

A Study of Correlation between Essential Hypertension and Hyperuricemia

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Research Article

Abstract: Aim: Aims of study were Comparison of serum uric acid between hypertensive and healthy subjects with Correlation of serum uric acid in relation to duration of essential hypertension. **Material and Method:** 100 patients with essential hypertension and 50 apparently healthy subjects were included in study. Sera were collected from them and measure serum uric acid with Uricase-Peroxidase method on automated chemistry analyzer. Unpaired T-test was used to assess the significant difference in the means of the studied variables in the different groups. **Results:** The mean level of Serum Uric Acid is higher in patients with essential hypertension comparing with the control group (5.0 ± 1.3 vs 4.4 ± 0.9 , $p < 0.001$). **Conclusion:** Hyperuricemia can be used as a simple biochemical marker in determining the severity and duration of hypertension. Hyperuricemia is associated with the duration of hypertension. As the duration increases the serum uric acid increases.

Key Words: Hyperuricemia, Hypertension, Serum Uric Acid.

Introduction

Hypertension is a major health burden and leading cause of death in the world. Although it is common in economically developed countries, than in developing countries, it is a greater population burden in the latter because of much larger population¹. The Asia Pacific cohort studies collaboration clearly demonstrated the log linear relationship of blood pressure with ischemic & hemorrhagic stroke, ischemic heart disease, congestive cardiac failure, renal insufficiency, obstructive sleep apnoea and cardio vascular death¹. Association between hypertension and hyperuricemia was recognized when a family with a unique and unfortunate pedigree attended Hammer Smith hospital in 1957. The father and six of the seven siblings had hyperuricemia, while the mother and all the siblings had hypertension². This raised the question whether a raised serum uric acid was common in patients with hypertension. Raised serum uric acid has been reported to be associated with an increased risk of coronary heart disease and is commonly encountered with essential hypertension, even untreated hypertension, and type II diabetes, which are in turn associated with coronary heart disease. It is not known whether raised

serum uric acid increases the risk of hypertension and type II diabetes independently of known risk factors such as age, obesity, alcohol consumption, and physical activity³. Uric acid is powerful risk marker seen in untreated hypertensives⁴. It is an independent predictor of mortality in patients with coronary heart disease⁵. A 10-year follow-up data demonstrated that increasing quartiles of serum uric acid are associated with incident hypertension in a dose dependent manner⁶. The strength of association between uric acid and future risk of HTN is so great that it has been proposed as a target for treatment to prevent the development of hypertension⁷. A direct relationship was found between blood pressure and uric acid, with a 10 mmHg blood pressure increase for each 0.5 mg/dl incremental rise in serum uric acid⁸. Uric acid induces renal vasoconstriction mediated by endothelial dysfunction with reduced Nitric acid level and activation of Renin Angiotensin System. This induces hypertension⁹. Uric Acid stimulates vascular smooth muscle cell proliferation mediated by stimulation of mitogen-activated protein kinase, cyclooxygenase 2, platelet derived growth factor. So elevated uric acid predicts severity of Heart failure and need for heart transplantation in patients with chronic heart failure¹⁰. Messerli et al.¹¹ found in a study that mild asymptomatic hyperuricemia is associated with decreased renal blood flow, without affecting glomerular filtration rate. Increased renal vascular and systemic hypertensive vascular disease paralleled the raising serum uric acid levels. These suggest that unexplained hyperuricemia in patients with hypertension most likely reflect early renal vascular involvement. Increased sympathetic out flow alter renal sodium handling by increasing arterial pressure, decreased blood flow and decreased uric acid excretion. This increases S. UA. Raised UA increases purine oxidation and reactive oxygen species and Angiotensin receptor activation. All these leads to hypertensive vascular injury. There is positive correlation

between serum uric acid, cholesterol, triglyceride and index of body size¹². SUA was directly related to body mass index(BMI), creatinine, triglyceride, LDL cholesterol, components of metabolic syndrome and inversely proportional to HDL cholesterol. There is significant association of SUA with preclinical Target organ damage namely LVH, carotid atherosclerosis, microalbuminuria, in untreated essential hypertensive patients regardless of other cardiovascular risk factors¹³. Indeed, recently soluble uric acid has been recognized to not be inert but rather to have several pro-inflammatory & antioxidant features⁶ that could either be beneficial or detrimental to humans. Therefore, the aim of our study was to measure the serum concentrations of uric acid in a group of essential hypertensive patients with no clinical signs of associated pathologies or organ damage and no family histories of coronary or cerebrovascular atherosclerotic disease and to find out whether raised serum uric acid levels were correlate with duration and severity of hypertension.

