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Association between hyperuricemia and hypertension: a case–control study

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the association between hyperuricemia and systemic arterial hypertension.

METHODS: This was a case–control study where individuals aged >18 years were included, who were divided into hypertensive and non-hypertensive groups, excluding those with incomplete information in medical records or with the chronic kidney disease epidemiology collaboration <60 mL/min/1.73 m³. Systemic arterial hypertension was categorized as a dependent variable, while the independent variables were hyperuricemia (i.e., primary variable), sex, education, the practice of physical activity, alcoholism, smoking, diabetes mellitus, chronic kidney disease, a family history of systemic arterial hypertension, age, isolated hyperlipidemia, and mixed hyperlipidemia. Statistical analysis included the univariate and multivariate data analysis, performed by adjusting the logistic regression models using the software R (R Core Team [2018]).

RESULTS: Out of 103 patients evaluated, 75 patients were included in this study. In hypertensive patients, hyperuricemia was more frequent (p=0.029), being present in 18.9% individuals. In the univariate analysis, a statistically significant association was found between hyperuricemia and systemic arterial hypertension (OR 10.9; 95%CI 1.29–1420.0; p=0.023); however, in the multivariate analysis, when adjustment was made for age, the only control variable that persisted in the model, this association ceased to be significant (OR 8.5; 95%CI 0.87–1157.0; p=0.070).

CONCLUSIONS: There was no independent association between hyperuricemia and systemic arterial hypertension. The latter was associated with diabetes mellitus, chronic kidney disease, and age.

KEYWORDS: Hypertension. Uric acid. Hyperuricemia.

INTRODUCTION

Cardiovascular diseases (CVDs) represent the leading cause of death today, causing approximately 17.3 million deaths annually, which corresponds to about 31.5% of all causes and 45% of noncommunicable causes[1]. In Brazil, the rates are quite similar to those detected worldwide, with a mortality rate for CVD corresponding to 31% of all causes of death and 42% of the non-communicable causes[2].

Among the primary causes, systemic arterial hypertension (SAH) accounts for 45% of the cardiac deaths, while 51% of deaths are caused by stroke, affecting 36 million adults in Brazil and costing more than 15 million dollars annually to the public health system[2,3]. In Brazil, Chor et al. in a study with 15,103 public servers in six capitals verified a prevalence of 35.8% SAH, with a predominance among men (40.1 *versus* 32.2%)[4]. SAH is a multifactorial condition and is associated with several other pathologies, such as diabetes mellitus (DM), chronic kidney disease (CKD), and obesity[3].

Hyperuricemia is defined as the presence of serum uric acid levels >7 mg/dL for men and >6 mg/dL for women[5]. High consumption of meat, alcohol, and fructose and use of diuretics are risk factors for its presentation[5-7].

Several epidemiological studies have pointed out the association between high levels of uric acid and CVD, such as

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hypertension, CKD, vascular dementia, metabolic syndrome, preeclampsia[8,9], and type one DM[10]. Nevertheless, establishing a causal relationship between hyperuricemia and hypertension, mainly due to the coexistence of other risk factors, has always been challenging[9,11].

Some experimental models seek to explain this relation based on the inhibition of uricase (or urate oxidase), an enzyme responsible for degrading uric acid into allantoin[8,11,12]. In these studies, rats with uricase inhibited due to oxalic acid administration developed severe hyperuricemia and hypertension[8]. Moreover, other hypotheses are mainly based on the mechanisms of induction of renal vasoconstriction mediated by endothelial dysfunction and the renin-angiotensin-aldosterone system[11-13], as detailed in Figure 1.

This study aims to evaluate the association between hyperuricemia and SAH, controlled by the other classic risk factors for SAH.

METHODS

A total of 103 patients from a Federal Teaching Hospital were evaluated from November 2017 to September 2018.

In this case-control study, the case group comprised patients with SAH and the control group was composed of non-hypertensive patients.

Patients who were aged above 18 years, who were diagnosed with SAH, who did not have CKD (CKD Epidemiology Collaboration [CKD-EPI] <60 mL/min/1.73 m^3), and who had documented uric acid levels in the past three years were included in this study. Regarding the diagnosis of SAH, 68 patients with systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg who were measured and confirmed in an outpatient clinic were included. For the control group, 35 patients without a diagnosis of SAH and CKD, who had documented uric acid levels, were included. Patients whose medical records did not contain complete information regarding the variables studied and normotensive patients taking medication with the potential to raise the serum uric acid level were excluded.

