Original Research Article

Evaluation of serum uric acid in essential hypertension

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Received: 26-11-2021 / Revised: 16-12-2021 / Accepted: 01-01-2022

Abstract

Background: In this study we wanted to evaluate the relationship between serum uric acid (SUA) levels and hypertension, the relation between severity of hypertension to the serum uric acid levels and the relation between duration of hypertension and serum uric acid levels. **Methods**: This is a case control study conducted among 100 patients of which 50 were cases and 50 controls. The study was conducted over a period of 2 years from September 2016 to September 2018 in the department of general medicine at S.V.S hospital Mahbubnagar. **Results:** The study showed significantly higher SUA levels in cases (7.8 ± 0.6 mg/dL) when compared to that of controls (4.3± 0.8 mg/dL) (P<0.0001). The proportions of hyperuricemia among males with and without hypertension were 88.5% and 0% respectively and similarly among females with and without hypertension were 100% and 0%. No significant correlation was found between the serum uric acid levels and severity of hypertension (P>0.05).The SUA levels in stage 2 hypertension were not significantly different among both males and females when compared to those with stage I hypertension (P>0.05). Also, there was no significant correlation was between the serum uric acid levels and duration of hypertension and (P>0.05). The SUA levels in those with duration of hypertension ≥ 5 years were not significantly different among both males and females when compared to those with duration of hypertension <5 years (P>0.05). **Conclusions**: Hyperuricemia is seen in hypertensives. Severity of hypertension is not related to the serum uric acid levels. Duration of hypertension had no significant impact on the serum uric acid levels.

Keywords: Serum Uric Acid, Hypertension, Hyperuricemia

Introduction

Uric acid is a heterocyclic compoundof carbon,nitrogen,oxygen, and hydrogenwith the formula$C_5H_4N_4O_3$. It forms ions and salts known as urates and acid urates such as ammonium acid urate. Uric acid is a product of the metabolic breakdown of purinenucleotides.

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

The concept that uric acid may be involved in hypertension is not a new one. In fact, in the paper published in 1879 that originally described essential hypertension, Frederick Akbar Mohamed noted that many of his subjects came from gouty families. He hypothesized that uric acid might be integral to the development of essential hypertension[1]. Ten years later, this hypothesis reemerged when Haig[2] proposed low purine diets as a means to prevent hypertension and vascular disease. In 1909, the French academician Henri Huchard noted that renal arteriolosclerosis (the histologic lesion of hypertension) was observed in three groups: Those with gout, those with lead poisoning, and those who have a diet enriched with fatty meat. All of these groups are associated with hyperuricemia[3]. The association between elevated serum uric acid and hypertension was observed and reported repeatedly in the 1950s to 1980s but received relatively little sustained attention because of the lack of a mechanistic explanation[4-6]. Twenty-five to 40% of adult patients with untreated hypertension have hyperuricemia (>6.5 mg/dl), and this number increases dramatically when serum uric acid in the high-normal range is included[7,8].

In certain special cases of hypertension, such as cyclosporine-associated hypertension and preeclampsia, the correlation between elevated serum uric acid and hypertension is >70%[9]. Despite these observations, the lack of a causal mechanism led to mild elevations of serum uric acid being largely ignored in medical practice. Uric acid was removed from routine laboratory panels, such as the serum metabolism and chemistries-20 (SMAC20), in the early 1980s and is not considered a risk factor for hypertension by either the American Heart Association[10] or the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[11].

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[12].

This study was done to determine whether raised serum uric acid levels were an independent risk factor for developing hypertension.

Objectives

1. To assess the relationship between serum uric acid levels and hypertension.
2. To assess the association between serum uric acid levels and severity of hypertension.
3. To assess the association between serum uric acid levels and duration of hypertension.

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Methods

This is a case control study conducted among 100 patients of which 50 were cases with hypertension and 50 were age and gender matched controls without the disease. The study was conducted over a period of 2 years from September 2016 to September 2018 in the department of general medicine at S.V.S hospital Mahbubnagar.

Inclusion Criteria

For cases

Adult male and female patients aged more than 18 years who were diagnosed hypertensives according to JNC VII classification for hypertension were included as cases.

For controls

Age and gender matched patients without hypertension or any other condition known to cause hyperuricemia were considered as controls.

