Does serum uric acid act as protector in patients with acute ischemic stroke and hyperglycemia? A clinical based evidence

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Abstract

Introduction and objectives: To explore if the clinical neurological damage that hyperglycemia could produce may be attenuated by elevated levels of serum uric acid (SUA). **Methods:** Prospective registry that included patients with acute ischemic stroke admitted within 24 h after the event. We divided them into three groups according to their levels of fasting blood glucose (FBG) (FBG < 140 mg/dL, FBG 140-180 mg/dL, and FBG ≥ 180 mg/dL) and subdivided them according to SUA levels (> 6 mg/dL in women and > 7 mg/dL in men). We assessed the worsening of both neurological (based on National Institute of Health Stroke Scale [NIHSS]) and functional damage based on Rankin scale. **Results:** We analyzed 504 patients (53.9% men). Type 2 diabetes mellitus was present in 163 (32.4%) patients and hyperuricemia in 118 (23.4%). The persons belonging to the FBG groups were increasing their neurological (NIHSS) and functional (Rankin) punctuation when their glucose levels raised ($p = 0.07$). Overall, the groups with hyperuricemia had lower but not significant scores in stroke severity (NIHSS) comparing to the groups without hyperuricemia ($p = 0.1$). In the logistic regression model, the odds ratio to have a NIHSS score higher than 16 increased as glucose levels were higher and again decreased in the groups with hyperuricemia without reach statistical significance. **Conclusion:** In patients with acute ischemic stroke with hyperglycemia, we found a non-significant tendency between SUA and lower clinical neurological damage. Further studies with larger samples and prospective follow-up are needed to confirm this potential protective role.

Key words: Uric acid. Hyperglycemia. Ischemic stroke. Cerebrovascular diseases.

Introduction

Stroke is a major cause of death and disability around the world. Hyperglycemia in hospitalized patients with and without a history of diabetes mellitus (DM) is reported in up to 40% of critically ill patients and 32% of general medicine and surgery patients¹. In the case of

patients with acute stroke, hyperglycemia is accounted for at least 50% in each subtype, including lacunar strokes². It has been also reported that the presence of hyperglycemia is associated with a worse functional outcome in these patients³. Several mechanisms have been postulated for these observations. Among them, it is well known that the blood-brain barrier is

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vulnerable to hyperglycemia, presumably through the liberation of lactic acid and free radicals that could otherwise promote more ischemic injury by intensifying lipid peroxidation and in a vicious circle more free radical formation⁴. In this setting, high serum uric acid (SUA) levels have shown to be beneficial to improve the prognosis of patients with acute ischemic stroke⁵, related with its ability to scavenge oxygen radicals, being the central nervous system one of the best sites where uric acid exerts this antioxidant effects⁶.

The aim of the study is to explore if the clinical neurological damage that hyperglycemia could produce may be attenuated by elevated levels of SUA. We hypothesize that the antioxidant effect of uric acid in acute ischemic stroke should weaken the deleterious effect in the brain that increasing glycemia has.

Methods

Patients were enrolled through a stroke registry supported by Zafra County hospital that included consecutive ischemic stroke patients admitted within 24 h after the event and followed up for 1 year. The enrollment began the 1st January 2005-31st January 2012. Patients had to sign out the consent to participate in the registry under an ethics committee-approved protocol. Previous reports from this registry were published formerly^{7,8}.

The confirmation of stroke was based on the clinical evaluation and computed tomographic scan or magnetic resonance imaging scan of the brain carried out within 24 h of the event. The subtypes of stroke were grouped according to the TOAST classification⁹. We excluded patients with intracerebral hemorrhage, subarachnoid hemorrhage, cerebral venous sinus thrombosis, and late admission (> 24 h after stroke onset). All patients were treated with either antiaggregant or anticoagulant drugs, depending on the etiology, and with antihypertensive agents. Thrombolysis was not performed in any case.