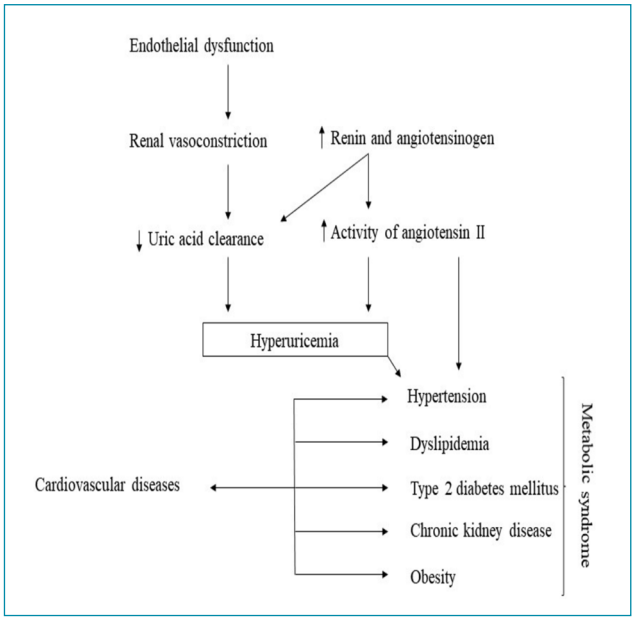

Figure 1. Theoretical rationale for the possible mechanisms of association between hypertension and hyperuricemia, and of these with cardiovascular risk factors. Adapted from Indraratna et al.[13].

To assess the possible association between hyperuricemia and SAH, the statistical analysis was unfolded in two stages. In the first stage, simple logistic regression models were adjusted to check whether not only hyperuricemia but also other sociodemographic and clinical characteristics showed a statistically significant association with SAH. In the second stage, after verifying that hyperuricemia and SAH showed a statistically significant association, multiple logistic regression models were adjusted to assess the independent effect of hyperuricemia on SAH, after controlling for other clinical and sociodemographic characteristics that could be confounding factors.

The sample size calculation considered the earlier data from Nossent et al.[6], which showed an OR 7.7 for the risk of SAH in patients with hyperuricemia and a prevalence of asymptomatic hyperuricemia of 9%. Thus, the minimum sample size to obtain a power of 90% with 95%CI in the 1:1 cases/control ratio and margin loss of 5% was 74.

The statistical significance of the OR tests was evaluated using the likelihood ratio test, and their 95%CI were obtained by a method based on the likelihood function. In all tests, a significance level of 5% was adopted. The statistical analysis was performed using the R software (R Core Team [2018]).

The research protocol entitled "Uric acid as predictor of systemic hypertension" was approved according to the opinion number 2,383,186, with CAAE number 77473717.3.0000.5208.

The data were collected from medical records; therefore, there was no contact with the selected patients, and the requirement for informed consent was waived by the Ethics Research Committee.

RESULTS

During the study period, 103 patients were evaluated. Of these, only 75 patients presented data regarding uric acid levels and were included in this study.

Table 1 shows the results of the univariate analysis of the association between SAH and the sociodemographic and clinical variables of the sample studied.

Table 1. Univariate analysis of the association between systemic arterial hypertension (SAH) and sociodemographic and clinical variables.