Exclusion Criteria

Patients with diabetes mellitus, ischaemic heart disease, secondary hypertension, gout or extra-articular manifestations of hyperuricemia, obesity (body weight exceeding 25% of body weight), on treatment of drugs known to cause hyperuricemia (e.g. thiazide diuretics), those with h/o alcohol abuse, renal disease, and pregnancy induced hypertension were excluded from the study.

Data Collection and Measurements

The data was collected using a semi-structured questionnaire that consisted of 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.

The patients were asked to fast for 12 hours and to avoid smoking and heavy physical Exercise 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[41]. 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^2.

Statistical Analysis

Data was analysed by Microsoft Excel and Graph PadPrism software. Data was summarized by mean ± SD for continuous and percentages for categorical data. The comparison between control and cases was done by unpaired 't 'test for continuous parametric data. The association between the variables was done by Fisher's exact test. A *P*-value of <0.05 was considered statistically significant.

Results

The age of the study subjects ranged from a minimum of 30 years to 89 years in both cases and controls. Among both cases and controls, 70.0% (35/50) were males and 30.0% (15/50) were females. The mean systolic blood pressures among cases and controls were 147±10.3 mmHg and 115.3±5.6 mmHg. Similarly the diastolic blood pressures among cases and controls were 94.1±4.6 mmHg and 74.9±4.4 mmHg. Both were noted to be significantly higher in cases compared to controls (*P*<0.05). [Table-1]The systolic blood pressure among cases varied from 100 mmHg to 122 mmHg and among controls it varied from 100 mmHg to 170 mmHg. The diastolic blood pressures varied from 70 mmHg to 80 mmHg among cases and 88 mmHg to 110 mmHg among controls. The serum uric acid levels varied from 2.7 mg/dL to 6.2 mg/dL among cases and 6.4 mg/dL to 9.6 mg/dL among controls. The association between serum uric acid with stage of hypertension and duration of hypertension was not statistically significant (*P*>0.05). [Tables 2 and 3].

Variables	Variables in Mean±SD		*P*-value
	Cases (n=50)	Controls (n=50)	
Systolic BP in mm of Hg	147±10.3	115.3±5.6	<0.0001*
Diastolic BP in mm of Hg	94.1±4.6	74.9±4.4	<0.0001*
Serum Uric acid in mg/dL	7.8±0.6	4.3±0.8	<0.0001*
*indicates statistically significant difference at *P*<0.05			
Table-1 Comparison of means of blood pressure and serum uric acid levels			

Male Cases	Stage of Hypertension		*P*-value
Serum Uric Acid (mg/dl)	**Stage I**	**Stage II**	
≤7	3 (75.0)	01 (25.0)	0.39
>7	28 (90.3)	03 (9.7)	
Female Cases	**Stage of Hypertension**		**1.00**
Serum Uric Acid (mg/dl)	**Stage I**	**Stage II**	
≤ 6	00 (0.0)	00 (0.0)	
>6	10 (66.7)	05 (33.3)	
Table-2 Association between Serum Uric Acid Values With Stage of Hypertension among males and females			

Male Cases	Duration of hypertension		*P*-value
Serum Uric Acid (mg/dl)	**<5**	**≥5**	0.55
≤7	03 (75.0)	01 (25.0)	
>7	26 (83.9)	05 (16.1)	
Female Cases	**Duration of hypertension**		
Serum Uric Acid (mg/dl)	**<5**	**≥5**	1.00
≤6	00 (0.0)	00 (0.0)	
>6	11 (73.3)	04 (26.7)	
Table-3 Association between Serum Uric Acid Values with duration of Hypertension among males and females			

Discussion

Elevated 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[13]

In few studies, the association of SUA with cardiovascular disease was uncertain after multivariate adjustment as in the Framingham Heart Study (1985) and the ARIC study (1996), but in others the association remained certain and significant.

Because elevated serum uric acid is correlated with several risk factors including renal dysfunction, hypertension, insulin resistance, hyperhomocystenemia and hyperlipidemia, it is debated whether SUA is an independent cardiovascular risk factor.

In the present study the incidence of hyperuricemia in cases is 31 male cases out of 35cases showed hyperuricemia. 88.5% males cases showed hyperuricemia. 100% female cases showed hyperuricemia irrespective of stage, while in controls no male and female showed hyperuricemia.

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 hypertensives. Kolbe (1965) in his study of 46 hypertensive patients found 26 to be having increased SUA levels (56 %)[14].

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.[1] In a study by C. J. Bulpitt (1975), 48 % male hypertensives and 40 % female hypertensives had their SUA level in the hyperuricemic range[15].

