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Research article

URIC ACID AND HYPERTENSION: DOES URIC ACID LICK THE JOINTS AND BITES THE HEART?

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ABSTRACT

Background: Uric acid a metabolic end product of purine degradation is implicated in gout as aetiology. Its increased levels have also been associated with hypertension, cardiovascular morbidity and mortality. Few studies have been conducted, especially in India to elucidate association of uric acid with prehypertension.
Aims: This study intends to assess the association of serum uric acid levels with blood pressure in normotensive, prehypertensive and hypertensive population. It also intends to check whether there is an incremental rise of serum uric acid with increasing blood pressure. **Material and methods:** Two hundred outpatients who met inclusion and exclusion criteria and consented formed study population. Blood pressure of each participant was measured followed by venipuncture to collect venous blood for measurement of serum uric acid. Participants were categorised into 4 groups as Normal, Prehypertension, Hypertension –Stage 1, Hypertension Stage -2 as per Joint National Committee 7 classification. Data was analysed to know levels of serum uric acid among the four categories and to verify association of uric acid with blood pressure. **Results and Conclusions:** Stepwise increase in serum uric acid levels was observed along with increasing blood pressure. Strong positive linear correlation was observed between serum uric acid levels and mean blood pressure (Pearson's correlation coefficient r = 0.74; p< 0.0001). Uric acid was associated (r = 0.442) with blood pressure in prehypertension population. Serum uric acid levels are associated with prehypertension and hypertension and are independent and strong predictors of cardiovascular mortality.

Keywords: Blood pressure, Prehypertension, Uric acid.

INTRODUCTION

Uric acid is an end product of purine degradation in humans and is primarily excreted through urine. Serum uric acid levels are regulated by dietary purine intake, endogenous metabolism of purines, and its urinary excretion rate. In the process of evolution 15 million years ago, two mutations rendered uricase gene non-functional in humans and great apes. Consequently uric acid is not converted to readily water soluble and easily excreted product allantoin, thus resulting in higher serum uric acid levels in humans and great apes.[1]

As early as in 1848 AD, Sir Alfred Garrod demonstrated that Gout, an inflammatory disease of joints was associated with Hyperuricemia i.e, increased levels of serum uric acid (>7mg/dl in males and >6mg/dl in females).[2] Gout is a disease of joints characterised by the deposition of monosodium urate crystals in joint space causing inflammation and painful joints.

A few years later, in 1874 AD, Frederick Mohamed postulated for the first time that "People with high blood pressure belong to gouty families" suggesting

the possible association of Hyperuricemia with high blood pressure. [3]

Association of elevated serum uric acid with hypertension was further reported by many researchers. At the end of the 19th century many studies demonstrated that uric acid was also associated with cardiovascular morbidity. However, lack of possible mechanism by which hypertension and uric acid are associated led to conclusion that uric acid is not a true risk factor for cardiovascular disease. [4-9]

Amidst contradicting reports, Mohamed's hypothesis that uric acid has a causative role in hypertension remains controversial even after over 130 years.

Recent animal studies and clinical observations indicate the possible direct causal role of uric acid in pathogenesis of hypertension by various mechanisms.[10] Of late, increasing evidence is being gathered suggestive of association and causal role of uric acid in hypertension and cardiovascular morbidity. [11]

Hitherto studies conducted have not assessed the association of serum uric acid levels blood pressure in prehypertensives and its incremental rise with increasing blood pressure. So in this study we intend to assess the association of serum uric acid levels with blood pressure in normotensive, prehypertensive and hypertensive participants. We also intend to check whether there is an incremental rise of serum uric acid with increasing blood pressure.

MATERIALS AND METHODS

Our study was conducted at Regional Diagnostic Laboratory of District Hospital, Bidar, a teaching hospital affiliated to the Bidar Institute of Medical Sciences, Karnataka, India. Study spanned over a period of 3 months from August to October 2013. Institutional Ethical committee approval was taken before commencement of study and our procedures were in accordance with the Helsinki Declaration of 1975, as revised in 2000.[12]

The subjects for this prospective study were outpatients who visited regional diagnostic laboratory for routine investigations. Two hundred participants (103 men and 97 women) of age group 20 to 60 years formed the study population.

Subjects who fulfilled below mentioned inclusion and exclusion criteria were informed and explained about the study and after their informed written consent were included in the study.

Inclusion and exclusion criteria: Paediatric and psychiatric patients, pregnant women, diagnosed cases of essential secondary hypertension, medications like uricosuric drugs and antihypertensive drugs were excluded in the study.

Study participants were made to sit comfortably on a chair for five minutes. Systolic and diastolic blood pressures were measured twice by auscultatory method with a mercury sphygmomanometer (cuff size, 12.5 x 40 cm) on the right arm. The first and fifth phases of Korotkoff's sounds were taken as the criteria for SBP and DBP respectively. The mean of two consecutive readings was recorded and used for analysis.[13] Mean of systolic and diastolic blood pressure was calculated (SBP+DBP/2) and noted as mean blood pressure.

