

# Observation of Serum Uric Acid Levels in Essential Hypertension

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## ABSTRACT

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**Background & Objectives:** 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 see if there is a relationship between the serum uric acid levels and severity & duration of hypertension

**Methodology:** The study was carried out in VSS Medical college hospital the study period was of 16 months from December 2010 to April 2012 a total of 300 patients were studied of which 150 were cases and 150 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 a rise in SUA levels in cases to highly significant  $p=.001$  when compared to that of controls. A positive correlation was found between the severity of hypertension, the patients who were found to be having stage 2 hypertension had an increase in SUA levels which was highly significant  $p=.006$  when compared with those with stage 1 hypertension. We also found a positive correlation between SUA levels and the duration of hypertension patients with a duration of hypertension  $\leq 5$  years had a significant increase in the SUA levels  $p=.001$  than those patients with hypertension for a duration of  $<5$  years

**Conclusion:** With the results based on the study carried out we concluded that there can be a direct relation between hyperuricemia and hypertension. Also the study showed that the SUA levels were significantly increased in patients with Stage 2 hypertension in comparison with those with stage 1 hypertension showing that the severity of hypertension also related to the SUA levels. 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. Serum uric acid can be used as a prognostic factor in essential hypertension

**Keywords:** Serum uric acid, Hypertension

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## INTRODUCTION

Uric acid is the ultimate catabolic product of purine metabolism in humans and higher primates.<sup>1</sup> Uric acid was first discovered in 1776. A Swedish chemist Scheele isolated it from a urinary tract stone.<sup>2</sup> Hypertension is found to be commonly associated with hyperuricemia. So early investigators proposed uric acid as having a causal role in hypertension. But later it is postulated that an elevation of uric acid in hypertension could be a consequence of reduced renal function, the use of diuretics, the presence of hyperinsulinemia and oxidative stress, or elevated renal vascular resistance, which are commonly present in this condition. As such, hyperuricemia is not considered a true risk factor for hypertension by the Joint National Committee, nor is it considered a cardiovascular risk factor by most expert organizations.<sup>3</sup> Recent studies have challenged this long-standing theory. Some studies have reported that hyper-

uricemia can predict the development of hypertension even in individuals lacking features of the metabolic syndrome.<sup>4</sup> If hyperuricemia precedes the development of hypertension then it cannot simply be a secondary phenomenon. Evidence supporting a causal role of uric acid in hypertension has come from experimental studies in laboratory animals. Humans do not express uricase, an enzyme that degrades uric acid to allantoin. As a consequence, humans have higher levels of uric acid and also cannot regulate blood levels as effectively as most mammals. To determine the effect of uric acid on BP in laboratory animals, uric acid levels in rats were increased by administering oxonic acid, which is a uricase inhibitor. Interestingly, raised uric acid levels in rats resulted in increased BP and the development of microvascular disease (resembling arteriosclerosis) in the kidneys.<sup>5</sup> The mechanism of hypertension was shown to be caused by a uric acid-mediated reduction in endothelial nitric oxide levels and stimulation of renin

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expression. Studies in humans have also correlated uric acid levels with both endothelial dysfunction and elevated plasma renin activity. Several controlled clinical trials have reported that lowering of uric acid with xanthine oxidase inhibitors improves endothelial function under a variety of conditions. So we had done this study to observe if there is any direct relation between uric acid and essential hypertension excluding renal, cardiovascular and metabolic syndrome in an Indian background.

## AIMS AND OBJECTIVES

1. To study the relationship between serum uric acid levels and hypertension.
2. To study the relation between severity of hypertension to the serum uric acid levels.
3. To study the relation between duration of hypertension and serum uric acid levels.

## MATERIALS & METHODS

The present study entitled "Observation of Serum Uric Acid Levels in Essential Hypertension" included 150 cases of essential hypertension which were again divided on the basis of stage and duration and equal number of controls matching with age and sex to that of controls admitted to V.S.S.M.C. Hospital, Burla during the study period of December 2010 to July 2012. Adult male and female patients > 18 years of age diagnosed as hypertensive according to JNC VII classification for hypertension were included as cases; patients were excluded if they had any of the following Diabetes Mellitus, Ischaemic Heart Disease, Renal Disease, Cerebrovascular accident, Dyslipidemia, All cases of secondary hypertension, Clinical Findings of gout or extra-articular manifestations of hyperuricemia, Obesity (body weight exceeding 25% of normal body weight), H/o alcohol abuse, H/o drugs known to cause hyperuricemia, e.g. thiazide diuretics, H/o pre-eclampsic toxemia. 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). Serum uric acid was measured by using Uricase / PAP method Uric acid + H<sub>2</sub>O Uricase Allantion + H<sub>2</sub>OH<sub>2</sub>O<sub>2</sub> + Phenolic chromogens Peroxidase Red coloured compound.

