e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2024; 14(12); 38-44

Original Research Article

To Assess the Levels of Serum Uric Acid in Hypertensive Retinopathy

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Received: 14-09-2024 / Revised: 17-10-2024 / Accepted: 11-11-2024
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Conflict of interest: Nil

Abstract

Introduction: One of the microvascular side effects of hypertension that develops gradually is hypertensive retinopathy (HR). Gout is predisposed to by hyperuricemia, which is associated with metabolic syndrome. Additionally, it was considered a stand-alone risk factor for hypertension. SUA may be linked to certain eye conditions, according to a number of studies. The purpose of this study is to highlight how metabolic parameters affect heart rate, and it is hypothesized that SUA gave doctors valuable information about when to perform fundoscopic exams on hypertensive patients.

Aim: To study the serum uric acid concentration (SUA) in patients of hypertensive retinopathy and relationship between both.

Methodology: Observational cross sectional study was conducted to observe the relationship between serum uric acid and hypertensive retinopathy. Two groups cases 120 (with HR) and controls 120 (without HR) were compared. Serum uric acid was measured by Erba Mannheim XL 640 machine at MBS Hospital Kota. Hypertensive Retinopathy was assessed using indirect ophthalmoscope.

Results & Conclusion: The data analysis of the cases showed the mean SUA level to be 6.2398(mg/dl) and the controls showed the mean SUA level of 5.5926(mg/dl). A two sample t-Test to compare the means of Serum Uric Acid Level (mg/dl) for Cases and Controls. Significance value (p value) for the test was achieved 0.015 (significant). Thus the study conclude that serum uric acid level is associated with incidence of Hypertensive Retinopathy. And according to ANOVA test it was also found that serum uric acid is associated with severity of Hypertensive Retinopathy. It was hypothesized that SUA gave doctors helpful information for scheduling funduscopic exams in hypertension patients and highlighted the impact of metabolic variables on HR.

Introduction

Hypertension is most important risk factor for CVD in India. GBD [Global Burden Of Diseases] Study has estimated that hypertension led to 1.6 million deaths and 33.9 million disability-adjusted life years in 2015 and is most important cause of disease burden in India.

Uric acid was first discovered in 1776. A Swedish chemist Scheele isolated it from a urinary tract stone.

About half a century later, British doctor Alfred Baring Garrod demonstrated using chemical isolation that gouty individuals had abnormally high uric acid levels. Garrod developed a logical connection between hyperuricemia and gouty patients' symptoms in later research. It was discovered that hypertension and hyperuricemia were related when a family with an unusual and regrettable lineage visited Hammer Smith Hospital in 1957. [1]. A patient's mother and all seven of his siblings had hypertension, whereas the patient's father and six of his siblings had hyperuricemia. This prompted the inquiry as to whether elevated serum uric acid was typical of hypertensive patients. Elevated serum uric acid (SUA) levels are a hallmark of hyperuricemia (HU); these levels are brought on by either an excess or a deficiency of uric acid (UA), a byproduct of purine metabolism in humans. HU is characterized physiochemically as SUA values greater than 7 mg/dL. [2]. The primary causes of elevated SUA production include under-excretion of UA as a result of renal dysfunction, use of thiazide and loop diuretics, excessive physical activity, and consumption of purine-rich foods (red meat, seafood, beans), high-fat dairy products, alcohol, and sweetened soft drinks. [3]

Hyperuricemia is a predisposing condition for gout and is linked with metabolic syndrome [4] . Additionally, it was thought to be a separate risk

factor for high blood pressure. According to two meta-analyses of published prospective studies, for every 1 mg/dl increase in SUA level, the overall risk for incident hypertension rose by 13% and 15%, respectively. [5].

Numerous studies have suggested that SUA is correlated with some ocular diseases , especially diabetic retinopathy [6]. It is not well recognized that a developing nation like ours has such compelling facts. The purpose of this study was to examine the association between SUA and hypertensive retinopathy (HR) and to ascertain whether elevated blood uric acid levels were a risk factor for hypertension and hypertensive retinopathy in our Indian subcontinent. The purpose of this study is to highlight how metabolic parameters affect heart rate, and it is hypothesized that SUA gave doctors valuable information about when to perform fundoscopic exams on hypertensive patients.

