapy (16). HL was diagnosed by fasting serum total cholesterol ≥240 mg/dL, low-density lipoprotein cholesterol ≥130 mg/dL, triglycerides ≥200 mg/dL, and/or receiving lipid-lowering medication (17). Atrial fibrillation (AF) was diagnosed using a standard 12-lead electrocardiogram. Additional relevant factors such as CHD, valvular heart disease, history of recurrent stroke, and smoking (at least five tobacco products per day) must be considered. Total number of vascular risk factors was recorded for each group. Blood samples were taken from peripheral veins after overnight fasting within 24 hours of hospitalization. Serum UA levels exceeding local laboratory reference values of 7 mg/dL in men and 5.7 mg/dL in women were considered hyperuricemia.

Exclusion criteria included conditions that could impair UA production or excretion, such as active infections, cancer, gastrointestinal disease, renal or hepatic insufficiency, chronic alcoholism, and the use of medications such as

immunosuppressants and chemotherapeutic agents. In accordance with the ethical principles of the Declaration of Helsinki, all participants gave written informed consent before the study. The study was approved by the University of Health Sciences Türkiye, Bakırköy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital Clinical Research Ethics Committee (approval no: 569, date: 06.09.2016).

Statistical Analysis

Continuous quantitative variables are presented as means and standard deviations (SDs), while categorical variables are shown as counts (n) and percentages (%). The Shapiro-Wilk test was employed to assess the normality of the data distribution. The independent samples t-test and the Mann-Whitney U test were used to compare two independent groups based on quantitative data. The correlation between variables was evaluated using Spearman's rho test. Categorical variables were compared using Pearson chi-square or Fisher's exact tests where appropriate. Odds ratio (OR) and 95% confidence interval (CI) were calculated. The logistic backward regression method was used to investigate the cause-effect relationships. Receiver operating characteristic analysis was performed to evaluate the relationship between the two conditions. A p-value of <0.05 was considered indicative of statistical significance. All statistical analyses were conducted using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 14 (MedCalc Software, Ostend, Belgium).

RESULTS

In Group 1 (n=110), 37.3% (n=69) of the patients were female, with a mean age of 63.30 (SD=14.21) years. Similarly, in Group 2 (n=83), 37.3% (n=52) were female, and the mean age was 61.87 (SD=11.75) years (Table 1). In terms of comorbidities, HT (p<0.001), HL (p=0.007), AF (p<0.001), and CHD (p=0.047) were statistically significant in Group 1, higher than in Group 2 (Table 1).

Hyperuricemia was present in 29.09% of Group 1 and 12.04% of Group 2 (Table 1). The mean serum UA levels for each group were 5.5 mg/dL in Group 1 and 4.8 mg/dL in Group 2, with Group 1 exhibiting significantly higher levels (p<0.0019) (Table 1). The UA threshold of 5.6 mg/dL was identified with an OR of 3.74, sensitivity of 49%, and specificity of 79% (p<0.001) (Table 2 and Figure 1). Multiple logistic regression analysis (95% CI) showed that HL (OR: 4.079, 95% CI: 1.806, 9.214; p=0.001), AF (OR: 12.140, 95% CI: 3.710, 39.725; p<0.001), and serum UA levels exceeding 5.6 mg/dL (OR: 3.107, 95% CI: 1.424, 6.781; p=0.004) were significantly associated with an increased risk of ischemic stroke (Table 3).

