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**Kirankumar Meti**  
Assistant professor, Dept of  
General Medicine, SDM  
Medical College, Dharwad,  
Karnataka.

**Jagadeesh Gaddeppanavar**  
Senior Resident, Dept of  
General Medicine, Gadag  
Institute of Medical sciences  
Gadag, Karnataka.

**Aravind Karinagannanavar**  
Assistant professor, Dept of  
Community Medicine, Mysore  
Medical College and Research  
Centre, Mysore, Karnataka.

**Shashikantha**  
Dept of General Medicine,  
Adichunchanagiri Institute of  
Medical Sciences, B.G.Nagara,  
Nagamangala, Karnataka.

**Girish I**  
Dept of General Medicine,  
Basaveshwar Medical College,  
Chitradurga, Karnataka.

#### Correspondence

**Aravind Karinagannanavar**  
Assistant professor, Dept of  
Community Medicine, Mysore  
Medical College and Research  
Centre, Mysore, Karnataka.

## Estimation of serum uric acid level in essential hypertension and its correlation with severity and duration of hypertension

**Kirankumar Meti, Jagadeesh Gaddeppanavar, Aravind Karinagannanavar, Shashikantha, Girish I**

#### Abstract

**Back ground:** The association of raised serum uric acid levels with various cardiovascular risk factors has often led to the debate of whether raised serum uric acid levels could be an independent risk factor in essential hypertension. Hence we carried out a study to examine the possibility of hyperuricemia causing hypertension, to see if there is a relationship between the serum uric acid levels and severity & duration of hypertension.

**Objectives:** 1.To study the relationship between serum uric acid levels and hypertension. 2 To study the association of serum uric acid level to Severity and Duration of essential hypertension.

**Methodology:** The study was carried out in Sri Adhichunchungiri institute of medical science the study period was of 18 months from August 2011 to February 2013 a total of 200 patients were studied of which 100 were cases and 100 controls. The patients were included if they satisfied the JNC VII criteria for hypertension. They were excluded if they were having any other condition known to cause raised serum uric acid levels & secondary hypertension.

**Results:** The study showed that serum uric acid levels were raised in patients with hypertension in comparison to normotensives. The Mean SUA levels between cases and controls were  $6.29 \pm 1.1$  and  $4.0 \pm 0.9$  mg/dl respectively. t-value= 15.47, p - value <0.0001. The mean serum uric acid levels in hypertensive patients with different age group ie 40-49; 50-59; 60-70 years of age was  $6.42 \pm 1.49$ ;  $6.87 \pm 1.36$ ;  $7.0 \pm 1.31$ mg /dl respectively. The mean serum uric acid levels in male hypertensive's was  $6.5 \pm 1.1$ mg/dl and female hypertensive's was  $6.1 \pm 1.1$ mg/dl SUA levels in the severity of hypertension showed a mean serum uric acid level in hypertensive's with SBP 140-159 and DBP 90-99 mm Hg of  $5.4 \pm 0.9$  mg/dl and in those with blood pressure  $\geq 160/100$  mm Hg  $7.0 \pm 0.6$  mg /dl the t-value of 10.6 and p- value <0.001 which was significant. SUA level in patients with hypertension < 5 years was  $5.7 \pm 1.3$ mg/dl those with  $\geq 5$  years was  $7.2 \pm 1.1$  t-value of 10.3, p-value < 0.001 which was also significant.

**Conclusion:** Serum Uric Acid can be used as an early biochemical marker to determine the severity and duration of hypertension.

**Keywords:** Serum Uric Acid, Hypertension, JNC VII, Hyperuricemia.

#### Introduction

Uric acid, which serves no biochemical function other than being an end product of purine metabolism, was first discovered in 1776. A Swedish chemist Scheele isolated it from a urinary tract stone. In 1797, a British chemist Wallaston detected uric acid in a tophus which was removed from his own ear. About 50 years later Alfred Baring Garrod, a British physician showed by chemical isolation that uric acid was abnormally high in gouty patients. In subsequent studies Garrod formulated a rational relationship between hyperuricemia and symptomatology of gouty patients. 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 hypertension [1]. This raised the question whether a raised serum uric acid (SUA) 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 2 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 2 diabetes independently of known risk factors such as age, obesity, alcohol consumption, and physical activity [2]. Estimation of serum uric acid in hypertensive patients is a simple but reliable means by which additional information regarding the severity and duration can be obtained.