Aims and Objectives

Aims: To study the serum uric acid concentration (SUA) in patients of hypertensive retinopathy and relationship between both.

Objectives

1) To evaluate association between SUA and hypertensive retinopathy.
2) Relationship of hyperuricemia with severity of hypertensive retinopathy.

Methodology

1) Source of study

Study place: Outpatient department, Department of Ophthalmology, Government medical college Kota, Rajasthan.

2) Study duration: 18 Months

Study design: Observational Cross Sectional Study

1) Method of data collection: after taking informed consent, detailed history regarding patients name, age, sex, occupation, address, presenting symptoms, duration, progression, and associated conditions was recorded. Detailed history of hypertension such as duration, type of treatment, overall control etc. noticed. According to previous studies Total Sample size of 240 patients was enrolled in this study of which, 120 patients (Hypertensive) was taken as case (Hypertensive retinopathy) and, 120 patients was taken as control (hypertensive without hypertensive retinopathy). Hypertensive group was further sub-categorized into two groups stage 1 (H1) and stage 2 (H2) based on Stage of hypertension (According to JNC VII classification of hypertension).

Inclusion Criteria: All patients of either sex, in all age groups diagnosed to have hypertension [stage 1 (H1) and stage 2 (H2) based on Stage of hypertension (According to JNC VII classification of hypertension)] with or without taking treatment, who developed hypertensive retinopathy as a complication.

Exclusion Criteria:

- Patients with known case of nephrolithiasis
- Patients with carcinoma or on chemotherapy
- Patients who are chronic alcoholic
- Patients on diuretics as treatment of hypertension
- Patients with diabetes and dyslipidemia.
- Patients with pregnancy induced hypertension.
- Difficult gradable fundus examination, for the reason of serious opacity of refractive media or terrible fixation vision.

Fundoscopy was carried out in both eyes through direct and indirect ophthalmoscope with hand held Volk 20 diopter lens in order to determine the presence and severity of hypertensive retinopathy according to the Keith-Wagener-Barker (KWB) system.

Table 1: Keith Wagener Barker (KWB) grades.

Grading	Findings
Grade 1	Generalized arteriolar constriction - seen as `silver wiring` and vascular tortuosities
Grade 2	As grade 1 + irregularly located, tight constrictions - Known as `(AV) nicking` or `AV nipping
Grade 3	As grade 2 + with hard exudates, cotton wool spots and flame-hemorrhages.
Grade 4	As above but with swelling of the optic disc (papilledema)

Statistical Analysis: A Microsoft Excel spreadsheet was used to enter the data, and the SPSS 10.0 software suite was used for statistical analysis. For independent samples, the unpaired two-tailed student "t"-test was used to test for significance of mean differences, and the Pearson coefficient was used to evaluate correlations. If the "p" value was less than 0.05, significance was taken into account.

Results

During the 24 months study period a total of 240 patients were studied of which 120 patients were cases who were categorized into group of hypertensive retinopathy and 120 were controls who were hypertensive patients without hypertensive retinopathy.

- **Age Distribution**: Among the 240 patients, the majority of both cases (hypertensive retinopathy) and controls (hypertension without retinopathy)

were in the 41-50 years age group, with the fewest in the 71-80 years group.

- **Sex Distribution**: There were more male patients than female patients in both groups, with 71 males and 49 females in the cases, and 67 males and 53 females in the controls.
- **Serum Uric Acid (SUA) Levels**:
  - **Cases**: 29.16% had SUA >7 mg/dl, and 70.83% had SUA ≤7 mg/dl.
  - **Controls**: Only 6.66% had SUA >7 mg/dl, and 93.33% had SUA ≤7 mg/dl.
  - The mean SUA level was significantly higher in cases (6.24 mg/dl) than in controls (5.59 mg/dl), with a p-value of 0.015.
- **SUA and Retinopathy Severity**: SUA levels increased with the severity of hypertensive retinopathy. The highest mean SUA level was observed in Grade 4 hypertensive retinopathy (7.91 mg/dl). A significant difference in SUA levels was found between Grades 1, 3, and 4.