As per Joint National Committee (JNC)[7] classification of blood pressure, Participants were categorised as normal if systolic blood pressure (SBP) was <120mm of Hg and Diastolic blood pressure (DBP) was <80mm of Hg; prehypertensive if SBP/DBP is 120-139/or 80-89 mm of Hg; Stage 1 Hypertensive if SBP/DBP is 140-159/or 90-99mm of Hg and were categorised as Stage 2 hypertensives if SBP/DBP is ≥160/or ≥100 mm of Hg.[14]

Under aseptic precautions, venipuncture was performed on median cubital vein and 2ml of blood was collected into a sterile evacuated plastic tube with red stopper with no additives. Blood samples were allowed to clot at room temperature for 30 minutes. Samples were centrifuged at 1500g for 15 minutes for serum separation.[15]

Serum uric acid levels were measured by modified Trinder's method[16, 17] using ERBA XL 300 fully automated analyser. To ensure quality, daily internal quality control samples were run and day to day coefficient of variance (CV) was <5%. The laboratory also had an external quality assurance programme in place.

Statistical Analysis: Statistical analysis of participant data was performed using "IBM SPSS Statistics 20" software. The data was analysed to measure age-sex distribution of participants, to categorise participants as normal, prehypertension, Stage-1 hypertension and stage-2 hypertension along with their mean blood pressures and mean serum uric acid levels. Pearson's correlation coefficient was calculated to elucidate the statistically significant association between serum uric acid levels and blood pressure.[18]

RESULTS

Characteristics of study population: The demographic characteristics of the study population are summarised in table 1. Study population comprised of 200 participants of whom 103 were men and 97 were women..

Table: 1. Age sex distribution of study population with mean blood pressure

Age (years)	Number of Males	Number of females	Blood pressure* (mm of Hg)
20 - 30	35	44	98.08 ± 9.09
31 - 40	14	14	101.96 ± 13.13
41 - 50	17	15	107.21 ± 14.27
51 - 60	37	24	112.23 ± 12.69

* mean ± standard deviation

Mean age of the study population was 40.06±13.8 years and mean age of males and females was 41.98 ± 13.48 years and 38.03 ± 13.91 years respectively. The mean blood pressure of study population showed an increasing trend with age

The prevalence of undiagnosed hypertension in population was 22% (n = 44) and of undiagnosed prehypertension was 42% (n = 84), put together comprising nearly 65% of study population. A stepwise increase in serum uric acid levels was observed when study population was categorised into four groups namely, Normal, Prehypertension, Hypertension stage-1, Hypertension stage-2 based on the JNC 7 classification of blood pressure. Similar increasing trend in mean serum uric acid level was observed along with mean blood pressure of the study population. (Table-2)

Table: 2. Serum uric acid and blood pressure in normotensives, prehypertensives and hypertensives

JNC 7 BP classification[14] (SBP/DBP mm of Hg)	Males	Females	Serum Uric acid* (mg/dl)	Blood Pressure* (mm of Hg)
Normal (<120/ and <80)	30	42	5.09 ± 0.65	92.95 ± 4.7
Prehypertension (120-139/ or 80-89)	47	37	5.70 ± 0.73	104.08 ± 5.21
Hypertension Stage-1 (140-159/ or 90-99)	18	14	6.81 ± 0.77	119 ± 6.94
Hypertension Stage-2 (≥160/ or ≥ 100)	8	4	7.59 ± 0.57	136.41 ±6.86

* mean ± standard deviation

Statistically highly significant (p<0.0001) difference in mean serum uric acid was observed between normal and prehypertension categories; and also between prehypertension and hypertension stage-1 JNC 7 categories. Similar but less profound, statistically significant difference (<0.01) was noted between Stage-1 and Stage-2 hypertension categories.

A strong positive linear correlation was observed between serum uric acid levels and mean blood pressure (Pearson's correlation coefficient r = 0.74). Correlation is highly significant at the 0.05 level (2-tailed) and the P-value is < 0.0001. (Figure 1). Similar correlation was also noted between serum uric acid and systolic blood pressure (r = 0.746) and diastolic blood pressure (r = 0.609). Uric acid was associated strongly (r = 0.442) with blood pressure in the prehypertension population while a weak correlation (r = 0.113) was observed in normal population.