Data collection

Upon admission, a comprehensive medical history and detailed physical examination were performed. The National Institute of Health stroke scale (NIHSS)¹⁰, Charlson co-morbidity index (CCI)¹¹, and Rankin score¹² assessed stroke severity, co-morbidity, and disability. Hypertension was defined as blood pressure $\geq 140/90$ mmHg and for the use of antihypertensive medications. Subjects with a history of Type 2 DM (T2DM) and those receiving

anti-diabetic medications were categorized as having T2DM. Subjects who smoked at least 1 cigarette/day at the time of enrollment were considered as smokers. At last, dyslipidemia was considered when the patient or the caregiver reported a positive history for this condition, and alternatively, we considered diagnostic the chronic usage of statin or ezetimibe or fasting low-density lipoprotein (LDL)-cholesterol levels > 100 mg/dL.

The laboratory data (creatinine, urea, uric acid, glucose, sodium, potassium, hematocrit, total cholesterol, LDL, and high-density lipoprotein (HDL)-cholesterol, triglycerides, and platelets) were recorded at the immediate next day after admission and under fasting condition.

Patients distribution and outcomes

We have distributed the patients according to their fasting blood glucose (FBG) in three groups: FBG < 140 mg/dL, FBG 140-180 mg/dL, and FBG ≥ 180 mg/dL¹³. In turn, each of these three groups has been subdivided based on the presence or absence of hyperuricemia (SUA > 6 mg/dL in women and > 7 mg/dL in men)¹⁴. As a result, we have six pre-specified groups (Fig. 1).

The present analysis is referred to the time of admission so to assess the outcome, we have used the value of NIHSS and the Rankin score at admission. We have considered NIHSS as a continuous variable and additionally we have evaluated the pre-specified subgroups according to the clinical neurologic severity score as follows: mild (≤ 8 points), moderate (9-15 points), and severe (≥ 16 points)¹⁵. In the case of Rankin score, we have considered punctuation lower than 2 as a good prognosis.

Statistical analysis

According to pre-specified groups, qualitative and categorical data were expressed as absolute number and percentage, and to compare them in univariate analysis, we used the Chi-square test. Quantitative data were expressed as median and interquartile range; to compare them, we used ANOVA test when the distribution of variables was parametric and Kruskal–Wallis test in the remainder. To assess significant differences between the pairs of basal glucose groups (groups 1 and 2, groups 3 and 4, and groups 5 and 6) related to the prognostic variables (NIHSS and Rankin Score), the t test was used when variables were normally distributed and the Wilcoxon test was used in the remainder. Logistic regression analysis was used to investigate whether the pre-specified groups were

Figure 1. Chartflow of the study.

associated with the outcome. We constructed two models. In the first model, a bad prognosis was assessed using an NIHSS score ≥ 16 ¹⁵. The following variables were evaluated as potential confounders: age, sex, creatinine, CCI, systolic blood pressure, LDL cholesterol, and triglycerides. In the second model, a good prognosis was assessed using a Rankin score ≤ 2 points. We selected the same variables as previously.

All the statistical analyses were done with R version 3.3.2 (The R Foundation for Statistical Computing c/o Institute for Statistics and Mathematics, Wirtschaftsuniversität Wien Welthandelsplatz 1; 1020 Vienna, Austria). A $p < 0.05$ was considered statistically significant.

