Original Article

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Association between Serum Uric Acid Levels and Primary Open-angle Glaucoma: A Cross-sectional Study

Biochemistry Section

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ABSTRACT

Introduction: There is an intricate association between serum Uric Acid (UA) levels and Primary Open Angle Glaucoma (POAG). UA levels in the blood are known to be a good indicator of antioxidant function, and a decrease in UA plays a key role in the pathogenesis of POAG. However, the association of serum UA and Uric Acid Creatinine Ratio (UACR) in POAG cases in the Indian population remains unexplored.

Aim: To investigate the association of serum UA levels and serum UACR with POAG.

Materials and Methods: This cross-sectional study was conducted among patients who attended the Outpatient Department (OPD) of Opthalmology at Maharajah's Institute of Medical Sciences, Vizianagaram, Andhra Pradesh, India. The duration of the study was one year and six months, from January 15, 2021 to July 15, 2022. The study included 200 recently diagnosed patients with POAG, who were divided into three groups based on Intraocular Pressure (IOP): Group 1 (mild) with an IOP of 21-30 mmHg, group 2 (moderate) with an IOP of 31-50 mmHg, and group 3 (severe) with an IOP greater than 51 mmHg. Age and gender-matched 199 healthy subjects were included as the control group. Blood samples were collected from the study subjects after obtaining informed consent and were tested for serum UA (using the modified Trinder method) and serum creatinine (using Jaffe's method) in a semiautomatic analyser (Erba chem 7). The data were analysed using Statistical Package for Social Sciences (SPSS) version 21.0 software and MS Excel 2007.

Results: The mean age of the study participants of all three groups was found to be 51.19±5.06 years with 46.7% male and 53.3% female subjects. The serum UA levels were 5.55±0.74 mg/dL in the mild POAG group, 4.1±0.5 mg/dL in the moderate POAG group, and 2.67±0.6 mg/dL in the severe POAG group (p-value <0.001). The present study also found that among the three study groups of POAG, UA levels were the lowest in the severe POAG group, followed by the moderate POAG group, and then the mild POAG group. This pattern was observed in both the males and females population.

Conclusion: The present study found that serum UA levels were decreased in POAG patients compared to the normal healthy control group. Furthermore, the study revealed a significant negative association between serum UA levels and serum UACR levels with the severity of POAG.

Keywords: Antioxidant, Intraocular pressure, Irreversible blindness, Oxidative stress

INTRODUCTION

Glaucoma is the third most common cause of irreversible blindness in India [1]. According to a study conducted in 2020 [2], 12 million people in India had glaucoma, with 1.5 million patients experiencing blindness. Alarmingly, 75% of cases remain undiagnosed [1,2], representing the submerged portion of the iceberg. The global burden of glaucoma was estimated to be 3.54% [3], while in India, it was found to be 2.10% in urban populations and 1.45% in rural populations in 2020 [4,5]. Glaucoma manifests as a progressive visual field defect, gradually causing tunnel vision and peripheral vision loss, along with structural damage to the optic disc [6]. In India, POAG has a higher prevalence compared to primary angle-closure glaucoma [4]. POAG is a multifactorial disease with diverse causative factors [7-9]. Oxidative stress is an important contributor to the pathophysiology of glaucoma [10,11], leading to physiological and morphological changes in aqueous humour outflow and subsequent damage to retinal ganglion cells [12,13].

The UA is naturally present in human blood as a byproduct of purine catabolism and acts as a major water-soluble antioxidant molecule. It scavenges strong oxidant superoxide and nitrogen radicals [14]. A study by Benoist d'Azy C et al., found that levels of oxidative stress biomarkers were increased, while antioxidative stress markers were decreased in subjects with POAG [10]. This suggests that UA levels in the blood can serve as an indicator of antioxidant function in POAG. Serum UA levels can vary among individuals based on their kidney function and purine catabolism. Serum Urine Albumin-to-Creatinine Ratio (UACR) provides an accurate measure of UA levels in the serum [15], reflecting the actual antioxidant activity in the human body. A literature search revealed no previous studies on the association between serum UA levels and POAG in the Indian population. Therefore, the present study was conducted to investigate the association between serum UA and POAG.