In conclusion, elevated SUA levels are associated with hypertensive retinopathy and its severity.

Table 2: Results Summary in Tabular Form

Category	Cases	Controls
Total Number of Patients	120	120
Age Distribution		
31-40 years	22	18
41-50 years	39	50
51-60 years	38	38
61-70 years	19	13
71-80 years	2	1
Sex Distribution		
Males	71	67
Females	49	53
SUA Level Distribution		
0-7 mg/dl	85	112
>7 mg/dl	35	8
Mean SUA Level (mg/dl)	6.2398 ± 1.14759	5.5926 ± 0.93633
Significance (p-value)	0.015	
SUA and Retinopathy Severity		
Grade 1	Mean SUA = 5.7862 ± 1.02328	
Grade 2	Mean SUA = 6.5013 ± 1.09459	
Grade 3	Mean SUA = 7.3446 ± 0.48266	
Grade 4	Mean SUA = 7.9073 ± 0.47165	

Key Observations:

- The majority of both cases and controls were in the 41-50 years age group.
- There were more male patients than female patients in both cases and controls.
- Serum uric acid (SUA) levels were significantly higher in cases compared to controls (p = 0.015).
- SUA levels increased with the severity of hypertensive retinopathy, with the highest levels in Grade 4 retinopathy.

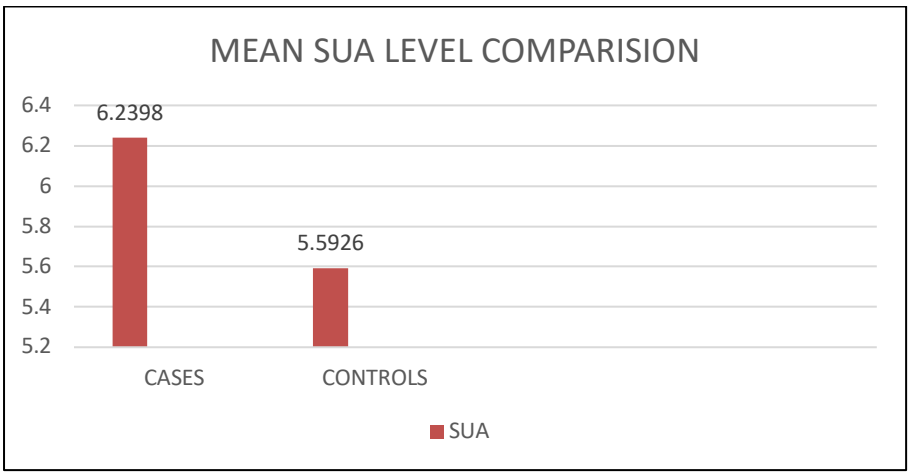

Figure 1: Mean sua level in cases and controls

A two sample t-Test to compare the means of Serum Uric Acid Level (mg/dl) for Cases and Controls of Hypertensive Retinopathy was performed with test data feed in SPSS software and confidence level of 95% (p value =0.05).

Significance value (p value) for the test was achieved 0.015 which is lower than assumed significance (i.e $p < 0.05$). The result directs us to reject Null Hypothesis (H_0). Hence it was proved that the alternative hypothesis is correct (i.e. Mean Serum Uric Acid level are different in both cases and controls of Hypertensive Retinopathy) with 95% confidence level.