Results

We analyzed 504 patients (272 men, 53.9%) with a mean age of 75 ± 10.5 years. T2DM was present in 163 (32.4%) patients and hyperuricemia in 118 (23.4%). Regarding the three groups based on FBG levels, the first group (FBG < 140 mg/dL) included 355 (70.4%) patients, the second group (FBG 140-180 mg/dL) included 80 (15.9%), and the third group (FBG > 180 mg/dL) included 69 (13.7%) patients. The clinical and laboratory data of these groups, along with those that presented hyperuricemia or not, are shown in table 1. The main differences among the FBG based groups were the prevalence of hypertension, dyslipidemia, and

T2DM, which were higher through the groups with higher FBG ($p = 0.004$, $p = 0.003$, and $p = 0.00$, respectively), the greater comorbidity in the groups of higher FBP ($p = 0.00$) and the lower HDL cholesterol levels across the groups of higher FBG ($p = 0.00$). In the setting of patients with or without hyperuricemia, the prevalence of hypertension, dyslipidemia, and T2DM was again higher in patients with hyperuricemia ($p = 0.00$, $p = 0.04$, and $p = 0.01$, respectively). In addition, patients with hyperuricemia had higher comorbidity (CCI = 8 ± 3.6 points, $p = 0.00$) and greater levels of creatinine (1.2 ± 0.6 mg/dL, $p = 0.00$) with more usage of diuretic drugs (43.2% vs. 27.7%, $p = 0.001$).

Regarding the six pre-specified groups, we found significant differences (Table 2) in the age ($p = 0.03$), history of DM ($p = 0.00$), hypertension ($p = 0.00$), and dyslipidemia ($p = 0.00$). The heart rate was significantly increased through the six groups ($p = 0.01$) likewise the HDL cholesterol was lowering ($p = 0.003$). Again, the levels of creatinine were significantly higher in the groups with hyperuricemia, groups 2, 4, and 6 ($p = 0.00$), as well as treatment with diuretics ($p = 0.001$).

Outcomes

NIHSS SCORE

The patients belonging to the FBG groups were increasing their NIHSS punctuation when their glucose

Table 1. Baseline characteristics of patients according to the fasting blood glucose (FBG) and serum uric acid levels

Variable	Hyperglycemia groups			p	Serum uric acid groups		p
	FBG < 140 mg/dL	FBG 140-180 mg/dL	FBG > 180 mg/dL		Hyperuricemia	Normouricemia	
N	355	80	69		118	386	
Age (years)	74.3 (10.9)	78.2 (9)	76.2 (9.1)	0.007	76.7 (11)	74.7 (8.4)	0.3
Sex (Male)	200 (56.3)	39 (48.7)	33 (47.8)	0.25	57 (48.3)	215 (55.7)	0.17
Hypertension	288 (81.1)	73 (91.2)	65 (94.2)	0.004	112 (94.9)	314 (81.3)	0.0004
Dyslipidemia	145 (40.8)	40 (50)	43 (62.3)	0.003	63 (53.4)	165 (42.7)	0.04
T2DM	60 (16.9)	43 (53.7)	60 (86.9)	0.00	49 (41.5)	114 (29.6)	0.01
Tobacco	66 (18.6)	10 (12.5)	12 (17.4)	0.4	15 (12.7)	73 (18.9)	0.12
SBP (mmHg)	160.8 (28.4)	158.5 (26.8)	159.3 (27.7)	0.7	161 (29.6)	160 (27.5)	0.74
DBP (mmHg)	87.2 (15.8)	86 (14.5)	85.5 (17.1)	0.63	87.6 (15.8)	86.5 (15.7)	0.5
HR (bpm)	78 (16.1)	81.6 (15.6)	84.2 (17.4)	0.008	81.1 (18.4)	78.9 (15.7)	0.2
NIHSS	8.4 (5.1)	9.2 (5.6)	9.9 (5)	0.07	8.4 (5.4)	8.9 (5.2)	0.22
Rankin score	2.9 (1.2)	3.1 (1.2)	3.3 (1.3)	0.07	3 (2)	3 (2)	0.99
CCI	7 (2.5)	7.9 (2.1)	8.5 (2.5)	0.00	8 (3.6)	7 (3.4)	0.00
FBG (mg/dL)	101.3 (19.5)	156.4 (11.4)	240.7 (52.3)	0.00	8 (3.6)	7 (3.4)	0.00
Creatinine (mg/dL)	1.13 (0.6)	1.1 (0.5)	1.1 (0.4)	0.85	1.2 (0.6)	0.9 (0.4)	0.00
SUA (mg/dL)	5.4 (1.7)	5.1 (1.7)	5.2 (1.5)	0.3	7.2 (1.1)	4.7 (1.8)	0.00
Hemoglobin (g/dL)	13.5 (1.9)	13.5 (1.9)	13.4 (1.8)	0.8	13.3 (3.1)	13.6 (2.4)	0.1
hsCRP (mg/dL)	1.7 (2.3)	2.4 (3.1)	1.7 (1.8)	0.06	0.8 (1.7)	0.8 (1.8)	0.9
HDL-Chol	44.1 (12.9)	42.5 (13.5)	37.8 (9.8)	0.00	41 (13)	42 (16)	0.34
LDL-Chol	117.5 (34.2)	118.9 (41.8)	112.1 (34.6)	0.43	112 (40)	115 (50)	0.34
TREATMENT							
ACEi/ARB	248 (69.8)	52 (65)	53 (76.8)	0.28	82 (69.5)	271 (70.2)	0.88
Statins	221 (62.2)	54 (67.5)	48 (69.6)	0.4	71 (60.9)	252 (65.3)	0.31
Diuretics	106 (29.8)	36 (45)	16 (23.2)	0.009	51 (43.2)	107 (27.7)	0.001