MATERIALS AND METHODS

A cross-sectional study was conducted in the OPD of Opthalmology at Maharajah's Institute of Medical Sciences, Vizianagaram, Andhra Pradesh, India. The duration of the study was one year and six months, from January 2021, to July 2022. The study protocol received approval from the Institution's Ethics Committee (IEC number IEC/108/21). Written informed consent was obtained from all study participants for the use of their clinical data in research.

Inclusion criteria: Recently diagnosed cases of open-angle glaucoma without any prior treatment, aged 18 years or older. The diagnosis of POAG was based on the presence of an open anterior chamber angle and glaucomatous damage in visual fields of one or both eyes, or IOP higher than 21 mmHg without any visual field defect [16]. If both eyes of a patient were affected by POAG, the eye with the highest IOP was selected for the study. Age and gender-matched individuals without glaucoma, who visited the institution for general ophthalmic complaints such as spectacle correction or dry eye, were included as controls in the study.

Exclusion criteria: Both cases and controls with conditions that can affect visual field tests other than glaucoma, such as diabetic retinopathy, hypertensive retinopathy, age-related macular

degeneration, and stroke, were excluded from the study. Additionally, patients with glaucoma under treatment, normotensive glaucoma, pseudoexfoliative syndrome, secondary glaucoma, those who underwent cataract or refractive surgery, had retinitis pigmentosa, or had acute systemic illness. Patients taking medication that could alter serum UA levels were also excluded from the study.

Sample size calculation: The study enrolled 200 recently diagnosed cases with POAG and 191 healthy controls who visited the Institution during the study period, using convenience sampling.

Study Procedure

The study participants were divided into three groups based on IOP: group 1 (mild) with IOP of 21-30 mmHg, group 2 (moderate) with IOP of 31-50 mmHg, and group 3 (severe) with IOP >51 mmHg [17,18]. Detailed clinical history was obtained from all study participants, including demographic details such as age and sex. A comprehensive ocular examination was performed in the ophthalmology department, including assessments of best-corrected visual acuity, IOP, anterior segment examination using a slit lamp biomicroscope with a 90D lens, detailed fundus examination, and visual field examination to confirm the diagnosis.

After obtaining informed consent, a 5 mL blood sample was collected from all subjects under aseptic conditions. The blood samples were analysed for serum UA (using the Modified Trinder method) and serum creatinine (using Jaffe's method) using a semi-automated chemistry analyser (Erba chem 7). The cut-off biological reference values were taken according to the kit manufacturer's instructions: For males, serum UA levels were considered to be 4.4-7.6 mg/dL, while for females, the range was 2.3-6.6 mg/dL. Serum creatinine levels for males were considered to be 0.7-1.4 mg/dL, and for females, the range was 0.6-1.1 mg/dL. The serum UA to UACR for both males and females was considered to be 3.5-6.

STATISTICAL ANALYSIS

The data were analysed using International Business Machines (IBM) SPSS Statistics version 21.0 software and MS Excel 2007. Qualitative variables were expressed as frequencies (n) and percentages (%), while quantitative variables were expressed as means and Standard Deviation (SD). The Student's unpaired t-test was used for mean comparisons between two groups. A p-value <0.05 was considered statistically significant.

RESULTS

In the present study, age and gender were not found to be statistically significant factors among the three groups. The mean serum UA and UACR levels were significantly higher in the mild POAG group compared to the moderate POAG group and the severe POAG group. The gender-based analysis of serum UA showed a strong association, with significantly higher levels among males. This association was also found in the gender-wise analysis of the parameter, with a p-value <0.001 for both male and female subjects [Table/Fig-1].

There was no statistical difference in age and gender between the cases and controls. Serum UA and serum UACR showed a significant association between the cases and controls, with a p-value <0.001. Both male and female subjects showed a significant association with serum UA and UACR levels (p-value <0.001) [Table/Fig-1]. The present study demonstrated that serum UA levels and UACR significantly decreased (p-value less than 0.001) with an increase in intraocular pressure in untreated POAG study groups. This effect was particularly evident in the severe POAG group compared to the control group [Table/Fig-2,3].