## RESULTS

The Serum Uric Acid levels in male cases ranged from 3.2 mg/dl to 9.5 mg/dl and female cases ranged from

3.1 mg/dl to 9.4mg/dl. The Serum Uric Acid levels in male controls ranged from 2.8 – 8.4mg/dl and female controls ranged from 2.5 - 8.2mg/dl.

Table 1. Uric acid values in the cases and controls

Category	Number	Mean (Mg/dl)	Standard Deviation	P Value	t value
Cases	150	5.453	± 1.24	0.001	5.871
Controls	150	5.145	± 1.042		

The total number of cases were 150 (both male and female), the data analysis of the cases showed the mean SUA level to be 5.453 with a standard deviation of 1.24 (5.453 ± 1.24). The total number of controls were 150 (both male and female), the data analyzed showed a mean SUA level of 5.145 with a standard deviation of 1.042 (5.145 ± 1.042). The t-value was found to be 5.871 and the p value = .001 which was significant. This showed that there was a significant rise in serum uric acid levels in patients with hypertension when compared to normotensive.

Table 2. Uric acid values in different stages of hypertension

Stage of hypertension	Number	Mean (Mg/dl)	Standard Deviation	P Value	t value
Stage 1	48	4.98	± .70	0.0006	3.295
Stage 2	102	5.67	± 1.37		

The severity of hypertension was divided into stage 1 and stage 2 based on the JNC VII classification of hypertension. In the study done at our hospital the total number of patients assessed to have stage 1 hypertension was 48 patients (both male and female patients), the total number of patients having stage 2 hypertension was 102 (both male and female patients). The data analysis for SUA levels in the stages of hypertension showed a mean serum uric acid level in stage 1 hypertension of 4.98 with a standard deviation of .70. The mean serum uric acid levels in stage 2 hypertensive patient were 5.67 with a standard deviation of 1.37. The t-value was 3.295 and a p-value of .0006 which was significant. The data analyzed showed that there was a significant rise in uric acid in patients who were having stage 2 hypertension i.e. those with a SBP e" 160 and a DBP e" 100 than those with stage 1 hypertension.

Table 3. Uric acid values based on duration of hypertension

Duration of hypertension	Number of patients	Mean (Mg/dl)	Standard Deviation	P Value	t value
< 5 years	88	4.864	± .79	0.001	8.918
? 5 years	62	6.361	± 1.261		

The duration of hypertension was divided into 2 categories - those with hypertension for duration of

hypertension < 5 years and those with duration of hypertension  $\geq$  5 years. The total number of patients with hypertension for duration of < 5 years was 88, and the total number of patients with duration of hypertension  $\geq$  5 years was 62. The mean SUA level in patients with hypertension < 5 years was 4.864 with a standard deviation of 0.79. The mean SUA level in patients with hypertension  $\geq$  5 years was 6.361 with a standard deviation of 1.261. The analyzed data showed a t-value of 8.918 and a p-value = .001 which showed that there is significant increase in SUA levels in patients with hypertension  $\geq$  5 years than those with a duration of < 5 years.

## DISCUSSION

The present study entitled observation of serum uric acid level in essential hypertension included 150 cases of essential hypertension which were again divided on the basis of stage and duration of hypertension and equal number of controls matching with age and sex to that of cases admitted to V.S.S.M.C. Hospital, Burla during the study period of December 2010 to July 2012. In the present study 109 cases were males and 41 cases were females. Controls were 150 matched with age and sex. Number of male patients was more than female patients (2.6:1.0) which is in agreement with fact that males are more prone for hypertension. Mean age of cases was 52.8 $\pm$ 14.5. Mean age of controls was 52.34 $\pm$ 14.2. In cases age was in the range of 20-83 years and in controls it was 20-86 years. Maximum number of patients were having age between 50-69 underlining the fact that age itself a risk factor for hypertension. Maximum number of patients (34%) who were detected to have hypertension for first time was in 50-59 age group. Mean age was 53.9 $\pm$ 2.5. 24% were detected to have hypertension in the age group of 60-69. 18% of cases in 40-49 age group. 11% cases in 30-39 age group. 8% of cases in 20-29 age group. 2% of cases in 70-79 age group. 1% cases in 80-89 age group. It was observed that dizziness was the first symptom in 34% of cases studied. 20% of cases were having headache as initial symptom. Blurred vision (6%), syncopal attacks,<sup>2</sup> Hypertensive Emergency<sup>1</sup> were among the other symptoms. 27% of cases were detected during screening for other diseases. Only 10% of cases were detected as a part of routine medical check up as recommended by WHO. So it underlines the importance of hypertensive screening program. It was observed that 77% of patients were taking anti-hypertensive medications regularly as prescribed by their physician but 25% of patients were not taking their medications regularly. 6% of patients were not

