

Serum Uric Acid Levels and Its Correlation with the Severity of Hypertension: Case-Control Study

¹.Dr. Divyanshu Martand, ². Dr . Nitin Dinesh, ³. Dr .Saurabh Raj,
⁴. Dr. Sanjay Kumar*,

Junior Resident, Department of Medicine, Nalanda Medical College and Hospital, Patna, Bihar, India.

Junior Resident, Department of medicine, Nalanda Medical College and Hospital, Patna, Bihar, India.

Junior Resident, Department of medicine, Nalanda Medical College and Hospital, Patna, Bihar, India.

Assistant Professor, Department of medicine, Nalanda Medical College and Hospital, Patna, Bihar, India.

Corresponding Author: Dr. Sanjay Kumar

Received: 18 Aug 2020 Revised: 25 Sep. 2020 Accepted: 18 Oct. 2020 Published: 12 December 2020

ABSTRACT

Aims: This study was carried out to assess the serum uric acid levels in essential hypertension and its correlation with the severity and known duration of hypertension.

Material and methods: The observational and case control study was conducted in the Department of Medicine, Nalanda, Medical College and Hospital Patna, Bihar, India for one year. A total of 140 patients were taken into the study with an equal proportion of cases and controls of 1:1. 70 patients were taken as cases that were known cases of essential hypertension irrespective of treatment status and were graded into different stages of hypertension as per JNC VII guidelines.

Results: Out of 70 cases, 33 (47.14%) were male patients and 37 (52.86%) were female patients. Mean BMI in cases was 24.04 kg/m² whereas it was 24.37 kg/m² in case of controls which was comparable among the two groups. Overall mean systolic BP in cases was 170 mmHg and mean diastolic BP was 103 mmHg. Overall, 23 (32.86%) patients were grouped in stage 1. 39(55.71%) patients in stage 2 and 8 (11.43%) patients in isolated systolic hypertension (ISH). Maximum patients were in stage 2 among both males (60.60%) and females (51.35%). Mean systolic and diastolic blood pressure in stage 1 was 147.22 mmHg and 95.21 mmHg. In stage 2 it was 187.07 mmHg and 113.11mmHg respectively. In ISH systolic BP was 147.85 mmHg and diastolic BP was 86.12 mmHg. Among cases the range of serum uric acid level in males was 1.90-11.70 with mean value of 7.31 whereas in females range of serum uric acid level was 1.31-10.80 with mean value of 7.14.

Conclusion: The serum uric acid is significantly elevated in hypertensive as compared to normotensive individuals.

Keywords: serum uric acid, hypertension, severity

I. INTRODUCTION

Hypertension is the emerging public health problem of adult population across the globe, affecting one in every four individuals.¹ The etiological factors associated with hypertension is difficult to predict because hypertension results from a complex interaction of genes and environmental factors.¹ Previous researches have already studied the role of serum uric acid in development of hypertension. The reasonable mechanism for the development of hypertension in hyperuricemia includes: (a) uric acid induced activation of renin-angiotensin system and action on glomerular apparatus.^{2,3} (b) increased insulin resistance and hyperinsulinaemia, causing decreases excretion of uric acid, sodium, potassium from renal tubules.^{4,5} and (c) uric acid action in proliferation of vascular smooth muscle⁶ endothelial dysfunction with decrease nitric acid production.^{7,8} However, there are numerous confounding factors including metabolic syndrome, diabetes mellitus, chronic kidney disease, obesity, alcohol consumption, salt intake, fluid volume status etc. in the association of hyperuricemia and hypertension. Frederick Mohamed first time reported that serum uric acid was associated with raised blood pressure in 1870s.⁹ The mechanism(s) by which UA may engender organ damage is still incompletely understood, but there is increasing evidence that endothelial dysfunction is a fundamental mechanism whereby this substance may affect cardiovascular and renal function and structure.¹⁰ Serum uric acid was proved to be an predictor for hypertension by various authors in their researches.¹¹⁻¹³ Various mechanisms such as inflammation and smooth muscle cell proliferation in kidneys and activation of renin-angiotensin-aldosterone system play a role in development of hypertension through involvement of uric acid.¹⁴⁻¹⁶

In order to know the correlation between hypertension and serum uric acid, present study has objectives to assess the serum uric acid levels in all stages of hypertension and its association with the duration of hypertension.