	SAH		OR (95%CI)	p*
	Yes	No		
	n (%)	n (%)		
Hyperuricemia				0.023
Yes	10 (100.0)	0 (0.0)	10.9 (1.29–1420.0)†	
No	43 (66.2)	22 (33.8)	1.0	
Sex				0.489
Male	24 (70.6)	10 (29.4)	1.4 (0.56–3.31)	
Female	44 (63.8)	25 (36.2)		
Schooling				0.354
Up to first degree (incomplete/complete)	12 (63.2)	7 (36.8)	2.1 (0.43–10.74)	
Second or third degree (incomplete/complete)	4 (44.4)	5 (55.6)	1.0	
Physical activity practice				0.506
More than 150 min/week	4 (100.0)	0 (0.0)	0.4 (0.003–4.84)†	
Less than or up to 150 min/week	15 (78.9)	4 (21.1)	1.0	
Alcoholism				0.177
Yes	9 (52.9)	8 (47.1)	0.5 (0.15–1.41)	
No	39 (70.9)	16 (29.1)	1.0	
Smoking				0.075
Yes	1 (25.0)	3 (75.0)	0.1 (0.01–1.48)	
No	48 (69.6)	21 (30.4)	1.0	
Diabetes				0.028
Yes	23 (82.1)	5 (17.9)	3.1 (1.05–8.96)	
No	45 (60.0)	3 (40.0)	1.0	
Chronic kidney disease				0.026
Yes	11 (91.7)	1 (8.3)	6.7 (1.22–124.8)	
No	56 (62.2)	34 (37.8)	1.0	
Family history of SAH				0.692
Yes	27 (60.0)	18 (40.0)	1.3 (0.37–4.46)	
No	7 (53.8)	6 (46.2)		
Age (years)				<0.001
≤60	22 (44.9)	27 (55.1)	7.1 (2.76–18.04)	
>60	46 (85.2)	8 (14.8)	1.0	
Isolated hyperlipidemia				0.658
Yes	11 (61.1)	7 (38.9)	0.8 (0.27–2.28)	
No	48 (66.7)	24 (33.3)	1.0	
Mixed hyperlipidemia				0.453
Yes	4 (80.0)	1 (20.0)	2.2 (0.24–20.91)	
No	52 (64.2)	29 (35.8)	1.0	

*Verisimilitude ratio test; †OR and 95%CI estimated using the Firth method.

In the univariate analysis of the association between hyperuricemia and SAH, hyperuricemia was more frequent among cases than controls (18.9% *versus* 0%, p=0.023). The OR of SAH was approximately 11 times higher in patients with hyperuricemia compared with those without hyperuricemia.

To control the possible confounding effect of these variables on the association between hyperuricemia and SAH, the multivariate logistic regression model was adjusted, in which the explanatory variables chosen were those with p<0.20 in the univariate analysis (Table 1); however, alcoholism and smoking were excluded, considering that the absence of information about the levels of uric acid among smokers and drinkers would lead to a considerable reduction in the sample size.

Table 2 presents the results of the adjustments of the initial multivariate logistic model and the final multivariate logistic model, the latter obtained from the initial model through the "backward" selection process, where in each step, the variable with the highest p>0.05 was removed from the resulting model. Thus, the variables DM and CKD were excluded in the process.

The results of the final model showed that after adjustment in the variable age, hyperuricemia was not significantly associated with SAH, although the OR of SAH in patients with hyperuricemia was 8.5 times higher than the corresponding OR in those without hyperuricemia.

Table 2. Initial and final multivariate models to assess the effect of hyperuricemia as a possible factor associated with the occurrence of systemic arterial hypertension.

	Initial model		Final model	
	OR (95%CI)	p	OR (95%CI)	p*
Hyperuricemia	6.8 (0.67–92.8)	0.112	8.5 (0.87–1157.0)	0.070
Age >60 years	6.3 (2.07–22.12)	0.001	7.1 (2.37–24.22)	<0.001
Diabetes	2.1 (0.60–8.88)	0.249		
Chronic kidney disease	1.6 (0.24–17.49)	0.653		

*Verisimilitude ratio test; OR and 95%CI estimated using the Firth method.

DISCUSSION

The difficulty in establishing a causal relationship between hyperuricemia and SAH has been frequently reported in the literature, since it is difficult to separate hyperuricemia as an isolated risk factor for SAH, considering that it usually coexists with several other cardiovascular risk factors[9]. Nevertheless, several recent studies have indicated hyperuricemia as an independent risk factor for the development of SAH, besides being a marker of CVDs[7].

In a Brazilian study developed with 204 patients, a significant association of hyperuricemia with stroke (OR 2.38; 95%CI 1.2–7.24), SAH (OR 7.76; 95%CI 2.72–15.76), hyperlipidemia (OR 5.05; 95%CI 1.59–11.32), peripheral neuropathy (OR 3.49; 95%CI 1.52–12.23), and arterial thrombosis (OR 4.95; 95%CI 1.98–15.34) was observed[14].

