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RESEARCH ARTICLE

Role of hyperuricemia in patients with essential hypertension: A hospital-based case–control study

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ABSTRACT

Background: Essential hypertension (EHT) poses as a major health issue in developed countries. It shows a strong association with cardiovascular disease and significantly contributes to patient morbidity and mortality, as well as economic burden. The association of hyperuricemia with EHT is demonstrated by several researchers. It is postulated that increased serum uric acid (SUA) level is thought to play a pathogenic role in the evolution of EHT. **Aim and Objective:** The aim of this study was to establish the relationship between SUA and EHT and also to determine the correlation coefficient between SUA levels and blood pressure (BP) in subjects with EHT. **Materials and Methods:** This hospital-based case–control study included 50 newly diagnosed and untreated hypertensive patients of all genders in age group of 35–65 years having BP ≥140/90 mm Hg as cases. Fifty age- and sex-matched and normotensive subjects were included as controls. Patients with history of diabetes mellitus, renal diseases, chronic liver disease, familial hyperlipidemia, gout, smoking, alcohol consumption, obesity, and patients on lipid lowering drugs were excluded from the study. SUA was measured in all study and control subjects by standard method. **Results:** Mean SUA level was significantly higher in EHT group (7.83 ± 0.16) as compared to control group (4.99 ± 0.31) ($P < 0.001$). Positive and significant correlation was found between SUA and systolic BP ($R^2 = 0.59$, $P < 0.001$), diastolic BP (DBP) ($R^2 = 0.59$, $P < 0.001$), and mean BP ($R^2 = 0.62$, $P < 0.001$). Hyperuricemia was observed in significantly higher proportion in cases ($n = 47$, 94%) as compared to controls ($n = 6$, 12%) ($P < 0.001$). **Conclusions:** Increased SUA level has significant association with EHT after regulating several confounding factors. The count of hyperuricemic individuals as well as mean SUA level was significantly higher in newly diagnosed cases of hypertension in comparison to normotensive controls. There was significant positive association between SUA and BP in hypertensive cases.

KEY WORDS: Hypertension; Hyperlipidemia; Hyperuricemia

INTRODUCTION

Essential hypertension (EHT) poses as a major health issue in developed countries today and almost one billion people are affected worldwide.[1] It shows a strong association with cardiovascular disease and significantly contributes to patient morbidity and mortality, as well as economic burden.[2] It accounts for 90% of all the cases of hypertension. In India, according to a survey by ICMR, the prevalence varies from 17% to 21%. It occurs commonly in the age group between 30 and 65 years and may be a consequence of interaction between environmental and genetic factors.[3] The association of hyperuricemia with EHT was reported by several researchers such as Grayson *et al*.[4] and Jin *et al*.[5] Sundstrom *et al*.[6] postulated that increase in serum uric acid (SUA) level is thought to play a pathogenic role in the evolution of EHT. Uric acid is an important risk marker in

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essential hypertensives. This increase in blood pressure (BP) in hyperuricemia is brought about by several mechanisms. A few worthy mentions are endothelial dysfunction, caused by the decreased production of nitric oxide (NO),[7] systemic inflammation due to lipid oxidation and enhanced platelet aggregation, and expression of the C-reactive protein within vascular endothelium.[8] The activation of renin angiotensin system and vascular smooth muscle proliferation is other important factors which induce EHT. A positive association has been convincingly proved by various studies between SUA level and stroke, myocardial infarction, and coronary heart disease among patients with EHT.[9,10]

This study was conducted to establish the relationship between SUA and EHT and also to determine the correlation coefficient between SUA levels and BP in subjects with EHT.

MATERIALS AND METHODS

This hospital-based case–control study was carried out in the outpatient unit of the Department of Medicine, Government Medical College, Calicut, India between April 2015 and March 2016.