II. MATERIAL AND METHODS

An observational case control study was conducted in the Department of Medicine, Nalanda, Medical College and Hospital Patna, Bihar, India for 1 year.

Methodology

The study group comprised of hypertensive patients visiting the out-patient medicine department or admitted in the hospital. Age and sex marked controls were taken into study. A total of 140 patients were taken into the study with an equal proportion of cases and controls of 1:1. 70 patients were taken as cases who were known cases of essential hypertension irrespective of treatment status and were graded into different stages of hypertension as per JNC VII guidelines.¹⁷ Rest 70 patients were taken as control who were age and sex matched without any co-morbidity. The diagnosis of essential hypertension was established and the patients were categorized into various stages of hypertension according to JNC-VII report. Patients who were having history of secondary hypertension, diabetes, hypothyroidism, hyperparathyroidism, pregnancy induced hypertension, ischemic heart disease, congestive cardiac failure, obesity (body weight exceeding 25% of ideal weight), alcohol abuse, renal insufficiency, glomerulonephritis, pyelonephritis, hereditary nephropathy, gout, lymphoproliferative or myeloproliferative disorders etc. Patients on management with drugs altering uric acid levels such as thiazides, loop diuretics, pyrazinamide, allopurinol, levodopa, ethambutol, cytotoxic drugs etc. were also excluded from this study. General physical examination including height and weight and systemic examination was recorded. Body mass index (BMI) was calculated manually using formulae weight (kg)/(height(meter)). Relevant laboratory investigations (blood fasting sugar, urea, creatinine, liver function test, lipid profile) were also recorded from the medical record. Essential hypertension was diagnosed in the absence of an identifiable cause. The patients were categorized into the various stages of hypertension as per the JNC-VII report. Blood pressure was noted as the average of 2 or more readings at each of the 2 or more visits or on alternate days in admitted patients. Hyperuricemia was defined as the serum uric acid >7.0 mg/dl in adult males, >6.0 mg/dl in adult females. Blood samples were taken in the early morning venous blood sample after the patient is kept fasting for 12 hours. Serum uric acid was measured by photometric method in clinical chemistry Medsource C Sense 100 automatic analyzer.

Statistical analysis

All the data obtained from the patients of the study group was put in Microsoft excel sheet. Data was summarized and analyzed using appropriate statistical techniques via Statistical package for social sciences (SPSS) software. Data were expressed in mean±standard deviation (SD). Parametric data were analyzed using t-test and one-way ANOVA. P value less than 0.05 were considered significant.

III. RESULTS

In this case control study, cases and controls were in the ratio of 1:1. Cases versus controls were closely matched as per their age, mean age in cases was (50.74) years whereas in controls it was (48.12) years (Table 1).

Table 1: Age distribution in two groups.

Age	Case (n=70)	Control (n=70)	p-value
Age (years) (Mean±SD)	50.74±9.41	48.12±8.11	>0.05

Out of 70 cases, 33 (47.14%) were male patients and 37 (52.86%) were female patients. Among the controls, 39(55.71%) were males whereas 31(44.29%) were female patients. Gender distribution was equal among groups. Mean BMI in cases was 24.04 kg/m² whereas it was 24.37 kg/m² in case of controls which was comparable among the two groups.

Overall mean systolic BP in cases was 170 mmHg and mean diastolic BP was 103 mmHg. Among controls overall mean systolic BP was 116 mmHg and mean diastolic BP was 75 mmHg. Cases were further grouped into stages according to JNC VII criteria of BP staging.

Overall, 23(32.86%) patients were grouped in stage 1.39(55.71%) patients in stage 2 and 8 (11.43%) patients in isolated systolic hypertension (ISH). Maximum patients were in stage 2 among both males (60.60%) and females (51.35%) (Table 2)

Table 2: Gender distribution in the three hypertensive stage as per JNC VII criteria.¹⁷

Stages of hypertension	Number of patients (%)		
	Males (n=33)	Females (n=37)	Total (n=70)
Stage 1	9 (27.27)	14(37.84)	23 (32.86)
Stage 2	20 (60.60)	19(51.35)	39 (55.71)
Isolated systolic	4 (12.12)	4(10.81)	8 (11.43)

Mean systolic and diastolic blood pressure in stage 1 was 147.22 mmHg and 95.21 mmHg. In stage 2 it was 187.07 mmHg and 113.11mmHg respectively. In ISH systolic BP was 147.85 mmHg and diastolic BP was 86.12 mmHg (Table 3).