**Objectives**

1. To study the relationship between serum uric acid levels and hypertension.
- 2 To study the association of serum uric acid level to Severity and Duration of essential hypertension.

**Methodology**

**Source of data:** Patients attending Sri Adichunchanagiri Institute of Medical Sciences as in patients and out patients

**Type of Study:** Descriptive Study

**Study design:** Case series study.

**Sample size:** The study population comprised of 100 patients fulfilling inclusion criteria as cases and 100 normotensive subjects as control.

**Study Period:** This study conducted for duration of 18 months from August 2011 to February 2013

**Sampling Technique:** Non Probability purposive sampling

**Inclusion criteria**

All patients between 40-70 years of age with essential hypertension of both the genders will be included in the study as cases.

The diagnosis of essential hypertension is established according to JNC 7 criteria [3]

Normotensive subjects as control

**Exclusion criteria**

Patients with Diabetes, hypothyroidism, hyperparathyroidism, Ischemic heart disease, congestive cardiac failure, Gout, Obesity (BMI > 25kg/m2), Alcohol abuse, Renal insufficiency, glomerulonephritis, pyelonephritis, hereditary nephropathy, Drugs causing hyperuricemia– Levodopa, Ethambutol, Pazinamide, Nicotinic acid Cytotoxic drugs, low dose aspirin, Thiazide diuretics.

Controls were patients without hypertension or any other condition known to cause hyperuricemia and were matched for age and sex with that of the cases.

**Method of Data collection and measurements**

The clinical examination consisted of a medical history, a physical examination, blood pressure measurement, anthropometric measurements, measurement of fasting serum uric acid levels and other parameters like Blood haemogram, Renal function tests (blood urea, serum creatinine), Electrocardiogram, Chest X-ray, Lipid profile (Total cholesterol, triglycerides, HDL- cholesterol, LDL- cholesterol), urine for protein and sugar. Renal artery Doppler, urinary vanillil mandelic acid and metanephrine

levels to rule out secondary hypertension in suspected cases of secondary hypertension.

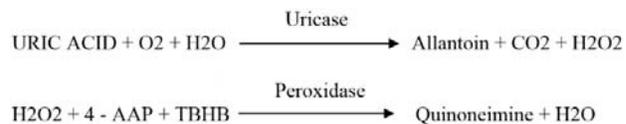
The patients were asked to fast for 12 hours and to avoid smoking and heavy physical Exersice for more than 2 hours before the examinations. After a 5 min rest in a quiet room, systolic and diastolic blood pressures were measured in the sitting position twice at an interval of a few minutes on the right arm with a standard mercury sphygmomanometer on three separate occasions. Anthropometric measurements included height and body weight, which were measured while the subject was wearing light clothing without shoes. The body mass index was calculated as the weight in kilograms divided by the height in m<sup>2</sup>.

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 having Stage 1 hypertension, and those with SBP ≥ 160 or DBP ≥ 100 mm hg were labeled as Stage 2 hypertension.

**Method of Uric Acid estimation**

**Principle**

The principle for the determination of Serum Uric Levels was devised by Trivedi and Kabasakalian with a modified Trinder peroxidase method using TBHB.



The intensity of chromogen (Quinoneimine) formed is proportional to the uric acid concentration in the sample when measured at 510 nm (510 -550nm).

**Table 1:** Reagent Composition

<b>Reagent 1 Uric Acid Reagent</b>	
Active Ingredient	Concentration
4- Aminoantipyrine	0.5 mmol/L
TBHB	1.75 mmol/L
Uricase (Bacillus Sp.)	> 120 U/L
Peroxidase ( Horseradish)	> 500 U/L
Tris Buffer ( ph 8.25 ± 0.1 at 200C)	50 mmol/L
<b>Reagent 2 - uric acid standard</b>	
Uric Acid Standard	6 mg/dl

**Sample**

The Sample used was unhemolyzed serum or plasma separated from the cells as soon as possible. Recommended anticoagulants are heparin and EDTA. Uric acid is stable in serum or urine for 3 days at 20 – 25 °C.