ACEi/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CCI: Charlson Comorbidity Index; hsCRP: high sensitivity C-reactive protein; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL-Chol: HDL cholesterol; HR: heart rate; LDL-Chol: LDL cholesterol; NIHSS: National Institute of Health Stroke Scale; SBP: systolic blood pressure; SUA: serum uric acid levels. T2DM: type 2 diabetes mellitus.

levels raised ($p = 0.07$) but without reaching statistical significance (Table 1). This NIHSS score was modified downwards in the subgroups having hyperuricemia, again without reaching statistical significance ($p = 0.1$, Table 2, Fig. 2). In figure 2 may be also observed the sets according to the NIHSS score across the pre-specified groups. Overall, the groups with hyperuricemia (groups 2, 4, and 6) had lower but not significant scores in stroke severity (NIHSS) comparing to the groups without hyperuricemia (groups 1, 3, and 5). Finally, in the logistic regression model (Fig. 3), the odd ratio (OR) of the groups of FBG increased as glucose levels were higher and again, this OR

decreased in the groups with hyperuricemia, without statistical significance. Among the covariables included, the age was significantly related to a bad outcome (NIHSS > 16 points) with an OR 1.1, 95%CI 1.04-1.14, $p = 0.001$.

RANKIN SCORE

Regarding Rankin score, again the groups with higher FBG had a greater score in Rankin scale ($p = 0.07$), and when sub-classified according to the presence-absence of hyperuricemia, the score was lower in the groups with hyperuricemia ($p = 0.17$), especially in