Table 3: Mean blood pressure comparison between three hypertensive stage as per JNC VII criteria.¹⁷

Stages of hypertension	Mean±Standard Deviation	
	Systolic BP	Diastolic BP
Stage 1	147.22±6.33	95.21±3.12
Stage 2	187.07±11.36	113.11±4.87
Isolated systolic	147.85±10.87	86.12±3.14
P value	<0.0001	<0.0001

Among cases the range of serum uric acid level in males was 1.90-11.70 with mean value of 7.31 whereas in females range of serum uric acid level was 1.31-10.80 with mean value of 7.14. Overall mean value of cases was 7.22.

Among controls the range of serum uric acid level in males was 2.40-5.30 with mean value of 4.51 whereas in females range of serum uric acid level was 1.70-6.30 with mean value of 4.09. Overall range in levels of serum uric acid in controls was 1.71-6.31 with a mean value of 4.28 (Table 4).

Table 4: Gender based comparison of Serum uric acid level among cases and control group

Groups	Cases		Control		P value
	Range	Mean±SD	Range	Mean±SD	
Males	1.90-11.70	7.31±2.48	2.40-5.30	4.51±0.81	<0.0001
Females	1.31-10.79	7.14±2.29	1.70-6.30	4.09±1.12	<0.0001
Total	1.29-11.50	7.22±2.38	1.71-6.31	4.28±0.88	<0.0001

Overall mean serum uric acid levels in stage 1 hypertension was 6.52 mg/dl, in stage 2 it was 7.83 mg/dl and in ISH it was 6.22 mg/dl. Thus, the patients with higher value of blood pressure have higher levels of serum uric acid levels with stage 2 HTN having higher levels of uric acid than stage 1 HTN (Table 5).

Table 5: Comparison of mean serum uric acid level among three hypertensive stage as per JNC VII criteria.¹⁷

Stages of hypertension	Mean±Standard deviation		
	Males (n=24)	Females (n=26)	Total (n=50)
Stage 1	6.59±3.76	6.27±2.81	6.52±3.12
Stage 2	7.64±1.94	7.76±1.87	7.83±1.79
Isolated systolic	6.10±1.48	6.43±2.84	6.22±2.22
p value	0.452	0.268	0.109

Table 6: Comparison of mean serum uric acid level with duration of hypertension

Stages of hypertension	Number of patients (%)		P value
	<5 years (n=14)	>5 years (n=56)	
Stage 1	6.29±4.05	6.57±2.79	0.854
Stage 2	6.61±2.07	8.04±1.79	0.039
Isolated systolic	5.40±1.20	6.57±2.51	0.148

Out of 70 cases, 14 patients had HTN of less than 5 years duration out of which 8 were included in stage 1, 5 in stage 2, and 2 in ISH. Remaining 56 patients had HTN of greater than 5 years duration, out of which 13 were included in stage 1, 36 in stage 2 and 7 in ISH. Among patients with less than 5 years of duration of HTN, serum uric acid levels in stage 1 were 6.29 mg/dl, in stage 2 it was 6.61 mg/dl and in ISH the levels were 5.40 mg/dl. Among patients with greater than 5 years of duration of HTN, serum uric acid levels in stage 1 were 6.57 mg/dl, in stage 2 it was 8.04 mg/dl and in ISH the levels were 6.57 mg/dl. Thus, the patients with more duration of HTN have higher levels of serum uric acid. Levels of uric acid correlate with the duration and severity of blood pressure with stage 2 HTN having higher levels of uric acid than stage 1 (Table 6).