**Table 2:** Assay Procedure

Pipette into tubes marked	Blank	Standard	Sample
Working Reagent	1000 µl	1000 µl	1000 µl
Distilled Water	20 µl	-	-
Standard	-	20µl	-
Sample	-	-	20 µl

Mix and incubate for 5 minutes at 37 °C. Read the absorbance of standard and each sample at 510 nm (500 -

550 nm) or 510/630 nm on biochromatic analysers against reagent blank.

**Calculations**

$$\text{Uric acid (mg/dl)} = \frac{\text{Absorbance of sample} \times \text{concentration of standard}}{\text{Absorbance of standard standard (mg/dl)}}$$

**Linearity**

Upto 25mg/dl (1.5 mmol/L). For higher values, it is recommended to dilute the samples with normal saline, and repeat the assay. Multiply the results with dilution factor.

**Notes**

1. The color developed is stable for 15 minutes.
2. The reagent and sample volume may be altered proportionally to accommodate various analyzer requirements.
3. Specimens with Uric acid concentration greater than 1.5 mmol/L should be diluted with saline and reassayed. Multiply results by dilution factor.
4. S.I. unit conversion factor, mmol/L x 16.8 = mg/dl.

**Reference Values for SUA levels**

In Males: 3.4 - 7.0 mg/dl  
 In females: 2.4 - 6.0 mg/dl

**Plan of Analysis / Statistical Tools:** The data will be entered in excel and analyzed using Epi-info Software version 3.4.3. Descriptive statistics like frequencies and percentages were calculated. Ethical clearance certificate was obtained by Ethical Committee of the Sri Adichunchanagiri Institute of Medical Sciences before the study is started.

**Results**

The study was conducted from August 2011 to February 2013 a total of 200 patients were studied of which 100 patients were cases and 100 were controls who were patients without hypertension or any other condition known to cause raised serum uric acid levels.

**Table 3:** Age and sex distribution of cases and controls

Age (in years)	CASES (100)	CONTROLS (100)
40- 49	35	35
50- 59	23	23
60- 70	42	42
<b>Gender</b>		
Male	50	50
Female	50	50

The total number of male cases was 50 and the total no of female cases 50. The age group ranged from 40 years to 70 years. The total number of male controls was 50 and the total no of female controls were 50. The age group ranged from

40 years to 70 years. The controls were adjusted with the cases for age and sex.

**Table 4:** Serum uric acid levels and age of the hypertensive's

Age of the hypertensive's (In years)	Mean serum uric acid level ± SD
40-49	6.42±1.49
50-59	6.87±1.36
60-70	7.0± 1.31

In the present study the mean serum uric acid levels in hypertensive patients with different age group ie 40-49; 50-59; 60-70 years of age was 6.42±1.49; 6.87±1.36; 7.0± 1.31mg /dl respectively. This shows serum uric acid levels are higher in elderly hypertensive's than younger hypertensive's.

**Table 5:** Serum uric acid levels according to gender in Cases and Controls

	Cases (50)	Controls (50)
Males with Hyperuricemia	31(62%)	4 (8%)
Females with Hyperuricemia	30 (60%)	2 (4%)

**Table 6:** Mean of Serum uric acid levels according to gender in Cases and Controls

	Cases (50)	Controls (50)	t value	p value
Males with Hyperuricemia	6.5±1.1	4.3±1.0	10.46	<0.001
Females with Hyperuricemia	6.1±1.1	3.7±0.7	13.01	<0.001
Combined male and female	6.3±1.1	4.1±0.9	15.47	<0.001

The Serum Uric Acid levels in male cases ranged from 4.3 mg/dl to 8.6 mg/dl and female cases ranged from 3.7 mg/dl to 8.1 mg/dl. The Serum Uric Acid levels in male controls ranged from 3.2 – 7.6mg/dl and female controls ranged from 2.4 - 6.4mg/dl.