Table 1. Demographic characteristics and risk factors for stroke of each group

	Group 1 (n=110), n (%)	Group 2 (n=83), n (%)	p-value
Age (y) (mean±SD)	63.30±14.21/25-95	61.87±11.75/30-78	0.312*
Gender (female/male) (n, %)	41/69 37.3%	31/52 37.3%	1**
Hypertension	57 (51.8)	19 (22.9)	**<0.001** **3.6 (1.9-6.8)****
Diabetes mellitus	40 (36.4)	23 (27.7)	0.219**
Hyperlipidemia	49 (44.5)	21 (25.3)	**0.007** **2.4 (1.3-4.4)****
Atrial fibrillation	31 (28.2)	4 (4.8)	**<0.001** **7.6 (2.6-22.9)****
Coronary heart disease	23 (20.9)	8 (9.6)	**0.047** **2.5 (1.05-5.9)****
Valvular heart disease	1 (0.9)	0 (0.0)	1**
Smoking tobacco	9 (8.2)	0 (0.0)	**0.011** 15.6 (0.9-272.5)***
History of recurrent stroke	5 (4.5)	0 (0.0)	0.071
	Median (min.- max.)	**Median (min.- max.)**	
Total number of vascular risk factors	2 (0-6)	1 (0-3)	**<0.001***
Hyperuricemia	10 (12.04)	32 (29.09)	-
Serum UA level (mg/dL)	5.5 (2.8-11)	4.8 (2.3-9.4)	**<0.001***

*: Mann-Whitney U test, **: Chi-square test (or Fisher's exact test), ***: Odds ratio with 95% confidence interval, SD: Standard deviation, min.: Minimum, max.: Maximum, UA: Uric acid

Table 2. Thresholds and diagnostic accuracy for uric acid levels in stroke: sensitivity, specificity, and predictive values

			Patient			Control				
	Cut-off	n	PPV (%)	Sensitivity (%)	n	NPV (%)	Spesivity (%)	AUC±Se	OR (95% CI)	p-value
Serum UA level (mg/dL)	≤5.6	56	45.9%	50.9%	66	54.1%	79.5%	0.637±0.039	3.01 (1.64-5.55)*	0.001*
	>5.6	54	76.1%	49.1%	17	23.9%	20.5%	0.662±0.038	3.74 (1.954-7.2)*	<0.001*

*: ROC analysis, AUC: Area under the curve, Se: Standard error, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, UA: uric acid, ROC: Receiver operating curve, OR: Odds ratio

Table 3. Independent risk factors for ischemic stroke determined by regression analysis

	B	SD	p-value	OR (95% CI) (min.-max.)
HL	1.406	0.416	0.001	4.079 (1.806-9.214)
AF	2.497	0.605	<0.001	12.140 (3.710-39.725)
Serum UA level (>5.6 mg/dL)	1.134	0.398	0.004	3.107 (1.424-6.781)
Constant	-2.397	0.440	<0.001	0.091

HL: Hyperlipidema, AF: Atrial fibrillation, UA: Uric acid, OR: Odds ratio, CI: Confidence interval, SD: Standard deviation, min.: Minimum, max.: Maximum

Correlation analysis revealed a relationship between serum UA levels and the total number of vascular risk factors (p=0.001) (Table 4). A correlation was also found between serum UA levels and increasing age (p=0.002) (Table 4). Similarly, a correlation was found between age and the total number of vascular risk factors (p=0.005) (Table 4). No correlation was found between serum UA levels and the NIHSS scores in terms of the severity of the stroke (p=0.527) (Table 4).