A total of 50 newly diagnosed and untreated patients of all genders in age group of 35–65 years and having BP ≥140/90 mm Hg were included in the study as cases. A total of 50 age- and sex-matched individuals, with systolic BP (SBP) in range of 100–140 mm Hg, and diastolic BP (DBP) in range of 60–90 mm Hg were included as controls. Patients having history of diabetes mellitus, renal diseases, chronic liver disease, gout, familial hyperlipidemia, and patients taking lipid lowering drugs were excluded from the study. Alcoholics, smokers, and obese patients were also excluded from the study.

A written voluntary informed consent was obtained from all the subjects. Patient data were compiled in a detailed pro forma, and requisite physical examination was performed. After an overnight fast (12 h), 3 ml of blood sample was collected by venous puncture. Serum was separated by centrifugation at 3000 rpm for 10 min. Patient's SUA level was determined by Modified Trinder method.[11] Serum creatinine was estimated to exclude renal disorder, whereas fasting blood glucose was estimated to exclude diabetes mellitus.

All data were analyzed using standard statistical software Statistical Package for the Social Sciences version 16. Significance testing of difference for Mean ± SD of two groups was done by student t-test or Mann–Whitney U-test based on the type of data. Pearson method was used to assess correlation between SUA and BP. Chi-square test and odds ratio were used to test association between hypertension and hyperuricemia. Statistical significance was established using $P < 0.05$.

Ethical approval was attained from the Institute Ethics Committee.

RESULTS

The mean level of SUA was significantly higher in the EHT group (7.83 ± 0.16) as compared to control group (4.99 ± 0.31) ($P < 0.001$). The demographic characteristics were comparable between cases and controls [Table 1]. Positive and significant correlation was found between SUA and SBP ($R^2 = 0.59$, $P < 0.001$), DBP ($R^2 = 0.59$, $P < 0.001$), and mean BP ($R^2 = 0.62$, $P < 0.001$) [Figures 1-3]. Hyperuricemia is best defined as SUA level ≥7 mg/dl (in men) or ≥6.0 mg/dl (in women).[12] Hyperuricemia was observed in significantly higher proportion in cases ($n = 47$, 94%) as compared to controls ($n = 6$, 12%) (Odds ratio 114; 95% confidence interval 27–500; $P < 0.001$). Hyperuricemic patients were at significantly higher risk for developing EHT (OR = 7.83; 95% confidence interval 3.68–16.64; $P < 0.001$).

DISCUSSION

In the present study, the mean SUA level was 7.83 ± 0.163 mg/dL in patients with EHT and 4.99 ± 0.179 mg/dL in the control group. The SUA values were significantly elevated in patients with EHT. This study demonstrated an increasing trend in mean SUA level and also in number of hyperuricemic individuals from control to hypertensive cases ($P < 0.001$). There was significant positive correlation between SUA and SBP ($R^2 = 0.59$, $P < 0.001$), DBP ($R^2 = 0.59$, $P < 0.001$), and mean BP ($R^2 = 0.62$, $P < 0.001$).

Elevated SUA levels in patient with EHT were also obtained by Anker *et al*.,[13] Zhang *et al*.,[14] and Krishnan *et al*.[15] Increase in SUA is an important risk factor in developing EHT.[16] High SUA level during childhood is associated with elevated BP in childhood as well as in adulthood.[17,18] This suggests that elevated SUA levels may have a role in the early onset of EHT. Elevated SUA levels are also associated with an increased risk for the development of cardiovascular disease.[19] During the past 50 years, epidemiological population-based studies convincingly proved a positive association between elevated level of SUA and cardiovascular disease among essential hypertensive patients.[19] The increase in BP and development of cardiovascular disease in hyperuricemic individuals is said to be mediated by endothelial dysfunction, systemic vascular inflammation, and vascular smooth muscle cell proliferation

Table 1: Characteristics of study population among two groups

Variables	Case (*n*=50)	Control (*n*=50)	*P*-value
Gender (Male/female)	25/25	29/21	0.42
Age (years) Mean±SD	51.6±8.9	51.6±9.7	0.97
Systolic BP (mm Hg) Mean±SD	161±9	120±7	<0.001
Diastolic BP (mm Hg) Mean±SD	104±5	81±3	<0.001
Mean BP (mm Hg) Mean±SD	122±6	95±4	<0.001