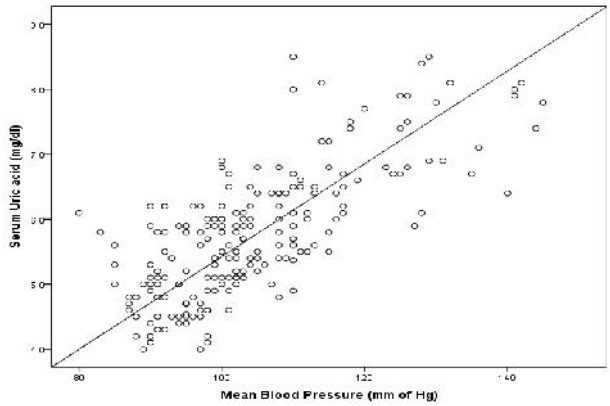

Fig 1: Scatter diagram showing correlation of serum uric acid levels with mean blood pressure.

DISCUSSION

Our prospective study consisting of 200 participants showed an association of serum uric acid with blood pressure in apparently healthy individuals, undiagnosed prehypertensive subjects and

hypertensive individuals. This is the first study conducted in India to elucidate the association of serum uric acid levels with blood pressure in prehypertensive population.

Study population comprised of adult individuals from 20 years to 60 years. Mean age of the study population was 40.06±13.8 years comparable to other similar studies that had a mean age of 42.3±0.2 years19 and 41.6 years.[20]

Although known hypertensive patients were excluded from the study, 22% (n = 44) of participants were hypertensivses and 42% (n = 84) were prehypertensives. Similar prevalence of prehypertension (39%) among adults in India[21] and Unitesd states of America[22] was reported by separate researchers. It is noteworthy that, a large percentage of the population who are at risk of developing hypertension (42%) and undiagnosed hypertensives (22%) who may develop cardiovascular morbidity go unnoticed.

Serum uric acid levels were positively (r = 0.740) and significantly (p < 0.0001) associated with blood pressure in our study. A similar positive and statistically significant correlation was observed by other researchers. [19, 20, 22, 23]

A stepwise incremental rise of serum uric acid was observed with increasing blood pressure when participants were categorised as per JNC7 classification as normal, prehypertension, hypertension stage-1, and hypertension stage-2. A similar incremental increase of uric acid was observed in a cross sectional study conducted in Japan. However this study categorised the participants based on Japanese society guidelines JSH-2009 rather than JNC 7 classification.[19]

A similar association (r = 0.15; p < 0.001) was demonstrated by a study on large prospective male cohort. They also demonstrated that serum uric acid was independently related to mortality from congestive heart failure and stroke. [20]

Positive association (r = 0.32) of serum uric acid with prehypertension independent of smoking BMI and other confounding factors was observed in a study.[22]

A study demonstrated significant (p < 0.0001) correlation between uric acid and prehypertension in adults but the study also noted, unlike our study, that the association was not statistically significant in older individuals over 65 years of age. [23]

In a nine year follow-up study, association of serum uric acid with incident hypertension was observed and stronger association was noted among blacks. [24]

PIUMA study, with a cohort of 1720 patients with follow-up of 12 years noted that, subjects with higher uric acid levels were at higher risk of developing cardiovascular events (relative risk 1.73; 95% confidence interval) than the subjects with lower uric acid levels. [25]

A study on 125 children (age group 6-18 years) with primary hypertension demonstrated the association of serum uric acid with systolic blood pressure (r = 0.80) and diastolic blood pressure (r = 0.66). [26] Another study in paediatric age group also observed the association of serum uric acid levels with ambulatory diastolic blood pressure (r = 0.29; p = 0.0033). [27]

Serum uric acid has long been associated with hypertension, the primary aetiology of cardiovascular morbidity. Several large cohort studies have demonstrated that serum uric acid was predictive of mortality due to ischaemic heart diseases in women. [28]

Few studies demonstrated the independent and significant association of uric acid with risk of cardiovascular mortality[29] and myocardial infarction. [30] It was observed in a study that serum uric acid level was a strong and independent predictor of cardiovascular mortality in middle aged men. [31]

Increased serum uric acid levels have been associated with elevated blood pressure and cardiovascular morbidity and mortality. But the causal role of uric acid in hypertension and pathogenesis of cardiovascular events has not been clear. [5- 9]

Recent studies have elucidated the plausible mechanisms that explain how elevated uric acid causes hypertension. Studies on animal models have shown that increased uric acid levels cause renal microvascular and tubular interstitial injury. Uric acid also increases juxtaglomerular renin production and decreases nitric oxide synthase expression in macula densa; collectively contributing to blood pressure elevation.[10]

CONCLUSION

Serum uric acid levels are associated with hypertension and are independent and strong predictors of cardiovascular mortality, myocardial infarction and coronary artery diseases in both sexes of different ethnic groups. So it may not an exaggeration

to state that “Uric acid licks the joints and bites the heart”

Limitations of the study: The study population was drawn from outpatients of a hospital that may not form a representative sample of the general population. Confounders like serum creatinine, serum uric acid, serum albumin, history of alcohol intake, and dietary protein and sodium consumption that alter serum uric acid and /or blood pressure were not taken into consideration.

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