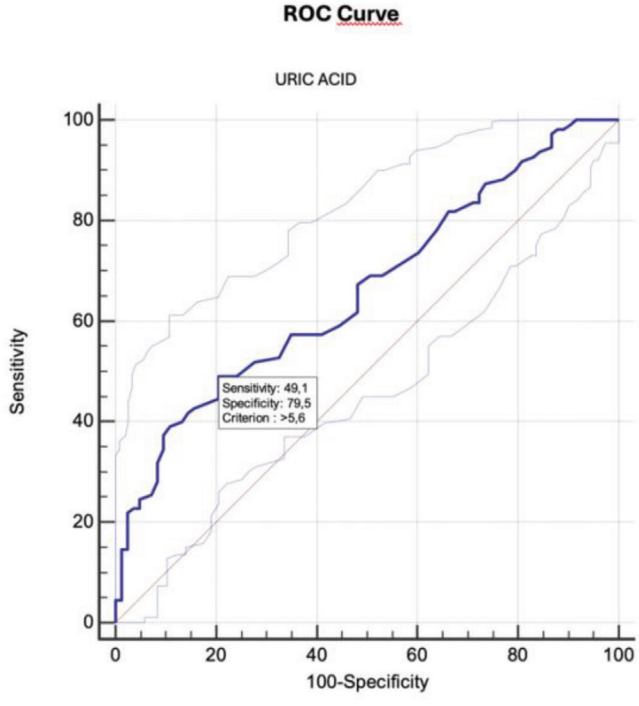

Figure 1. ROC analysis for diagnostic performance of serum uric acid levels in determining the risk of ischemic stroke

ROC: Receiver operating curve

DISCUSSION

Among the numerous biomarkers studied for their potential role in stroke, UA has garnered interest due to its dual roles as an antioxidant and a pro-oxidant. It is not yet clear whether it plays a protective role in cerebrovascular events or whether it is among the risk factors. Extensive research conducted in animal models has shown that administering UA reduces infarct size and improves neurological outcomes, supporting the idea that serum UA may serve a protective function in acute ischemic stroke (18). Clinical trials further support these findings, showing that high-dose external UA application, in addition to alteplase treatment, prevents clinical deterioration in acute ischemic stroke, as measured by the NIHSS, confirming this protective effect (19).

On the other hand, it is known that an endogenous increase in serum UA level is consistently associated with various diseases, such as HT, DM, and cardiovascular diseases (6-8). In vitro studies have also shown that hyperuricemia causes endothelial damage, thus, leading to thrombus formation, suggesting a pro-oxidant effect (20-22). This suggests that UA could be involved in the pathogenic mechanisms of stroke. These contradictory results suggest that one should be cautious before considering UA as benign in ischemic stroke.

Our study showed that serum UA concentration was significantly higher in patients with acute ischemic stroke compared with individuals without a history of stroke, suggesting that UA is a contributor to ischemic cerebrovascular events. When evaluating a novel risk factor, reported measurements need to be adjusted for known confounding factors. Although patients with acute stroke also have many vascular risk factors, our results showed that

Table 4. Correlation between serum uric acid levels, vascular risk factors, age and NIHSS scores

		p-value	p-value
Serum UA level	**Total number of vascular risk factor**	0.227	**0.001***
	Age	0.218	**0.002***
	NIH	0.061	0.527*
Total number of vascular risk factor	**Age**	0.202	**0.005***

*: Spearman's ρ test, UA: Uric acid, NIH: National Institutes of Health

high UA levels contribute to stroke susceptibility even after adjusting for these variables. This may lead us to conclude that UA plays a direct role in the pathophysiology of stroke in addition to the traditional vascular risk factors. Several meta-analyses have confirmed our findings and shown a consistent association between high UA levels and an increased incidence of ischemic cerebrovascular disease. Zhong et al. (23) demonstrated that hyperuricaemia is a predisposing factor for stroke in both sexes, focusing. Similarly, another meta-analysis showed that hyperuricemia may increase the incidence of stroke as well as the risk of mortality (24). Furthermore, research has shown that hyperuricemia not only contributes to the development of ischemic stroke, but also plays an important role in increasing the likelihood of recurrent stroke (25). This suggests that elevated UA levels may be a critical factor in both the occurrence and recurrence of cerebrovascular events.

On the other hand, there are some global epidemiologic studies suggesting that UA may not be a definitive risk factor for ischemic cerebrovascular events. In a prospective study of a large population of patients with HT but no previous stroke, hyperuricemia was not found to be a cause of ischemic cerebrovascular disease (26). Another result that has been suggested is that hyperuricemia is not associated with ischemic stroke, but it can lead to hemorrhagic stroke (27). Contradictory results in relation to hyperuricemia and cerebrovascular disease suggest that new perspectives are needed. A recent study has offered an innovative approach by highlighting the timing of UA accumulation (28). This suggests that early serum UA accumulation may lead to a higher risk of stroke compared to later accumulation, and emphasizes the need for optimal early control of serum UA levels.