IV. DISCUSSION

Hyperuricemia is commonly associated with hypertension. Serum uric acid has been closely linked to the development of hypertension and that it might be a marker of susceptibility or an intermediate step in the pathway leading to hypertension. Present study was carried out to assess the serum uric acid levels in essential hypertension and its correlation with the severity and known duration of hypertension. In our study, mean age in cases was 50.74 years whereas in controls it was 48.12 years. Out of 70 cases, 33 (47.14%) were male patients and 37 (52.86%) were female patients. Among the controls, 39 (55.71%) were males whereas 31 (44.29%) were female patients. Our study is closely matching as per age and gender distribution to the study of Reddy et al and Poudel et al.^{18,19} Mean age of our study patients was also similar to the study conducted by Eisen et al and Grayson et al.^{20,21} In our study, mean serum uric acid levels in cases was 7.22 mg/dl. Study conducted by Razak et al found the mean serum uric acid value of 8.03 mg/dl which was higher than our study. This difference is mainly due to majority of patients in their study were non-vegetarian by dietary habits while our state has mixed population who are both vegetarian and non-vegetarian by diet.²² Study done by Vishnu et al on Kerala population found the serum uric acid levels lower than our study, this difference may be due to mainly non vegetarian and pulse diet habits in our community while south Indians are mostly vegetarian by diet.²³ In our study, cases were further grouped into categories as per blood pressure according to JNC VII criteria of BP staging. Mean systolic blood pressures recorded in stage 1 hypertension, stage 2 hypertension and the isolated systolic hypertension in our study were in accordance with study of Vishnu et al and Ankit et al.^{23,24} The patients with higher value of uric acid levels have higher blood pressure with stage 2 HTN having higher levels of uric acid than stage 1 HTN. The results were similar to the study done by Tykarski et al.²⁵ The patients with more known duration of HTN had higher levels of serum uric acid as in the studies conducted by Neki et al found significant increase in serum UA levels in patients with increased known duration of hypertension.²⁶

It has been recently suggested that since uric acid may play a role in the formation of free radicals and oxidative stress which increase the risk of hypertension in subjects with raised serum uric acid levels. Besides, the longer duration and severity of hypertension lead to renal dysfunction in the form of nephrosclerosis leading to higher levels of serum uric acid.²⁷ Therefore increased uric acid levels could lead to increase in HTN and HTN in long term may lead to increased uric acid levels by renal dysfunction. So serum uric acid may be a powerful tool to help identify patients at high risk of hypertensive diseases. It is therefore prudent to ponder serum uric acid along with other risk factors, such as obesity and hyperglycemia, in the assessment of overall hypertensive risk.

The remaining key questions, which need to be explored, are whether uric acid has a causal role in hypertension, whether a reduction of uric acid level could achieve prevention of hypertensive complications, cardiovascular, and whether uric acid could be reduced to an optimal level whereby it no longer imposes an increased risk for essential hypertension. Uric acid lowering drugs may have additional benefit in controlling HTN as has been shown in some studies (Assadi et al and Shibagaki et al).^{28,29} Therefore the study of serum uric acid levels in HTN requires more further studies for better assessment of risk and control of HTN. In limitations, our research was conducted on limited population, whether the results may be generalized to other populations with different cultural and dietary backgrounds requires further study. Study group was small. It was an observational one point study.

V. CONCLUSION

Thus, based on the present study, we concluded that the serum uric acid is significantly elevated in hypertensive as compared to normotensive individuals. Hyperuricemia was present equally among both gender in stage II hypertensive patients and were higher in patients with prolong hypertension. So, serum uric acid can be used probably as an early biochemical marker to determine the severity of hypertension as stage 2 hypertensive had more elevation in serum uric acid levels as compared to other hypertensive patients. The levels of uric acid in individuals would prompt clinician to check the blood pressure resulting in early diagnosis and necessary intervention to treat hypertension at an early stage and effect of lowering of serum uric acid level in treating hypertension need to be studied.