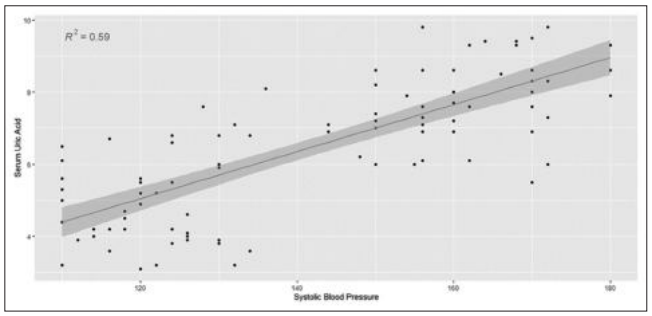

Figure 1: Scatter plot diagram showing correlation between SUA and SBP, P < 0.001

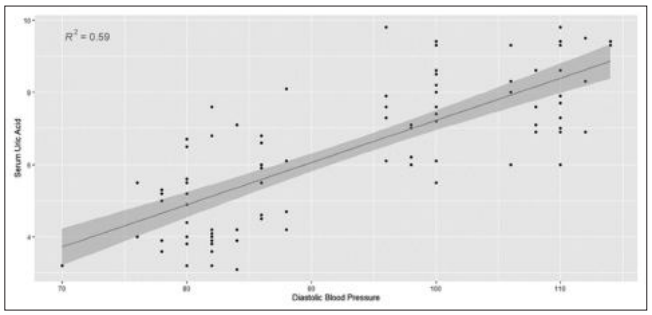

Figure 2: Scatter plot diagram showing correlation between SUA and DBP, P < 0.001

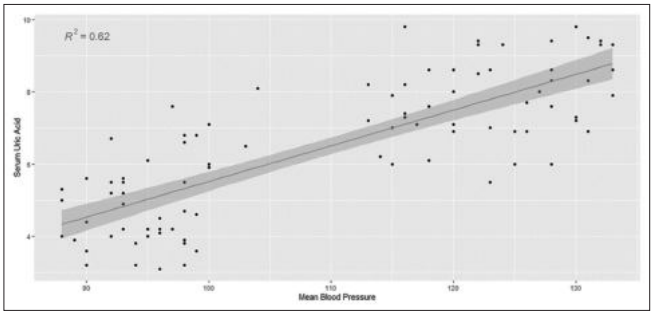

Figure 3: Scatter plot diagram showing correlation between SUA and MBP, P < 0.001

predominantly in renal microcirculation causing activation of renin angiotensin system.[20] Elevated SUA level decreases the NO level.[20,21] Uric acid rapidly and irreversibly reacts with NO that results in the formation of 6-aminouracil and thereby causes depletion of NO.[22] When the production of uric acid increases, reactive oxygen species (ROS) like superoxide also increases. In purine metabolism, xanthine oxidase enzyme acts on xanthine, producing uric acid along with generation of ROS.[23] ROS impairs NO production. Reduced NO causes endothelial dysfunction and inability of arteries and arterioles to dilate, resulting in the development of hypertension. Uric acid-induced systemic vascular inflammation is also an important factor which increases BP.[24] Oxidative stress that occurs, along with hyperuricemia, causes lipid oxidation, which triggers an immunogenic response and inflammation. Elevated SUA level may cause direct increase in systemic inflammation by other potential mechanisms such as enhanced platelet aggregation, stimulation of arachidonic acid metabolism in platelets, increased neutrophils, and production of C-reactive protein in vascular endothelium.[25] SUA enhances the production of mitogen activated protein kinase, platelet derived growth factor, and cyclooxygenase 2.[26] These factors induce vascular smooth muscle proliferation by extracellular matrix mediated adhesion and response on laminin 5. SUA also induces the activation of renin angiotensin system.[27] This increases the release of Angiotensin II, which has an immense effect on constriction of renal arterioles, which, in turn, increases arteriolar resistance and leads to the development of EHT. Hyperuricemia has been reported to be associated with metabolic syndrome.[28] Similar results of positive correlation between SUA level and BP were reported by several other studies.[29-35] In favor of our study, Assob *et al*. demonstrated that SUA level in prehypertensive subjects was significantly higher than control group ($P < 0.0001$) and there was positive correlation between SUA and SBP and DBP ($P < 0.0001$).[36] Contrary to our study, Hamdani IHAL did not find any significant difference in SUA level between hypertensive subjects and control group.[37] Another study conducted by Vucak *et al*. found no association between hyperuricemia and hypertension (OR 1.68).[38]