Ramsay (1979) in his study of 73 men with untreated hypertension had 18 with raised serum uric acid levels (25%)[16]. Messerli et al (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[17].

It certainly is possible that uric acid may be an earlier and more sensitive maker of decreased renal blood flow than serum creatinine. It has been recently suggested that since uric acid may play 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.

Several observations support this concept of free radical mediated inhibition of endothelium dependent vasodilation. An antioxidant deficiency in diet which produces hyperuricemia, contributes to the etiology of hypertension, and the antioxidant drugs also show a blood pressure lowering effect in both diabetic and hypertensive patients[18].

In a study by Tykarski (1991), 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. There was no difference in pre and post-secretory reabsorption of uric acid. They concluded that high prevalence of hyperuricemia in essential hypertension was caused by impaired renal excretion of uric acid[19]. Goldstein and Manowitz (1993) showed in an adolescent population that, with age, weight, height and sexual maturity controlled, SUA significantly predicted blood pressure even in adolescents[20].

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.

In gouty patients without advanced tophi, however renal failure and hypertension are rare. 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[21]. Fessel et al showed no appreciable loss of renal function in 112 patients with gout as compared to normal subjects followed up for 12 years[22]. In a study by Lawrence E Ramsay there was no evidence that hyperuricemia had a deleterious effect on renal function[23]. Canon et al considered that an impairment of renal function will raise the SUA levels more commonly than an increased SUA will cause renal damage[24].

Hence it is unlikely that hypertension arises as a result of raised SUA levels, but the possibility that 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.

Abdallah jeraiah et al In the study involving 49 known hypertensive (31 males and 18 females) and 16 healthy controls (without hypertension) reported serum uric acid levels from patients taken from various hospitals with hypertension increased significantly when compared with controls ($p < 0.001$). Male and female hypertensive patients had showed significant increase in serum uric acid levels when compared with controls ($p < 0.001$).

Selby et al conducted a nested case-control study of 1,031 cases of essential hypertension and 1,031 persistently normotensive controls from the Kaiser Permanente Multiphasic Health Checkup cohort in Northern California adjusting for the risk factors, forced vital capacity (p less than 0.001), serum uric acid ($p = 0.003$), serum cholesterol ($p = 0.012$), and heart rate ($p = 0.014$) remained independently predictive for essential hypertension[25].

Uric acid remained positively related to risk (odds ratio, fifth vs. first quintile = 2.19, 95% Cl 1.20-3.98).Both forced vital capacity and serum uric acid are closely linked to development of hypertension and may be markers of susceptibility or intermediate steps in pathways leading to hypertension[26].

Zainab Abdul Razak et al in their study in Iraq featuring 20 cases and 15 controls had a mean serum uric acid value of 8.03(3.50) mg/dl in comparison to 4.32(1.07) mg/dl with a significant p value of <0.05. The study showed that the serum levels of uric acid, CRP and total cholesterol were significantly higher in patients with hypertension than in healthy controls[27].

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 clear.

Later Messerli et al 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.

Tykarski in his study showed that SUA levels in hypertensives are due to impaired tubular secretion of urate.

In the present study incidence of hyperuricemia between cases and controls correlated significantly but not with the severity of hypertension. This correlated according to Cannon et al severity of hypertension had no relation to SUA level. But the Kinsey. Breckenridge[12] andTykarski et al studies showed correlation between severity of hyperuricemia and severity of hypertension.

In our study the incidence of Hyperuricemia in cases with stage 1 hypertension was 82 % and those with stage 2 hypertension was 18 % Breckenridge in his study showed an increasing incidence of hyperuricemia as the diastolic BP increased in his study, but there was

no tendency for hyperuricemia to occur, only with patients with more severe hypertension.

Kinskey also found that hyperuricemia was common in patients with more severe grades of hypertension. This was similar to the finding of Tykarski et al who encountered positive correlation between duration of hypertension and SUA in their study.

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 effects. As extensively reviewed by Puig and Ruilope[28], both uric acid and superoxide radicals are produced for the effect of xanthineoxidase in the late phase of purine metabolism. Superoxideradicals, which may cause tissue and vascular damage[29], are increased in subjects with essential hypertension[30]. 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[31].

Conclusions

Hyperuricemia is seen in hypertensives.Severity of hypertension is not related to the serum uric acid levels. Duration of hypertension had no significant impact on the serum uric acid levels.

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Conflict of Interest: Nil Source of support: Nil