Materials and Methods

The study was undertaken at Shree Sayajirao General Hospital and Medical College, Vadodara. The study parameters were analyzed at Clinical Chemistry Laboratory of Biochemistry Department of Medical college and S.S.G Hospital, Baroda. The subjects selected for study were grouped as follows:

Group I – Control group (n=50)

This group consisted of age and sex matched non-hypertensive subjects. They were free from any major ailment which could affect the parameters under study (No clinical history or investigative result showing involvement of any organ). They were taken from medical or paramedical staff, attendants of patients, indoor patients with status unrelated to hypertension (e.g. hernia, fractures etc.), persons coming to hospital for fitness purpose and outdoor patients of minor illness (e.g. common cold). Patients who come for health check-up were also included after taking proper history.

Group II – Essential hypertension patients (n=100)

Inclusion criteria:

1. Healthy normotensive subjects and Hypertensive subjects who were on anti-hypertensive therapy.
2. Age group 20 to 60 years and gender for appropriate match to avoid bias.
3. All biochemical and hematological investigations should be in normal limit.
4. Hypertension was diagnosed when on atleast 3 separate occasions:

Systolic Blood Pressure \geq 140 mmHg

Diastolic Blood Pressure \geq 90 mmHg

Exclusion Criteria:

The following patients were excluded from the study:

1. Patients with accelerated / Malignant Hypertension
Systolic Blood Pressure > 180 mmHg
Diastolic Blood Pressure >110 mmHg
2. Patients with secondary hypertension.
3. Patients with either of the following associated disease conditions:
 - a. CHF/Grade III retinopathy.
 - b. History of Stroke.
 - c. History of MI within 6 months.
 - d. History of Angina within 2 years.
 - e. Diabetes Mellitus (FBS>140 mg/dl).
 - f. History of Chronic infections, TB, Leprosy.
 - g. Familial hyperlipidemia.
 - h. History of hypersensitivity.
 - i. Abnormal kidney function.
 - j. Endocrine disease.
 - k. Pregnancy and lactation.
 - l. Gout.
 - m. History of Alcohol abuse.
 - n. Pre-eclampsic toxemia.
 - o. Patients on drugs known to cause hyperuricemia, e.g. thiazide diuretics.
 - p. Patients on lipid lowering drugs
 - q. Obese patients.
 - r. Smoking

Classification of Essential Hypertension:¹⁴

Hypertension was defined according to the JNC VII classification of hypertension as those with SBP of < 120 mm Hg and DBP of < 80 mm Hg as **normal**, those with SBP of 120- 139 mm Hg or DBP of 80 - 89 mm Hg were labeled **pre-hypertensive** were not taken up for the study, those with SBP 140 -159 mm Hg or DBP of 90 - 99 mm Hg were labeled as **stage I** were labeled as having Stage 1 hypertension, and those with SBP \geq 160 mmHg or DBP \geq 100 mmHg were labeled as **Stage 2** hypertension.

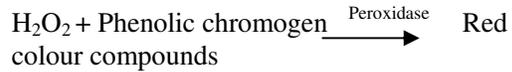
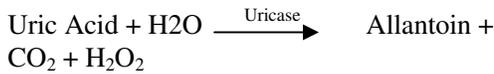
Study Design:

Informed consent of subjects included in the study was obtained for involvement in study groups and for venipuncture. After that a detailed history including personal data, present complaints and complication, treatment history, past history, family history and personal history was taken followed by thorough physical examination.