Study design and small sample size are few of the limitations of the study.

CONCLUSIONS

In the present study, increased SUA level has significant association with EHT after regulating several confounding factors. This study revealed that the count of hyperuricemic individuals as well as mean SUA level was significantly higher in newly diagnosed cases of hypertension in comparison to normotensive controls. There was significant positive association of SUA with SBP in newly diagnosed cases of hypertension. In our study, we found that patients living with EHT but not taking medication also usually had hyperuricemia as comorbidity. There is a forthcoming approach for treating hypertension by reducing SUA levels, especially in patients with new and recent onset primary hypertension. Therefore, monitoring SUA level is very important among newly diagnosed essential hypertensive individuals.

REFERENCES

1. Kotchen TA. Hypertensive vascular disease. In: Harrison's Principles of Internal Medicine. 18th ed., Ch. 247. Part. 10. Sec. 5. 2011. p. 2042-52.
2. Chiang CE, Chen CH. Hypertension in the Asia-Pacific region. J Hum Hypertens 2008;22:441-3.
3. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, *et al*. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet

2012;380:2224-60.
4. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: A systematic review and meta-analysis. Arthritis Care Res 2011;63:102-10.
5. Jin M, Yang F, Yang I, Yin Y, Luo JJ, Wang H, *et al*. Uric acid, hyperuricemia and vascular diseases. Front Biosci 2012;17:656-69.
6. Sundstrom J, Sullivan L, D'Agostino RB, Levy D, Kannel WB, Vasan RS. Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. Hypertension 2005;45:28-33.
7. Lippi G, Montagnana M, Salvagno GL, Targher G, Guidi GC. Epidemiological association between uric acid concentration in plasma, lipoprotein (a), and the traditional lipid profile. Clin Cardiol 2010;33:E76-80.
8. Sarmah D, Sharma B. A correlative study of uric acid with lipid profile. Asian J Med Sci 2013;4:8-14.
9. Vyas A, Patel NR, Vyas K. A study of correlation between essential hypertension and hyperuricemia. Int J Recent Trends Sci Technol 2013;7:76-9.
10. Verdecchia P, Schillaci G, Reboldi G, Santeusanio F, Porcellati C, Brunetti P. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension: The PIUMA study. Hypertension 2000;36:1072-8.
11. Trinder P. Quantitative determination of Uric Acid in human serum. J Clin Pathol 1949;22:246-50.
12. Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH. Rheumatoid Arthritis E-Book. Maryland, USA: Elsevier Health Sciences; 2008.
13. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, *et al*. Uric acid and survival in chronic heart failure: Validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003;107:1991-7.
14. Zhang W, Sun K, Yang Y, Zhang H, Hu FB, Hui R. Plasma uric acid and hypertension in a Chinese community: Prospective study and meta-analysis. Clin Chem 2009;55:2026-34.
15. Krishnan E, Kwoh CK, Schumacher HR, Kuller L. Hyperuricemia and incidence of hypertension among men without metabolic syndrome. Hypertension 2007;49:298-303.
16. Watanabe S, Kang DH, Feng L, Nakagawa T, Kanellis J, Lan H, *et al*. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. Hypertension 2002;40:355-60.
17. Alper AB Jr., Chen W, Yau L, Srinivasan SR, Berenson GS, Hamm LL. Childhood uric acid predicts adult blood pressure: The Bogalusa Heart Study. Hypertension 2005;45:34-8.