In a 5-year follow-up cohort study of 5,889 Japanese individuals aged between 30–85 years, on comparing a group with elevated uric acid levels and another with normal levels, an association was found between hyperuricemia and increased incidence of SAH (14.9 *versus* 6.1%; p<0.001), dyslipidemia (23.1 *versus* 15.5%; p<0.001), CKD (19.0 *versus* 10.7%; p<0.001), and obesity (8.9 *versus* 3.0%; p<0.001)[15].

In Brazil, Ferreira et al.[16] evaluated the association between levels of uric acid and cardiometabolic risk factors in 149 adults aged between 20–55 years. The authors suggested that higher levels of uricemia would be associated with greater fat mass and lipid alterations[16]. The association between hyperuricemia, cardiometabolic risk factors, and metabolic syndrome was also evaluated in a study by Silva et al. with 80 patients, who showed hyperuricemia in individuals with metabolic syndrome (5.1±1.6 mg/dL), in men with abdominal obesity, women with obesity, patients with lower HDL levels, and hypertensive individuals (p<0.05)[17].

Although more prevalent in older individuals, a relationship between hyperuricemia and primary hypertension in children has been pointed out[11]. In a group of 125 children and adolescents aged 6–16 years, a serum uric acid concentration >5.5 mg/dL was found in 89% of participants with primary hypertension, 30% of those with secondary hypertension, and 0% of those with white coat hypertension and the control group[18].

Palmer et al.[19] evaluated the levels of uric acid in a cohort study of 58,072 Danish individuals, seeking to establish an association between hyperuricemia, SAH, and ischemic events. No association was found between hyperuricemia and SAH, even when systolic and diastolic arterial pressures were evaluated separately.

Thus, the independent association between hyperuricemia and SAH is still not well established, mainly due to the

presence of comorbidities in the participants evaluated in clinical studies[7,19,20].

The main limitation of our study was the absence of information in medical records, which reduced our sample size. We have verified studies in the literature that evaluated the association between hyperuricemia and SAH in samples smaller than ours[17]. We emphasized that this is a case-control study whose design and sample are adequate to answer the clinical question raised. The study used the logistic regression techniques to control the effect of other variables that could influence the analysis of the association between hyperuricemia and hypertension.

CONCLUSIONS

No independent association was found between hyperuricemia and SAH. The latter was associated with the variables such as DM, CKD, and age.

AUTHORS' CONTRIBUTIONS

TTDB: Conceptualization, Methodology, Project administration, Writing – original draft. **LSB:** Writing – review & editing. **MAOSV:** Writing – review & editing. **ABMSL:** Methodology, Project administration. **SGL:** Conceptualization, Methodology, Project administration, Writing – review & editing.