Table 2. Baseline characteristics of patients according to pre-specified groups

Variable	Group 1 (n = 272)	Group 2 (n = 83)	Group 3 (n = 60)	Group 4 (n = 20)	Group 5 (n = 54)	Group 6 (n = 15)	p
Age (years)	76 (13)	77 (10)	79 (12)	83 (11.5)	79 (11)	76 (4)	0.03
Sex (male)	161 (59.2)	39 (46.9)	31 (51.7)	8 (40)	23 (42.6)	10 (66.7)	0.07
Hypertension	210 (77.2)	78 (93.9)	54 (90)	19 (95)	50 (92.6)	15 (100)	0.00
T2DM	39 (14.4)	21 (25.3)	29 (48.3)	14 (70)	46 (85.9)	14 (93.3)	0.00
Dyslipidemia	101 (37.1)	44 (53.1)	30 (50)	10 (50)	34 (62.9)	9 (60)	0.002
Tobacco smokers	55 (20.2)	11 (13.2)	8 (13.3)	2 (10)	10 (18.5)	2 (13.3)	0.52
CCI	6.4 (3)	8 (4)	7.2 (2.3)	9.2 (3.2)	8.8 (4.3)	7.6 (3.4)	0.00
SBP (mmHg)	160 (40)	160 (41)	160 (37.5)	156.5 (42)	155.5 (30)	160 (50)	0.94
DBP (mmHg)	87 (78)	89 (78)	81.5 (27.5)	85 (78.5)	80 (74)	87 (70)	0.81
HR (bpm)	76 (14)	78 (20)	80 (16.5)	78 (26)	80 (25)	80 (19)	0.01
FBG (mg/dL)	97 (29)	106 (30)	153 (17.5)	156.5 (27)	217 (75)	225 (39)	0.00
Creatinine (gr/dL)	0.9 (0.3)	1.3 (0.7)	0.9 (0.4)	1.2 (0.6)	1 (0.4)	1.1 (0.7)	0.00
SUA (mg/dL)	4.8 (1.7)	7.2 (1.4)	4.2 (2.1)	6.8 (0.6)	4.7 (1.7)	7.4 (0.6)	0.00
Hemoglobin (gr/dL)	13.6 (2.2)	13.3 (3.4)	13.7 (2.5)	12.4 (3.2)	13.4 (2.5)	13.1 (3.6)	0.52
LDL-Cholesterol (mg/dL)	115 (49)	113 (43)	114 (48)	117 (58)	111 (52)	100 (27)	0.72
HDL-Cholesterol (mg/dL)	43 (17.5)	42 (14)	41 (14)	37 (10.5)	37 (12)	38 (12)	0.003
hsCRP (mg/dL)	0.8 (1.4)	0.8 (1.6)	1 (3.1)	0.6 (1.7)	0.9 (2)	1.4 (2)	0.36
NIHSS	7 (6)	7 (7)	8 (7.5)	7 (7)	9 (6)	10 (8)	0.1
Rankin score	3 (2)	3 (2)	3 (2)	3 (2)	3 (2)	3 (3)	0.1
In-hospital mortality	2 (0.7)	4 (4.8)	0 (0)	0 (0)	2 (3.7)	1 (6.7)	0.6
TOAST							
I	99 (36.4)	27 (32.5)	17 (28.3)	8 (40)	24 (44.4)	5 (33.3)	0.7
II	73 (26.8)	25 (30.1)	19 (31.7)	6 (30)	14 (25.9)	3 (20)	
III	83 (30.5)	27 (32.5)	19 (31.7)	6 (30)	15 (27.8)	5 (33.3)	
IV	9 (3.3)	1 (1.2)	2 (3.3)	0 (0)	0 (0)	2 (13.3)	
V	8 (2.9)	3 (3.6)	3 (5)	0 (0)	1 (1.8)	0 (0)	
Treatment							
ACEi/ARB	189 (69.5)	59 (71.1)	41 (68.3)	11 (55)	41 (75.9)	12 (80)	0.5
Statins	174 (63.9)	47 (56.6)	40 (66.7)	14 (70)	38 (70.4)	10 (66.7)	0.6
Diuretics	71 (26.1)	35 (42.2)	24 (40)	12 (60)	12 (22.2)	4 (26.7)	0.001

ACEi/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CCI: Charlson Comorbidity Index; hsCRP: high sensitivity C-reactive protein; DBP: diastolic blood pressure; FBG: fasting blood glucose; HR: heart rate; NIHSS: National Institute of Health Stroke Scale; SBP: systolic blood pressure; SUA: serum uric acid levels. T2DM: type 2 diabetes mellitus; TOAST: classification of subtype of acute ischemic stroke⁹.

those whose FBG was more than 140 mg/dL; however, these differences were not statistically significant (Tables 1 and 2, Fig. 2). In a similar way, the prevalence of patients with Rankin score lower than 2 points was superior but not significant in the groups having hyperuricemia (being this prevalence lower as FBG was higher, Fig. 2).