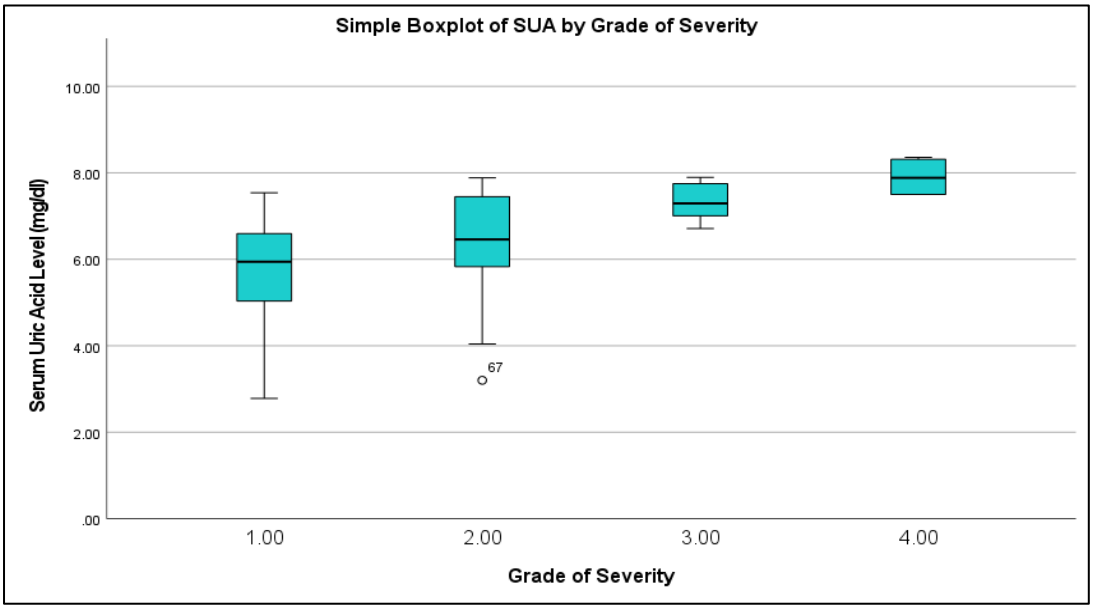

Figure 2: Sua level association with grade of severity of hypertensive retinopathy

A one-way ANOVA revealed that there was a statistically significant difference in mean Serum Uric Acid Level (mg/dl) between at least three groups ($F(3, 116) = [11.268]$, $p < 0.05$).

Tukey's HSD Test for multiple comparisons found that the mean value of Serum Uric Acid Level was significantly different between Severity-1 and Severity-3 ($p = 0.001$, 95% C.I. = [-2.6233, -0.4936]). Moreover, same significance was established between Severity-1 and Severity-4. Hence, there is enough proof of Severity Group 1, 3 and 4 are having different mean in Serum Uric Acid Level.

There was no statistically significant difference in mean exam scores between Severity-3 and Severity-4 ($p=0.816$).

Discussion

For hypertensive patients, identifying clinical characteristics that may be utilized to forecast the onset and course of retinopathy is vital.

Numerous research conducted in the last few years have suggested a link between uric acid and eye conditions. There have been reports of corneal uric acid crystals, band keratopathy, elevated intraocular pressure, asteroid hyalosis, conjunctival injection, and uveitis as ocular symptoms of gout, which is defined by an elevation in SUA. [7]. Patients with normal-tension glaucoma(NTG) have higher SUA levels than controls [8]. Both eyes' retinal vein occlusion (RVO) frequently coexists with hyperuricemia. [9]. Furthermore, uric acid contributed significantly to diabetic retinopathy (DR). All of the aforementioned studies demonstrated the detrimental effects on the eyes. Nonetheless, some research claimed that uric acid has antioxidant properties and might shield the retina from oxidative damage. Morsal and associates.[10] backed the idea that raising SUA levels could offer a therapeutic strategy for ARMD treatment. Numerous investigations have demonstrated significant connections between neuromyelitis optica and low uric acid. [11, 12]. Even though there was some inconsistency in the relationship between SUA and hypertensive retinopathy (HR), prior research has shown that SUA is a detrimental factor that exacerbates ocular diseases such as normal-tension glaucoma (NTG), retinal vein occlusion (RVO), and diabetic retinopathy (DR).[13-16]. Hypertensive Retinopathy (HR) and SUA levels were substantially correlated in this investigation; the findings confirmed that uric acid has a negative impact on HR. An increased risk of developing hypertension was linked to an increase in SUA. [17]. Thus, it was predicted in this study that uric acid tends to play a role in the pathophysiology of HR and facilitate its growth and progression. Although the hypothesis that uric acid mediates