taking any anti hypertensives. Compliance of patients was higher among the age group of 20-29 (100%). Compliance was drastically lower in 70-79 (42%), 80-89 (40%). Left ventricular hypertrophy (LVH) by ECG Criteria was observed in 47 cases (31%). Microalbuminuria was found to be present in 41 cases (27%). There were 27 patients having Hypertensive retinopathy (18%). Left ventricular hypertrophy was found to be more common followed by microalbuminuria and retinopathy. In the present study it was observed that 37% of patients were visiting their doctors 6 monthly for routine BP monitoring, while 22% of patients paid visit to their doctor every 3 monthly. Meanwhile 17% of patients visited their doctor monthly and 17% of patients yearly. 6% of patients had no visit to their doctors. In the present study it was observed that 37% of cases were below poverty line, 63% of cases were above poverty line, 52% of cases belonged to rural area and 48% belonged to urban area. But it is not appropriate comment on this aspect because of small number of cases. With the discovery by Garrod in the early 1800s that elevated serum uric acid was the cause of gout, hyperuricemia was proposed to have a causal role in a variety of cardiovascular and renal conditions, including hypertension, arteriosclerosis, kidney and heart diseases.<sup>6</sup> In a paper published in 1879 that originally described essential hypertension, Frederick Mohamed noted that many of his subjects came from gouty families. Subsequently, he hypothesized that uric acid might be integral to the development of essential hypertension.<sup>7</sup> Ten years later, this hypothesis reemerged when Haig proposed low-purine diets as a means to prevent hypertension and vascular disease.<sup>8</sup> By the mid-20<sup>th</sup> century, however, the causal association between uric acid and cardiovascular disease has been questioned, as it was recognized that the association of gout with cardiovascular disease might simply reflect that both have similar risk factors, such as obesity, hypertension, metabolic syndrome, kidney disease, etc.<sup>9</sup> In addition, large epidemiological studies produced contradictory results, while many of them failed to demonstrate an independent association of hyperuricemia and cardiovascular disease. Simultaneously, many studies overemphasized the role of uric acid as an antioxidant. Moreover, hyperuricemia, observed in chronic kidney disease (CKD) of any cause, was considered secondary either to a decrease in glomerular filtration rate (GFR) or to the hyperinsulinemia of the metabolic syndrome. Thus, hyperuricemia in CKD was described as a benign finding and uric acid was likely not a true cardiovascular or renal risk factor.

So even though the association between hyperuric-

mia and hypertension was repeatedly observed in the 1950s and through the 1980s but it received relatively little attention mainly due to the lack of an exact causal mechanism. Thus, mild elevations of serum uric acid were ignored in medical practice and uric acid was not considered a risk factor for hypertension by the most distinguished scientific societies (American Heart Association, Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure).<sup>10</sup> But the scenario changed after 1990s when several large epidemiological studies have been published that support the role of uric acid as an independent risk factor for the development of arterial hypertension.<sup>11</sup> Consequently, the skepticism over a potential uric acid and high BP association, prevalent in the previous decades, there has significantly changed. In 3300 individuals with normal BP and renal function and without known heart disease participating in the Framingham Heart Study, an independent correlation was found between serum uric acid levels and the development of arterial hypertension over a 4-year follow-up period.<sup>12</sup> Ramsay et al in one pioneer study found a significant relation between uric acid and hypertension. He enrolled 73 men with untreated hypertension in his study. Out of 73 men 18 cases were having hyperuricemia (25%). But this study had many limitations. mainly only men were included and small number of cases.<sup>13</sup> Messerli et al had an incidence of 72 % raised SUA in their study population of 39 established hypertensives.<sup>14</sup> In a study by Tykarski, he showed SUA concentration and the prevalence of hyperuricemia were significantly higher in hypertensive patients. They further demonstrated that tubular secretion of uric acid was significantly lower in hypertensive patients in comparison with normotensive subjects.<sup>15</sup> Breckenridge 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.<sup>16</sup> In a study by C. J. Bulpitt (1975), 48% male hypertensives and 40% female hypertensives had their S UA level in the hyperuricemic range.<sup>17</sup> The P IUMA 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 effects. As extensively reviewed by Puig and Ruilope,<sup>18</sup> both uric acid and superoxide radicals are produced for the effect of xanthine oxidase in the late phase of purine metabolism. Superoxide radicals, which may cause tissue and vascular damage,<sup>19</sup> are increased in subjects with essential hypertension. It would be important to clarify whether such increase is due, at