Finally, no significant differences were found regarding in-hospital mortality ($p = 0.6$, Table 2).

Discussion and conclusions

The patients of our cohort showed a worsening in their prognosis (neurological and functional damage) in those groups with higher levels of FBG; however, statistical significance was not reached. These groups had more patients with a history of either hypertension, dyslipidemia, or T2DM, and higher comorbidity what could influence on their prognosis apart from the

Figure 2. Results in neurological (NIHSS score) and functional (Rankin score) outcomes. On the top: comparisons of the pre-specified groups according to their distribution of both NIHSS and Rankin scores. On the bottom: percentage of patients by pre-specified groups according to the established cut-off points for both NIHSS and Rankin scores.

effects of hyperglycemia. In a similar way, the patients with hyperuricemia also had a higher rate of hypertension, dyslipidemia, T2DM, and comorbidities. However, in this setting, their neurological and functional outcomes did hardly differ from the patients without hyperuricemia.

Hyperglycemia has been related to higher mortality and morbidity after acute stroke independently of other adverse prognostic factors³. Several explanations may account for this observed association. These patients

could undergo more ischemic damage at the time of infarction as a result of wider underlying cerebral vasculopathy associated with T2DM and hypertension. In this regard, hyperglycemia is a well-known determinant of the broad transformations in both small cerebral blood vessels and large extracranial vessels seen in diabetic patients¹⁶. Hyperglycemia may also disorganize the blood-brain barrier¹⁷ and contribute to hemorrhagic infarct conversion¹⁸. However, above all, hyperglycemia has been shown to increase inflammation and oxidative

Figure 3. Logistic regression by pre-specified groups, regarding NIHSS and Rankin established outcomes.

stress¹⁹. In fact, increased oxidative stress is claimed to be triggered directly by acute (sudden-onset) hyperglycemia²⁰. On the contrary, high levels of SUA have been related to a better functional outcome in patients with acute ischemic stroke⁵, and this effect has been associated with its ability to scavenge oxygen radicals and protect the membranes from lipid peroxidation²¹.

In spite of the fact that our results were not statistically significant, there was a clear tendency to have a worse prognosis in the case of patients having hyperglycemia (groups 3 to 6) that ameliorated when simultaneously these patients also had hyperuricemia (groups 4 and 6). In the URICO-ICTUS, a randomized clinical trial that compared the administration of uric acid versus placebo in stroke patients treated with alteplase within 4.5 h of onset, the addition of uric acid to thrombolytic therapy did not increase the proportion of patients who achieved

good outcome after stroke compared with placebo²². However, in a post hoc analysis, uric acid was associated with reduced infarct growth and improved outcome in patients with hyperglycemia during acute stroke²³. Unlike to this study, uric acid levels in our patients could have been elevated for a longer time before the stroke and, therefore, could also be affected by its deleterious effects related to impair endothelium-mediated relaxation and vascular stiffness²⁴. This aspect could explain, on the one hand, the lack of significance on the outcomes in the groups 4 and 6 of our cohort, and on the other hand, the higher prevalence in these groups of either hypertension or T2DM.

Our study has several limitations. First, its data come from a registry, so the sample lacks randomization, and only patients with SUA data and without treatment for hyperuricemia were included, which might cause

selection bias. In addition, other variables not registered could influence on the results. Second, the sample size in the case of groups 4 and 6 might not be sufficiently large to detect a more robust difference between the groups. Finally, thrombolytic treatment was not performed in any case which may result in changes on the prognosis of the patients

In conclusion, in the setting of an acute ischemic stroke with hyperglycemia, we found a non-significant tendency between SUA and lower clinical neurological damage. This potential protective role must be confirmed by further studies with larger samples and prospective follow-up.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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