DISCUSSION

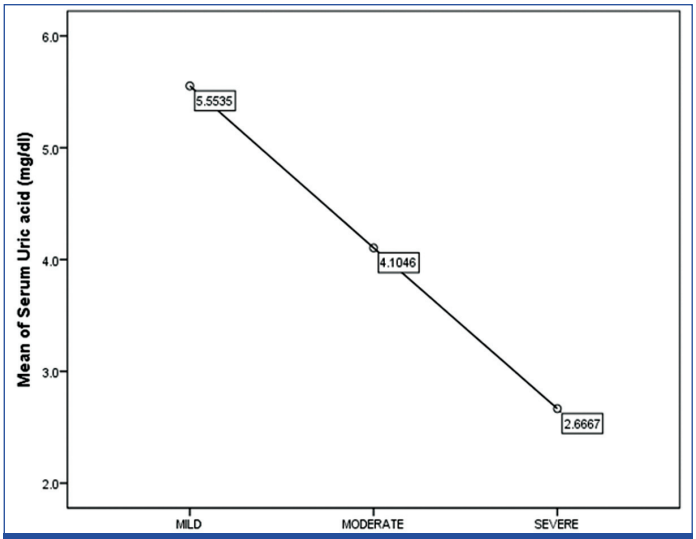
The present study investigated the association between serum UA and serum UACR in Indian subjects with mild, moderate, and severe POAG. The use of UACR was aimed at reducing potential interference arising from differences in renal function. Age and gender-matched subjects were selected as controls from the same rural areas of the district. UA is naturally produced in the human body during purine catabolism and excreted through the kidneys. A study by Waring WS reported that UA contributed up to two-thirds of the antioxidant activity in human blood [19]. Another study by De Lau LM et al., found a decreased risk of Parkinson's disease in subjects with higher UA levels in a large population-based cohort study [20]. It has been observed that oxidative stress alters aqueous humour outflow and increases intraocular pressure, leading to damage to retinal ganglion cells [12].

Previous studies have demonstrated that POAG patients have lower antioxidant activity in serum and aqueous humour [21-23]. Many studies have also shown increased oxidant activity in the serum and aqueous humour [22,24,25]. Tanito M et al., showed that serum antioxidant capacity reflects the local redox status of the eye [26]. It is also understandable that UA gets consumed by excess oxidising agents produced in POAG in both the serum and aqueous humour.

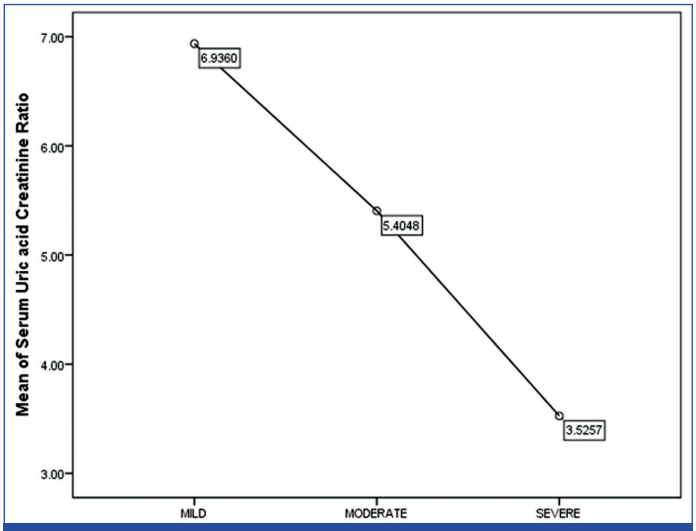
The present study investigated serum UA levels according to the severity in participants with POAG and found that among these groups, those with the most severe POAG had the lowest levels of UA. This pattern was observed in both the male and female