For each control/patient, overnight fasting blood sample was collected in fluoride vacutainer for FBS, EDTA vacutainer for hemoglobin and in plain vacutainer for other biochemical parameters. Urine sample was collected in universal container for albumin and sugar

estimation. Serum or plasma separated within an hour and stored at 2-8° C temperature till analysis was done.

Serum Uric Acid (URIC ACID) measure from samples with Uricase-Peroxidase method (also known as Uricase/PAP method).



Result and Analysis

The study included 50 were healthy controls and 100 were essential hypertensive patients. Data results are summarized in tables 1, 2, 3.

Table 1: Comparison of study groups

Number of patients			100	
Sex (M/F) %	26/24		51/49	
	Mean	SD	Mean	SD
Average age (years)	41	7	47	8
Average duration of HT (in year)	-	-	5	3
Average SBP	120	9	151	9
Average DBP	81	5	97	3

Table 2: Results of the control group and patients with essential hypertension

	Control (Mean ± SD)	Cases (Mean ± SD)	t value	P value
Systolic BP (mmHg)	120 ± 9	151 ± 9	42.18	<0.0001
Diastolic BP (mmHg)	81 ± 5	97 ± 3	69.40	<0.0001
Uric Acid	4.4 ± 0.9	5.0 ± 1.3	7.537	<0.0001

Table 3: Serum Uric Acid Levels Based on duration of Hypertension

Serum Uric Acid Levels Based on duration of Hypertension Duration of HT	Number of patients	Mean ± SD	t value	P value
< 5 years	37	4.8 ± 1.2	6.923	<0.0001
≥ 5 years	63	5.1 ± 1.3		

Interpretation was done according to p-value as follows:

- p<0.05—significant
- p<0.001—highly significant
- p<0.01—very significant
- p≥0.05 — not significant

Discussion

Our results revealed that the mean level of Serum Uric Acid is higher in patients with essential hypertension comparing with the control group (5.0 ± 1.3 vs 4.4 ± 0.9, p <0.001). Incidence of hyperuricemia in controls was 3% and the incidence of hyperuricemia in cases was 11%. This may give some indication about the correlation between elevated Serum Uric Acid level and hypertension. Elevated serum uric acid (SUA) levels have been associated with an increased risk for cardiovascular disease. The potential mechanisms by which SUA may directly affect cardiovascular risk include enhanced platelet aggregation and inflammatory activation of the endothelium. In few studies, the association of SUA with cardiovascular disease was uncertain after multivariate adjustment as in the Framingham Heart Study¹⁵ (1985) the association remained certain and significant. Because elevated serum uric acid is correlated with several risk

factors including renal dysfunction, hypertension, insulin resistance, hyper-homocystenemia and hyperlipidemia, it is debated whether SUA is an independent cardiovascular risk factor. Various other studies have also shown that increased SUA levels were seen in hypertensive patients. A. Breckenridge (1966) showed 274 of 470 patients on antihypertensive treatment (58%) had raised SUA levels and 90 of the 333 patients (27%) attending the clinic for the time had hyperuricemia¹⁶. Messerli et al.¹¹ (1980) had an incidence of 72 % raised SUA in their study population of 39 established hypertensives. Messerli and Frohlich et al. hypothesized that the frequent presence of hyperuricemia in hypertensive patients reflects underlying renal dysfunction or reduced renal perfusion. Three possible conclusions can be drawn from the association of hypertension with raised SUA levels -. Hypertension may arise as a result of hyperuricemia, hypertension can cause

hyperuricemia and the duration and severity of hypertension is related directly to the SUA levels.