The mean Serum uric acid level in male hypertensive's was 6.5 mg/dl with a standard deviation of 1.1 (6.5 ± 1.1) and in female hypertensive's it was 6.1mg/dl with standard deviation of 1.1 (6.1 ± 1.1). Mean serum uric acid in combined (male + female) hypertensive's was 6.3 mg/dl with standard deviation 1.1. The total number of controls were 100 (both male and female), the data analyzed showed a mean SUA level in male controls 4.3 mg/dl with standard deviation 1 (4.3 ±1) and female controls 3.7 mg/dl with standard deviation 0.7 (3.7 ± 0.7), combined (male + female) 4.1 mg/dl with standard deviation 0.9. The t-value was found to be 15.47 and the p value <0.0001 which was highly significant. This showed that there was a significant rise in serum uric acid levels in patients with hypertension when compared to normotensive.

**Table 7:** Serum uric acid level and severity of hypertension in Males

Severity of Hypertension	No. of cases	No. of Hyperuricemics	Percentage	Mean ± SD
Group A	23	4	17	5.6±0.7
Group B	27	27	100	7.3±0.5
t value = 9.9 p value < 0.001 HS				

**Table 8:** Serum uric acid level and severity of hypertension in Female

Severity of Hypertension	No. of cases	No. of Hyperuricemics	Percentage	Mean ± SD
Group A	19	1	5	5.1±0.8
Group B	31	29	94	6.7±0.5
t value = 8.7 p value < 0.001 HS				

**Table 9:** Serum uric acid level and severity of hypertension in both gender combined

Severity of Hypertension	No. of cases	No. of Hyperuricemics	Percentage	Mean ± SD
Group A	42	5	12	5.4±0.9
Group B	58	56	97	7.0±0.6
t value = 10.6 p value < 0.001 HS				

Hypertensive cases were divided into two groups, Group A with systolic blood pressure between 140-159 mmHg and DBP 90-99 mmHg and Group B with blood pressure ≥ 160/100mm Hg measured at the time of presentation. In the present study the total number of patients in Group A was 42 patients (both male and female patients), the total number of patients in Group B was 58 (both male and female patients). The data analysis for SUA levels in the Groups showed a mean serum uric acid level in Group A hypertensive patients

was 5.4 mg/dl with a standard deviation of 0.9 ( 5.4±0.9 ). The mean serum uric acid levels in Group B hypertensive patients was 7.0 mg/dl with a standard deviation of 0.6 (7.0±0.6). The t-value was 10.61 and a p-value of <0.001 which was highly significant. The data analyzed showed that there was a significant rise in serum uric acid level in patients who were having blood pressure of ≥ 160/100 mm Hg compared to those with blood pressure between 140/90 to 160/100 mm Hg.

**Table 10:** Serum Uric Acid Level and the Duration of Hypertension in Males

Duration of Hypertension	No. of cases	No. of Hyperuricemics	Percentage	Mean ± SD
< 5 years	26	9	35	6.1±0.7
≥ 5 years	24	22	92	7.3±0.9
t value = 9.3 p value < 0.001 HS				

**Table 11:** Serum Uric Acid Level and the Duration of Hypertension in Females

Duration of Hypertension	No. of cases	No. of Hyperuricemics	Percentage	Mean ± SD
< 5 years	23	6	26	5.3±1.8
≥ 5 years	27	24	89	7.1±1.0
t value = 8.4 p value < 0.001 HS				

**Table 12:** Serum Uric Acid Level & Duration of Hypertension in both gender combined

Duration of Hypertension	No. of cases	No. of Hyperuricemics	Percentage	Mean ± SD
< 5 years	49	15	31	5.7±1.3
≥ 5 years	51	46	90	7.2±1.1
t value = 10.3 p value < 0.001 HS				

The duration of hypertension was divided into 2 categories - those with hypertension for duration of hypertension < 5 years and those with duration of hypertension ≥ 5 years. The total number of patients with hypertension for duration of < 5 years was 49, and the total number of patients with duration of hypertension ≥ 5 years was 51. The mean SUA level in patients with hypertension < 5 years was 5.7 mg/dl with a standard deviation of 1.3. The mean SUA level in patients with hypertension ≥ 5 years was 7.2 mg/dl with a standard deviation of 1.1. The analyzed data showed a t-value of 10.3 and a p-value < 0.001 which showed that there is significant increase in SUA levels in patients with hypertension ≥ 5 years than those with a duration of < 5 years.