18. Feig DI, Johnson RJ. Hyperuricemia in childhood primary hypertension. Hypertension 2003;42:247-52.
19. Persky VW, Dyer AR, Idris-Soven EL, Stamler J, Shekelle RB, Schoenberger JA, *et al*. Uric acid: A risk factor for coronary heart disease? Circulation 1979;59:969-77.
20. Wannamethee SG, Shaper AG, Whincup PH. Serum urate and the risk of major coronary heart disease events. Heart 1997;78:147-53.
21. Wannamethee SG. Is serum uric acid a risk factor for coronary heart disease? J Hum Hypertens 1999;13:153-6.
22. Gersch C, Palii SP, Kim KM, Angerhofer A, Johnson RJ, Henderson GN. Inactivation of nitric oxide by uric acid. Nucleosides Nucleotides Nucleic Acids 2008;27:967-78.
23. Hare JM, Johnson RJ. Uric acid predicts clinical outcomes in heart failure: Insights regarding the role of xanthine oxidase and uric acid in disease pathophysiology. Circulation 2003;107:1951-3.
24. Grainger R, McLaughlin RJ, Harrison AA, Harper JL. Hyperuricaemia elevates circulating CCL2 levels and primes monocyte trafficking in subjects with inter-critical gout. Rheumatology 2013;52:1018-21.
25. Van Bortel LM, Spek JJ. Influence of aging on arterial compliance. J Hum Hypertens 1998;12:583-6.
26. Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, *et al*. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension 2003;41:1287-93.
27. Johnson RJ, Feig DI, Herrera-Acosta J, Kang DH. Resurrection of uric acid as a causal risk factor in essential hypertension. Hypertension 2005;45:18-20.
28. Karmakar S, Sarkar KC, Ray AN, Nath I, Kumar A, Arora N. A study on association of hyperuricemia among patients of metabolic syndrome attending outpatient department of North Bengal Medical College and Hospital. Natl J Physiol Pharm Pharmacol 2020;10:874-7.
29. Shah MI, Suthar RK, Soomro MA. Essential hypertension: Evaluation of serum uric acid at tertiary care hospital Hyderabad/Jamshoro. Professional Med J 2015;22:854-8.
30. Vittal BG, Bhaskara K, Naveenkumar GH. Uric acid and hypertension: Does uric acid lick the joints and bites the heart? Int J Med Res Health Sci 2014;3:104-9.
31. Turankar SA, Sonune K, Turankar AV. Study of serum uric acid in newly diagnosed essential hypertensive patients. World Res J Crit Care 2013;1:15-7.
32. Shrivastav C, Sharma S, Suhalka ML, Kaur M. Hyperuricaemia and essential hypertension: A case control study in Southern Rajasthan. Int J Res Med Sci 2016;4:78-83.
33. Kashem MA, Hossain MZ, Ayaz KM, Alam MB, Khan MH, Alam AB, *et al*. Relation of serum uric acid level and essential hypertension among patients without metabolic syndrome. J Dhaka Med Coll 2011;20:5-8.
34. Acharya V, Mishra PK. Hyperuricemia and oxidative stress in borderline hypertension. Biomedicine 2007;21:19-22.
35. Bano S, Joshi AR, Vaidya SM. Correlation between serum uric acid level with obesity indices and blood pressure in young males. Natl J Physiol Pharm Pharmacol 2019;9:1103-6.
36. NguediaAssob JC, Ngowe MN, Nsagha DS, Njunda AL, Waidim Y, Lemuh DN. The relationship between uric acid and hypertension in adults in Fako Division, SW region Cameroon. J Nutr Food Sci 2014;4:2.
37. Al-Hamdani IA. Estimation of serum uric acid, urea and creatinine in essential hypertensive patients. Tikrit Med J 2010;16:
38. Vučak J, Katić M, Bielen I, Vrdoljak D, Lalić DI, Kranjčević K, *et al*. Association between hyperuricemia, prediabetes, and prehypertension in the Croatian adult population-a cross-sectional study. BMC Cardiovasc Disorders 2012;12:117.

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