Parameters	Mild POAG (n=86)	Moderate POAG (n=66)	Severe POAG (n=48)	p-value	F-value	Control group (n=199)	p-value
Age (in years)	50.78±5.2	52±4.1	50.81±5.9	0.412	3.677	52.61±4.7	0.496
Gender (M/F)	39/47	31/35	23/25	0.943	0.12	108/91	0.6129
Serum Uric Acid (UA) (mg/dL)							
Total	5.55±0.74	4.1±0.5	2.67±0.6	<0.001	334.436	6.22±0.9	<0.001
Male	6.15±0.39	4.18±0.58	2.64±0.58	<0.001	783.245	6.72±0.74	<0.001
Female	5.05±0.58	4.03±0.42	2.69±0.63	<0.001	289.476	5.6±0.62	<0.001
Serum creatinine (mg/dL)							
Total	0.8±0.09	0.76±0.09	0.77±0.1	<0.001	29.862	0.87±0.09	<0.001
Male	0.83±0.07	0.76±0.1	0.75±0.11	<0.001	16.4	0.86±0.09	<0.001
Female	0.78±0.1	0.78±0.09	0.79±0.1	0.824	0.194	0.88±0.09	0.7869
Serum Uric Acid (UA) Creatinine Ratio (UACR)							
Total	6.94±0.86	5.4±0.88	3.52±0.97	<0.001	165.577	7.2±1.29	<0.001
Male	7.41±0.74	5.58±0.89	3.59±0.94	<0.001	324.05	7.85±1.2	<0.001
Female	6.54±0.74	5.24±0.84	3.47±1.01	<0.001	204.983	6.39±0.88	<0.001

[Table/Fig-1]: Comparison of age, gender, serum uric acid, serum creatinine, and serum uric acid creatinine ratio stratified as per glaucoma severity.
Analysis of Variance (ANOVA) F-test; POAG: Primary open angle glaucoma; M: Male; F: Female; n: Number; mg/dL: Milligram per decilitre; p<0.05 was considered significant



[Table/Fig-2]: Association between serum Uric Acid (UA) and types of Primary Open Angle Glaucoma (POAG).



[Table/Fig-3]: Association between serum Uric Acid Creatinine Ratio (UACR) and types of Primary Open Angle Glaucoma (POAG).

population. All the associations were statistically highly significant (p-value <0.001). In a previous study by Li S et al., it was found that baseline serum UA levels were significantly higher in subjects with non progressing Primary Angle Closure Glaucoma (PACG) compared to progressing PACG. In contrast, patients with lower baseline serum UA levels had a higher probability of developing glaucoma progression during the follow-up period [27]. These results suggest that decreased serum UA levels may be associated with an increased risk of developing POAG. The decreased levels of UA can be an indicator and a risk factor for developing POAG.

The study by Kim SW and Kang GW (2016) found that the male population had a higher risk of developing POAG than females [8]. This gender difference could be explained by higher oestrogen levels in females than in males. Oestrogen hormone has a great anti-inflammatory property regulated by pro-inflammatory genes at the molecular level [28]. The present study showed higher UA values in male subjects than in female subjects, which could be due to the smaller study population.

The present study demonstrated that serum UA levels in POAG subjects were significantly lower than those in the control subjects (p-value <0.001). Additionally, current study showed that serum UACR levels in POAG subjects were significantly lower than in the control subjects (p-value <0.001). On the other hand, a study by Yuki K et al., showed statistically significant higher UA levels in normotensive glaucoma subjects [29]. Another study by Mohammadi M et al., concluded that there was a higher UA level in glaucoma patients compared to controls, but this finding was not statistically significant [30]. In conclusion, based on the findings of the current study, it is hypothesised that there is a strong association between mean serum UA levels and serum UACR levels with POAG severity in untreated POAG subjects.

Limitation(s)

This research was conducted at a hospital facility in northern Andhra Pradesh. To achieve a more comprehensive perspective, it is essential to conduct the study at the community level, including sampling from each village. Additionally, conducting nationwide research can provide precise insights into the overall situation.

CONCLUSION(S)

The present study found that serum UA levels decreased in POAG patients compared to the healthy controls. It was also found that UA levels had a significant association with the severity of POAG. Therefore, serum UA and UACR can be used as potential biomarkers in patients with POAG to assess the severity of the disease. A more detailed study is required with a larger study population selected at the community level, including urban and rural populations from various parts of India.

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