least in part, to enhanced xanthine oxidase activity and whether inhibition of this enzyme by allopurinol may reduce CV risk.<sup>20</sup> Evidence supporting a causal role of uric acid in hypertension has come from experimental studies in laboratory animals. Humans do not express uricase, an enzyme that degrades uric acid to allantoin. As a consequence humans have higher levels of uric acid and also cannot regulate blood levels as effectively as most mammals.<sup>21</sup> To determine the effect of uric acid on BP in laboratory animals, uric acid levels in rats were increased by administering oxonic acid, which is a uricase inhibitor.<sup>22</sup> Interestingly raised uric acid levels in rats resulted in increased BP and the development of microvascular disease (resembling arteriosclerosis) in the kidneys.<sup>23</sup> The mechanism of hypertension was shown to be caused by a uric acid-mediated reduction in endothelial nitric oxide levels<sup>24</sup> and stimulation of renin expression. Studies in humans have also correlated uric acid levels with both endothelial dysfunction<sup>25</sup> and elevated plasma renin activity. But it is still not clear that whether uric acid can predict the hypertension and its severity as an independent factor. So the present study was conducted to observe the direct relation between uric acid and hypertension excluding other risk factors and diseases. Present study showed that there was a significant rise in serum uric acid levels in patients with hypertension when compared to normotensive. The t-value was found to be 5.871 and the p value 0 .001 which was significant. In the present study the incidence of hyperuricemia in controls was 12 % and the incidence of hyperuricemia in cases was 39 %. Present study observed the relation of uric acid to severity of hypertension. The data analyzed showed that there was a significant rise in hypertension in patients who were having 2 hypertension i.e. those with a SBP  $\geq$ 160 and a DBP  $\geq$  100 than those with stage 1 hypertension (SBP 140- 159 and DBP 90 - 99). The t-value was 3.295 and a p-value of .0006 which was significant. Present study observed the relation of uric acid to duration of hypertension. The analyzed data showed a t-value of 8.918 and a p- value 0.001 which showed that there is significant increase in SUA levels in patients with hypertension  $\geq$  5 years than those with a duration of < 5 years. Present study observed the relation of uric acid to hypertensive retinopathy. The analyzed data showed a t-value of 3.284 and a p-value 0.00137 which showed that there was a significant increase in SUA levels in patients with retinopathy. Present study also observed the relation of uric acid to microalbuminuria. The analyzed data showed at-value of 5.770 and a p-value 0.0001 which showed that there was a significant increase in SUA levels in patients with microalbuminuria. Present study also observed the

relation of uric acid to Left Ventricular Hypertrophy (ECG Criteria). The analyzed data showed a t-value of 8.900 and a p-value 0.0001 which showed that there was a significant increase in SUA levels in patients with Left Ventricular Hypertrophy.

In the present study increase in uric acid level between cases and controls correlated significantly with the severity and duration of hypertension. This correlated with both the Kinsey and Breckenridge studies, but according to Cannon et al severity of hypertension had no relation to SUA level. Our study agrees with the study of Tykarski et al in that there is a positive correlation between SUA and severity of hypertension.

In the present study there is a definite relationship in SUA levels between hypertensive patients and normotensive patients. There is a directly proportional relation in the levels of SUA in relation to the duration and severity of hypertension. There is a possibility of serum uric acid leading to hypertension by causing production of free radicals and oxidative stress.

Most of the available epidemiological evidence and present study suggests a significant role of serum uric acid as an independent and strong risk factor for hypertension. The link between serum uric acid and hypertensive risk has been found to be statistically significant. So serum uric acid may be a powerful tool to help identify patients at high risk of hypertensive diseases. It is therefore prudent to consider serum uric acid along with other risk factors, such as obesity, hyperlipidemia, 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. The epidemiological and experimental evidences are encouraging. However, these clarifications could only be sought through randomized clinical trials.

## CONCLUSION

With the present study which included 150 cases and 150 controls it was concluded that there was a significant relation between serum uric acid levels and essential hypertension. As serum uric acid level significantly increased in stage 2 hypertension compared to that of stage 1 hypertension there can be a direct relation between serum uric acid level and severity of hypertension. The study showed significant rise of

serum uric acid level in those patients having longer duration of hypertension. So serum uric acid level also can reflect the duration of hypertension. The study also showed significant rise of serum uric acid level in those patients having Microalbuminuria, Retinopathy, Left Ventricular Hypertrophy. Based on the study carried out it was concluded that SUA is an independent risk factor for hypertension. It can be correlated with severity and duration of hypertension. It can also be correlated with Microalbuminuria, Retinopathy, Left Ventricular Hypertrophy. So serum uric acid may be a powerful tool to help identify patients at high risk of hypertensive diseases.

## END NOTE

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**Conflict of Interest:** None declared

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