**Discussion**

In the present study the proportion of hyperuricemia in cases (hypertensive's) was 61% and the proportion of hyperuricemia in controls was 6 %

In the present study the mean serum uric acid levels in hypertensive patients with different age group ie 40-49; 50-59; 60-70 years of age was 6.42±1.49; 6.87±1.36; 7.0±1.31mg /dl respectively. This shows serum uric acid levels are higher in elderly hypertensive's than younger hypertensive's. The mean serum uric acid levels in male

hypertensive's was 6.5 ± 1.1mg/dl and female hypertensive's was 6.1 ± 1.1mg/dl. This shows the serum uric acid levels are higher in male hypertensive's than in female hypertensive's.

Various other studies have also shown that increased SUA levels were seen in hypertensive patients. Kinsey (1961) in his study with 400 hypertensive patients reported a 46 % incidence of hyperuricemia in hypertensive's [4]. Kolbe (1965) in his study of 46 hypertensive patients found 26 to be having increased SUA levels (56 %) [5].

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 hyperuricemia. In a study by C. J. Bulpitt (1975), 48 % male hypertensive's and 40 % female hypertensive's had their SUA level in the hyperuricemic range [6].

Ramsay (1979) in his study of 73 men with untreated hypertension had 18 with raised serum uric acid levels (25%) [7]. Messerli *et al.* (1980) had an incidence of 72 % raised SUA in their study population of 39 established hypertensive's [8].

In a study by Campo C *et al.* on 545 hypertensive male patients and 325 hypertensive female patient revealed that

serum uric acid levels were directly related to severity of hypertension in both male and female hypertensive's<sup>[9]</sup>.

Culleton BF in his study on 433 hypertensive patients (252 male and 178 female) revealed that in stage 1 hypertensive's 33% males and 20% females were hyperuricemic. In stage 2 hypertensive's 96% males and 92% females were hyperuricemic. Changes in serum uric acid (SUA) levels in stage 1 and stage 2 hypertensive's were statistically significant ( $p < 0.001$ ) for both male and females.

Tatsuno I *et al.*<sup>[10]</sup> in their study on 2310 hypertensive patients revealed that 23% of stage 1 hypertensive's were hyperuricemic and 95 % of stage 2 hypertensive's were hyperuricemics. Correlation between serum uric acid and stages of hypertension was found to be statistically significant ( $p < 0.05$ ).

In present study on 100 hypertensive's it was found that 6% of hypertensive's with SBP 140-159 mm Hg and DBP 90-99 mm Hg were hyperuricemic and 97 % of hypertensive's with blood pressure  $\geq 160/100$  mmHg were hyperuricemics. Correlation between serum uric acid and severity of hypertension was found to be highly significant ( $p < 0.001$ ).

In a study by Feig DL, *et al.*<sup>[11]</sup> revealed that changes in the serum uric acid levels with duration of hypertension was statistically significant ( $p < 0.001$ ) in both females and males. In other studies also by Dzielak DJ *et al.*<sup>[12]</sup>, Nagahama K *et al.*<sup>[13]</sup> and Delaval *et al.*<sup>[14]</sup> found similar significance ( $p < 0.001$ ).

In present study serum uric acid levels in hypertensive's with duration greater than 5 years was higher than in those with duration less than 5 years, is statistically significant ( $p < 0.001$ ).

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.

In a group of 80 patient's attending the Hammer Smith hospital gout clinic only 2 were hypertensive. In a study of gouty patients of Northern India by Kumar *et al.* they found that only one out of 30 patients had hypertension<sup>[15]</sup>.

In the present study incidence and severity of hyperuricemia between cases and controls correlated significantly with the severity of hypertension. This correlated with both the Kinsey and Breckenridge studies. Our study agrees with the study of Tykarski *et al.* in that there is a positive correlation between SUA and severity of hypertension<sup>[8]</sup>.

### Conclusion

There is a direct relation between hypertension and hyperuricemia. The study also showed SUA levels were higher in elderly hypertensive's than younger hypertensive's and SUA levels were higher in male hypertensive's than female hypertensive's. Also the study showed that the SUA levels were significantly increased with the severity of hypertension. The study also showed that the duration of hypertension had a significant impact on the SUA levels, those with a longer duration of hypertension had significantly raised SUA levels when compared with those of a lesser duration.

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