vascular injury is not new, it has only lately come to be widely accepted. By stimulating the proliferation of vascular smooth muscle cells and nitric oxide synthase, elevated SUA can cause endothelial cell dysfunction, a crucial stage in the development of atherosclerosis. According to rat models of hyperuricemia, hyperuricemia gradually causes hypertension. Vasoconstriction resulted from uric acid-dependent renin-angiotensin system activation and downregulation of nitric oxide (NO) generation during the first phase. At this point, lowering uric acid causes blood pressure to improve and vessels to relax. Uric acid-mediated arteriolosclerosis is the hallmark of the second phase, which progresses over time. Later uric acid reduction cannot reverse this process, which results in permanent sodium-sensitive hypertension. [18]. Similar physiological and anatomical characteristics are shared by the retinal vasculature and other target organs. The retinal vascular bed is likewise impacted by SUA's effects on the systemic blood vessels. According to physiology, there are four stages of HR: vasoconstriction, sclerosis, exudation, and complications. [19]. Vasospasm and vascular endothelium hypoxia-ischemia are the results of chronic vasoconstriction, which is triggered by high blood pressure. Vascular smooth muscle cells are the result of these processes.

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.

In the present study the incidence of hyperuricemia >7mg/dl in controls was 7% and the incidence of hyperuricemia >7mg/dl in cases was 29%.

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 [20]. Kolbe (1965) in his study of 46 hypertensive patients found 26 to be having increased SUA levels (56 %) [21].

According to A. Breckenridge (1966), 90 of the 333 patients (27%) who were visiting the clinic for the first time had hyperuricemia, and 274 of the 470 patients receiving antihypertensive medication (58%) had elevated SUA levels. 40% of female hypertensives and 48% of male hypertensives in a research by C. J. Bulpitt (1975) had SUA levels in the hyperuricemic range.[68]. In his 1979 research of 73 individuals with uncontrolled hypertension, Ramsay found that 18 of them had elevated serum uric acid levels (25%)[22]. In their research group of 39 established hypertensives, Messerli et al. (1980) found that 72% of the subjects exhibited elevated SUA.

The common occurrence of hyperuricemia in hypertension patients, according to Messerli and Frohlich et al., may indicate underlying renal dysfunction or decreased renal perfusion, hypertensive retinopathy, and other end organ damage. [23].

In addition to contributing to the aetiology of hypertension and hypertensive retinopathy, an antioxidant deficiency in the diet causes hyperuricemia. Antioxidant medications also have the ability to reduce blood pressure in people with diabetes and hypertension. [24].

In a study by Tykarski (1991), he showed SUA concentration and the prevalence of hyperuricemia were significantly higher in hypertensive patients. They concluded that high prevalence of hyperuricemia in essential hypertension was caused by impaired renal excretion of uric acid [25].

Goldstein and Manowitz (1993) showed that 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 severity of hypertensive retinopathy is related directly to the SUA levels.

In his investigation, Tykarski demonstrated that the reduced tubular secretion of urate is the cause of SUA levels in hypertensives. In the current investigation, there was a strong correlation between the severity of hypertensive retinopathy and the incidence and severity of hyperuricemia.

In this study it was found that there is definite relation of serum uric acid level with hypertensive retinopathy and its severity.

In order to provide an in-depth examination of the relationship between SUA and HR, a longer term follow-up study including more detailed factors is required.

Conclusion

This result concludes that the mean serum uric acid level of cases (SUA=6.2398) is higher than the mean serum uric acid level of controls (SUA=5.5926). Which clearly indicates that serum uric acid level is associated with incidence of Hypertensive Retinopathy. And according to ANOVA test it was also found that serum uric acid is associated with severity of Hypertensive Retinopathy.

The impact of metabolic variables on HR was highlighted, and it was hypothesized that SUA gave doctors valuable information about when to perform funduscopic exams on hypertensive patients. More research may be necessary to fully understand the underlying mechanism by which SUA supports HR. More research and clinical

studies are still required to determine whether SUA lowering can lower the risk of HR**.**

Acknowledgements

We wish to thank the MRU department of Government Medical College, Kota for the approval of this study and allowing us to carry the research.

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