REFERENCES

1. Townsend N, Nichols M, Scarborough P, Rayner M. Cardiovascular disease in Europe – epidemiological update 2015. Eur Heart J. 2015;36(40):2696-705. https://doi.org/10.1093/eurheartj/ehv428
2. Ribeiro ALP, Duncan BB, Brant LCC, Lotufo PA, Mill JG, Barreto SM. Cardiovascular health in Brazil trends and perspectives. Circulation. 2016;133(4):422-33. https://doi.org/10.1161/CIRCULATIONAHA.114.008727
3. Malachias M, Souza W, Plavnik F, Rodrigues C, Brandão A, Neves M, et al. 7ª diretriz brasileira de hipertensão arterial. Arq Bras Cardiol. 2016;107(3 Suppl 3):1-83. https://doi.org/10.5935/abc.20160152
4. Chor D, Ribeiro ALP, Carvalho MS, Duncan BB, Lotufo PA, Nobre AA, et al. Prevalence, awareness, treatment and influence of socioeconomic variables on control of high blood pressure: results of the ELSA-Brasil study. PLoS One. 2015;10(6):e0127382. https://doi.org/10.1371/journal.pone.0127382
5. Mallat SG, Al Kattar S, Tanios BY, Jurjus A. Hyperuricemia, hypertension, and chronic kidney disease: an emerging association. Curr Hypertens Rep. 2016;18(10):74. https://doi.org/10.1007/s11906-016-0684-z
6. Nossent J, Raymond W, Divitini M, Knuiman M. Asymptomatic hyperuricemia is not an independent risk factor for cardiovascular events or overall mortality in the general population of the busselton health study. BMC Cardiovasc Disord. 2016;16(1):256. https://doi.org/10.1186/s12872-016-0421-1
7. Stewart DJ, Langlois V, Noone D. Hyperuricemia and hypertension: links and risks. Integr Blood Press Control. 2019;12:43-62. https://doi.org/10.2147/IBPC.S184685
8. Johnson RJ. Why focus on uric acid? Curr Med Res Opin. 2015;31(Suppl 2):3-7. https://doi.org/10.1185/03007995.2015.1087979
9. Ni Q, Lu X, Chen C, Du H, Zhang R. Risk factors for the development of hyperuricemia: a STROBE-compliant cross-sectional and longitudinal study. Medicine (Baltimore). 2019;98(42):e17597. https://doi.org/10.1097/MD.0000000000017597
10. Shah P, Bjornstad P, Johnson RJ. Hiperuricemia como potencial fator de risco para diabetes tipo 2 e nefropatia diabética. J Bras Nefrol. 2016;38(4):386-7. https://doi.org/10.5935/0101-2800.20160061
11. Johnson RJ, Feig DI, Herrera-Acosta J, Kang DH. Resurrection of uric acid as a causal risk factor in essential hypertension. Hypertension. 2005;45(1):18-20. https://doi.org/10.1161/01.HYP.0000150785.39055.e8
12. Chen RJ, Chen MH, Chen YL, Hsiao CM, Chen HM, Chen SJ, et al. Evaluating the urate-lowering effects of different microbial fermented extracts in hyperuricemic models accompanied with a safety study. J Food Drug Anal. 2017;25(3):597-606. https://doi.org/10.1016/j.jfda.2016.07.003
13. Indraratna PL, Williams KM, Graham GG, Day RO. Hyperuricemia, cardiovascular disease, and the metabolic syndrome. J Reumatol. 2009;36(12):2842-3. https://doi.org/10.3899/jrheum.090500
14. Sheikh M, Movassaghi S, Khaledi M, Moghaddassi M. Hiperuricemia no Lúpus eritematoso sistêmico: está associada a manifestações neuropsiquiátricas da doença? Rev. Bras. Reumatol. 2016;56(6):471-7. https://doi.org/10.1016/j.rbre.2015.07.011
15. Kuwabara M, Niwa K, Hisatome I, Nakagawa T, Roncal-Jimenez CA, Andres-Hernando A, et al. Asymptomatic hyperuricemia without comorbidities predicts cardiometabolic diseases five-year Japanese cohort study. Hypertension. 2017;69(6):1036-44. https://doi.org/10.1161/HYPERTENSIONAHA.116.08998
16. Ferreira TS, Fernandes JFR, Araújo LS, Nogueira LP, Leal PM, Antunes VP, et al. Serum uric acid levels are associated with cardiometabolic risk factors in healthy young and middle-aged adults. Arq Bras Cardiol. 2018;111(6):833-40. https://doi.org/10.5935/abc.20180197
17. Silva HA, Carraro JCC, Bressan J, Hermsdorff HHM. Relation between uric acid and metabolic syndrome in subjects with cardiometabolic risk. Einstein (São Paulo). 2015;13(2):202-8. https://doi.org/10.1590/S1679-45082015AO3194
18. Feig DI, Johnson RJ. Hyperuricemia in childhood primary hypertension. Hypertension. 2003;42(3):247-52. https://doi.org/10.1161/01.HYP.0000085858.66548.59
19. Palmer TM, Nordestgaard BG, Benn M, Tybjærg-Hansen A, Smith GD, Debbie A, et al. Association of plasma uric acid with ischaemic heart disease and blood pressure: mendelian randomisation. BMJ. 2013;347:f4262. https://doi.org/10.1136/bmj.f4262
20. Li L, Yang C, Zhao Y, Zeng X, Liu F, Fu P. Is hyperuricemia an independent risk factor for new-onset chronic kidney disease? A systematic review and meta-analysis based on observational cohort studies. BMC Nephrol. 2014;15:122. https://doi.org/10.1186/1471-2369-15-122