The effect of UA levels on the severity of stroke is another question that needs to be clarified. Several studies suggest that higher serum UA levels are associated with more severe ischemic strokes, as determined by the scores on the NIHSS. For instance, high serum UA levels have been associated with poorer long-term functional outcomes and higher mortality rates post-stroke (29,30). This could be due to the pro-oxidant effects of serum UA under certain physiological conditions, which exacerbate neuronal injury. However, some studies do not confirm this correlation (31,32). Some studies even suggest that high baseline serum UA levels may be a biomarker for improved outcomes in patients with acute ischemic stroke (33,34). Our study indicated that there is no association between serum UA levels and the severity of stroke during the acute phase.

When discussing the effects of elevated serum UA levels, it is important to consider the factors that may influence these levels. It has been shown in the literature that vascular risk factors for stroke, such as age, HT, DM, and HL, contribute to higher serum UA levels due to impaired renal function (35). This complicates the cause-effect relationship between stroke, vascular risk factors, and serum UA levels. Our results further highlight this complexity. Consistent with the literature, we observed a corresponding increase in the number of vascular risk factors as serum UA levels increased. Furthermore, in our study, both serum UA levels and the number of vascular risk factors increased with age. This suggests that the relationship between UA and stroke risk is anything but straightforward; instead, it is shaped by age and the accumulation of vascular risks over time. These findings emphasise the importance of considering the broader clinical context when interpreting UA levels in relation to stroke risk.

In recent years, an increasing number of epidemiological and experimental studies have shown that UA can trigger pathological processes even at physiological limits, at which it is still soluble. Virdis et al. (36) showed that serum UA levels increase all-cause mortality at a cut-off value of 4.7 mg/dL, which is well below the standard thresholds used in clinical practice to define hyperuricaemia. Desideri et al. (37) even suggested redefining the "optimal health range" for UA levels as <6 mg/dL for both genders. At the outset of the study, we stratified UA levels based on gender-specific thresholds to account for the well-established physiological differences in UA metabolism between sexes. This approach ensured that we accurately captured the prevalence of hyperuricemia in both male and female populations according to their respective normal ranges. However, as

the study progressed and we analyzed serum UA levels as an independent risk factor for stroke, our findings indicated that the threshold value associated with an increased risk of stroke was consistently above 5.6 mg/dL, regardless of sex. By specifying a uniform threshold value of 5.6 mg/dL for both genders, we aimed to emphasize an important clinical finding: above this value, the risk of stroke increases regardless of the patient's gender. This finding could simplify clinical assessments and interventions aimed at stroke prevention, providing a more straightforward and universally applicable threshold.

Study Limitations

A limitation of our study is that it is retrospective and the number of patients is relatively small. Another limitation of the study is that although the groups were matched in terms of age and gender, there were some differences in vascular risk factors. We acknowledge that a study design with matched controls free of vascular risk factors might provide further insight into the independent role of UA. However, we believe that the current analysis offers valuable insights into the relationship between UA and stroke in a more clinically representative population. Given the ongoing debate in the literature regarding the role of UA in stroke, further studies are needed to provide greater clarity on this issue.

CONCLUSION

Understanding the effect of serum UA levels on stroke severity has significant clinical implications. Monitoring serum UA levels in acute stroke patients could aid risk stratification and individualized treatment planning. However, given the conflicting data, clinicians should interpret serum UA levels cautiously, considering the broader clinical context and comorbidities. Further research is needed to clarify whether lowering serum UA levels therapeutically could mitigate stroke severity or improve outcomes.

ETHICS

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Bakırköy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital Clinical Research Ethics Committee (approval no: 569, date: 06.09.2016).

Informed Consent: All participants gave written informed consent before the study.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: N.K.T., Concept: N.K.T., A.K., Design: H.K., A.K., Data Collection or Processing: N.K.T., Analysis or Interpretation: N.K.T., H.K., Literature Search: N.K.T., Writing: N.K.T., A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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