Uric acid which plays a role in the formation of free radicals and oxidative stress, the increased risk of hypertension in subjects with raised serum uric acid levels might be associated with this increased generation of free radicals. Hence the fact that raised SUA levels can lead to Hypertension cannot be entirely ruled out. As to the possibility that Hypertension can cause hyperuricemia, it is thought that hyperuricemia can result from either overproduction of uric acid or from under excretion of uric acid. Overproduction of uric acid can be measured by the rate of incorporation of acid precursors such as Glycine labeled N 15, into the uric acid pool. Such a study carried out in 4 hypertensive patients with raised SUA levels did not show any overproduction of uric acid. In the study of Breckenridge excretion of uric acid and uric acid clearance were lower in all hypertensive patients than in the normal group. When the uric acid clearance was expressed per 100ml of glomerular filtrate, there was no significant difference between normal subjects and hypertensive patients who had normal SUA levels, but the difference between those 2 groups and the hyperuricemic hypertensives was significant and they suggested a renal tubular abnormality in the handling of uric acid, the nature of the abnormality was not clear². Later Messerli et al.¹¹ showed that hyperuricemia in hypertensive is due to early renal vascular involvement, namely, Nephrosclerosis. SUA rises because of impaired renal tubular function, which is the main site of regulation of SUA due to nephrosclerosis. In the present study incidence and severity of hyperuricemia between cases and controls correlated significantly with the severity of hypertension. The PIUMA study demonstrates a strong independent association between SUA and CV risk in initially untreated and asymptomatic adult subjects with essential hypertension, but it is unable to answer the question of whether SUA exerts direct toxic effects¹⁷.

Conclusion

Hyperuricemia can be used as a simple biochemical marker in determining the severity and duration of hypertension. Hyperuricemia is associated with the duration of hypertension. As the duration increases the serum uric acid increases.

References

1. Chiang C, Chen C. Hypertension in the Asia-pacific region. *J Hum Hypertens*.2008; 22: 441-443.
2. A. Breckenridge "Hypertension and Hyperuricemia" .*The Lancet*. 1966; 287
3. Frohlich E .Uric acid: A risk factor for coronary heart disease. *The Journal of the American Medical Association*. 1993; 270:378-379.

4. 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 : A PIUMA Study. *Hypertension*. 2000; 36:1072-1078
5. Akanda M, Choudhury K, Ali M. Serum uric acid and its association with coronary artery disease.*J Cardiovasc*.2012.5(1):12-17.
6. Shankar A, Klein B, Klein R, Neito F .The association between serum uric acid level and long term incidence of hypertension: population-based cohort study. *J Hum Hypertens*.2006; 20(12): 937-945.
7. Reynolds T. Serum Uric Acid, the endothelium and hypertension: an association revisited. *J Hum Hypertens*.2007; 2: 591 – 593.
8. Mazzali M, Hughes J, Kim Y, Jefferson A, Kang D, Gordon K, Lan H, Kivlighn S, Johnson R. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension*. April 2001. 38: 1101-1106
9. Johnson R, Feig D, Acosta J, Kang D. Resurrection of uric acid as a causal risk factor in essential hypertension. *Hypertension* 2005; 45: 18-20.
10. Johnson R, Kang D, Feig D, Kivlingn S, Wantabe S, Tuttle K, Iturbe B, Acosta J, Mazzali M. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease?. *Hypertension*. 2003; 41: 1183-1190.
11. Messerli F, Forhlich E, Dreslinski G, Suarez D, Aristimuno G. Serum uric acid in essential hypertension: An indicator of renal vascular involvement. *Ann Intern Med*. 1980; 93: 817-821.
12. Benedek T .Correlations of serum uric acid and lipid concentrations in normal, gouty and atherosclerotic men. *Ann Int Med*.1967; 66: 851-861.
13. Viazzi F, Parodi D, Leoncini G, Parodi A, Falqui V, Ratto E, Vettoretti S, Bezante G, Sette M, Deferrari G, Pontremolial R. Serum uric acid and target organ damage in primary hypertension. *Hypertension*.2005; 45: 991-996
14. Anand P.JNC 7 guidelines and Indian scenario.*CME*.2004;139-144
15. Brand F, Kannel W, McGee D, Stokes J, Castelli W. Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. *Am J Epidemiol*1985; 121: 11-18.
16. 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 : A PIUMA Study. *Hypertension*. 2000; 36:1072-1078

Abbreviations:

SUA	Serum Uric Acid
CVD	Cardiovascular disease
FBS	Fasting blood sugar
HDL	Hi density lipoprotein
HT	Hypertension
LDL	Low density lipoprotein

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