REFERENCE

- [1]. Colledge NR, Walker BR, Ralston SH, editors. Davidson's principles and practice of medicine. 21st ed. Edinburg: Elsevier Churchill Livingstone; 2010.
- [2]. Kuroczycka-Saniutycz E, Wasilewska A, Sulik A, Milewski R. Urinary angiotensinogen as a marker of intrarenal angiotensin II activity in adolescents with primary hypertension. *PediatrNephrol*. 2013;28:1113–1119.
- [3]. Zhou X, Matavelli L, Frohlich ED. Uric acid: its relationship to renal hemodynamics and the renal reninangiotensin system. *CurrHypertens Rep*. 2006;8:120–124.
- [4]. BabinskaK, Kovacs L, Janko V, Dallos T, Feber J. Association between obesity and the severity of ambulatory hypertension in children and adolescents. *J Am SocHypertens*. 2012;6:356–363.
- [5]. Yoo TW, Sung KC, Shin HS, Kim BJ, Kim BS, Kang JH, et al. et al. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. *Circ J*. 2005;69:928–933.
- [6]. Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. *J Hypertens*. 2008;26:269–275.
- [7]. Higashi Y, Kihara Y, Noma K. Endothelial dysfunction and hypertension in aging. *Hypertens Res*. 2012;35:1039–1047.
- [8]. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. *J Am SocNephrol*. 2005;16:3553–3562.
- [9]. SwalesJD. Manual of hypertension. Oxford:Blackwell Science. 1995.
- [10]. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, Lan HY, Kivlighn S, Johnson RJ: Elevated uric acid increases blood pressure in the rat by a novel crystalindependent mechanism. *Hypertension* 2001; 38: 1101 –1106.
- [11]. Jossa F, Farinaro E, Panico S, Krogh V, Celentano E, Galasso R, et al. Serum uric acid and hypertension: the Olivetti heart study. *J Hum Hypertens*. 1994;8:677–81.
- [12]. Brand FN, McGee DL, Kannel WB, Stokes 3rd J, Castelli WP. Hyperuricemia as a risk factor of coronary heart disease: the Framingham study. *Am J Epidemiol*. 1985;121:11–8.
- [13]. Kansui Y, Ohtsubo T, Goto K, Sakata S, Ichishima K, Fukuhara M, et al. Association of serum uric acid with blood pressure in Japanese men. Cross-sectional study in work-site group. *Circ J*. 2011;75:2827–32.
- [14]. Zhang W, Sun K, Yang Y, Zhang H, Hu FB, et al. Plasma uric acid and hypertension in a Chinese community: prospective study and metaanalysis. *ClinChem* 2009;55: 2026-2034.
- [15]. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003;41: 1183-1190
- [16]. 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.
- [17]. Chobanian AV, Bakris GL, Black HR. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206- 52.
- [18]. Reddy RP, Monigari N, Hande M. Study of Serum Uric Acid in Essential Hypertension. *International J Sci Res Pub*. 2015;5(8):1-12.
- [19]. Poudel B, Yadav BK, Kumar A, Jha B, Raut KB. Serum uric acid level in newly diagnosed essential hypertension in a Nepalese population: A hospital based cross sectional study. *Asian Pacif J Trop Biomed*. 2014,4(1):59-64.
- [20]. Eisen A, Benderly M, Goldbourt U, Haim M. Is serum uric acid level an independent predictor of heart failure among patients with coronary artery disease? *Clin Cardiol*. 2013;36:110-6.
- [21]. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2011;63:102-10.
- [22]. Al- Sharifi ZAR, Al-Gebouri HG. Uric Acid and Endothelial Dysfunction in Essential Hypertension. *Karbala J Med*. 2010;4(3):914-8.

- [23]. Vishnu RS, Dash LK, Murmu M. Observation of Serum Uric Acid levels in essential hypertension. Kerala Med J. 2013;6(3):65-70.
- [24]. Vakil A, Vrkaraya P, Barafiwala V, Gamit K, Patel D, Nilesh D. Study of Serum Uric Acid Level in Hypertension. J Den Med Sci. 2017;16(4):69-73.
- [25]. Tykarski A. Evaluation of renal handling of uric acid in essential hypertension; hyperuricemia related to decreased urate secretion. Nephrol. 1991;59(3):364- 8.
- [26]. Neki NS, Tamilmani. A Study of Serum Uric Acid level in Essential Hypertension. JIMSA. 2015;28(1):13.
- [27]. Messerli FH, Frohlich ED, Dreslinski GR. Serum Uric Acid in Essential Hypertension: an indicator of renal vascular involvement. Ann Intern Med. 1980;93:817-21.
- [28]. Assadi F. Allopurinol enhances the blood pressure lowering effect of enalapril in children with hyperuricemic essential hypertension. J Nephrol. 2014;27:51-6.
- [29]. Shibagaki Y, Ohno I, Hosoya T, Kimura K. Safety, efficacy and renal effect of febuxostat in patients with moderate-to-severe kidney dysfunction. Hypertens Res. 2014;37:919-25.