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Association between Albuminuria and Primary Open-angle Glaucoma in non-diabetic subjects - A cross-sectional study in Northern Andhra Pradesh.

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Abstract

Background: Glaucoma is one of the major reasons for irreversible blindness in India. The global burden of Glaucoma was estimated to be 3.54% and India was found to be 2.3 – 4.7 % in the year 2020. Systemic vascular factors are shown to be a risk factor for the development of Primary open-angle Glaucoma (POAG). Albuminuria signifies widespread vascular damage in the human body. It is seen as an indicator for the identification of various cardiovascular and cerebrovascular diseases. Many studies have shown that Albuminuria can be used as an indicator for early diagnosis of POAG.

Objectives: To study the Association between Albuminuria and Primary Open-Angle Glaucoma in non-diabetic subjects.

Methods: This was a hospital-based cross-sectional study. The study included Recently diagnosed 200 patients with Primary Open-angle Glaucoma (POAG). They were categorised into 3 groups based on their Urine Albumin-Creatinine Ratio (UACR). Group 1 included 151 POAG Patients with UACR <30 mg/g. Group 2 included 19 POAG patients with UACR 31 – 300 mg/g. Group 3 included 32 POAG patients with UACR > 300 mg/g.

Results: Urine albumin had a highly statistically significant (P-Value 0.00) association with the Urine

Albumin-Creatinine ratio in all the 3 groups in our study. Urine Creatinine was not found to have a statistically significant association with UACR (P-Value >0.05 in all 3 groups). UACR was seen to be highly increased (Group 1 < Group 2 << Group 3) in group 3 compared to other groups. All the 3 groups had a statistically significant association (P-Value 0.00) in UACR concentration. The odds ratio significantly increased between Group 1 and Group 3. This quantified a strong association between UACR >300 mg/g and Primary Open-Angle Glaucoma.

Conclusion: Our study proved a strong Statistically significant association between High-grade Albuminuria recognised by high UACR and POAG.

Keywords: Albuminuria, Primary Open-Angle Glaucoma, Urinary Albumin, Urinary Albumin-Creatinine Ratio.

Introduction

Glaucoma is one of the major reasons for irreversible blindness in India. It is presented as a progressive Visual field defect that slowly causes Tubular vision with loss of peripheral vision associated with structural damage to Optic disc [1]. The global burden of Glaucoma was estimated to be 3.54% [2] and India was found to be 2.3 – 4.7 % [3,4] in the year 2020. The pathogenesis of Glaucoma has not been fully understood. Increased Intra Ocular Pressure (IOP) and insufficient blood supply to the Optic disc are found to be major causes. Systemic vascular factors are shown to be a risk factor for the development of open angle Glaucoma. The vascular perspective is supported by the increased incidence of Cardiovascular and Cerebrovascular mortality and morbidity in patients with Glaucoma [5-7].

Albuminuria signifies widespread vascular damage in the human body. It is seen in Patients with Diabetes, Hypertension, and patients with cardiovascular disease. Functional units of the kidney and eye have common Physiological and anatomical features. Many studies have shown an association between Albuminuria and Primary Open-angle Glaucoma (POAG). To date, Association between Open-angle Glaucoma and albuminuria has not been studied in India. Therefore, we investigate the association in this study.

Material and methods

Study design

This was a hospital-based cross-sectional study. The study included Recently diagnosed 200 patients with Primary Open-angle Glaucoma (POAG). They were categorised into 3 groups based on their Urine Albumin-Creatinine Ratio (UACR). Group 1 included 151 POAG Patients with UACR <30 mg/g. Group 2 included 19 POAG patients with UACR

31 – 300 mg/g. Group 3 included 32 POAG patients with UACR > 300 mg/g. Age and gender were matched among 3 groups. These were the patients who attended the Ophthalmology OPD of the Institution for 1.5 years from 15.01.2021 to 15.07.2022. the study protocol was approved by the ethics committee of the Institution. Informed consent was obtained from all the study participants.

Inclusion Criteria

Subjects in all 3 groups were recently diagnosed patients with Open-angle Glaucoma. Patients with one or both eyes affected by Glaucoma were selected. All the test subjects were non-diabetic, ages 19 years or higher. They were characterised by HbA1c less than 5.7% and without a history of Diagnosis of Diabetes.

Exclusion Criteria

Exclusion criteria included patients with conditions that affect Visual field tests other than Glaucoma such as Diabetic retinopathy, Hypertensive Retinopathy, Age-related macular degeneration, and Stroke. Patients with Glaucoma under treatment, Normotensive Glaucoma,

Pseudo exfoliative syndrome, patients who underwent cataract or Refractive surgery, retinitis pigmentosa, and acute systemic illness were excluded from the study.

Methods

Detailed clinical history was taken from all the subjects who participated in the study. Details including age, sex, blood sugar, and associated systemic complications like Neuropathy, Nephropathy, Hyperlipidemia, and Hypertension were noted. Complete ocular examination was done in the department of Ophthalmology which included Best corrected visual acuity, Intra Ocular Pressure (IOP), Anterior segment examination using slip lamp biomicroscope with 90D lens, Detailed Fundus examination, and Visual field examination.

After obtaining Informed consent from the subject, 5 mL of the blood sample was collected from all subjects under aseptic conditions.

Blood was tested for Fasting Blood sugar (GOD-POD method), and HbA1c (Cation exchange resin method) to separate Diabetic patients. Morning first Urine sample was collected from all the study participants. It was tested for Urinary Albumin (BCG dye method) and Creatinine (Jaffe's method) levels in Semiautomatic analyser Erba chem 7. Urinary albumin excretion was noted as urinary Albumin-Creatinine ratio (UACR) in milligrams per gram of creatinine.

Statistical methods

Data were analysed using IBM SPSS Statistics Version 21.0 and MS Excel 2007. Qualitative variables were expressed as frequency and percentages. Quantitative variables were expressed in Mean and Standard deviations.

The student unpaired test was used for a two-group mean comparison. For all statistical analyses, P <0.05 was considered statistically significant.

Results

All the 3 groups were analysed in detail. As seen in table 1.1, age was found to be matched between 3 groups with a P-Value of 0.946. subjects in all the 3 groups were found to be non-Diabetic.

FBS (P-Value 0.832) and HbA1c (P-Value 0.803) were also matched in all the 3 groups. The mean ± Standard deviation of Urine albumin was found to be 14.7 ± 4.9 mg/l in Group 1, 45.5 ± 10.5 mg/l in Group 2, and 377.19 ± 85.8 mg/l in Group 3. Urine albumin had a highly statistically significant (P-Value 0.00) association with the Urine Albumin-Creatinine ratio. This was seen in all the 3 groups in our study. Urine Creatinine was not found to have a statistically significant association with UACR (P-Value >0.05 in all 3 groups).

As seen in Tables 1.2 and 1.3, UACR was studied in the 3 groups individually. The mean ± Standard deviation of UACR was found to be 20.3 ± 5.2 mg/g in Group 1, 64.5 ± 14.5 mg/g in Group 2, and 519.2 ± 86.6 mg/l in Group 3. UACR was seen to be highly increased (Group 1 < Group 2 << Group 3) in group 3 compared to other groups. All the 3 groups had a statistically significant association (P-Value 0.00) in UACR concentration.

Table 1.4 showed post-HOC analysis between different variables in 3 groups of our study. Here Urine Albumin showed a highly statistically significant association (P-Value 0.000) with UACR in all the 3 study groups. Table 1.5 shows Odds Ratio between the 3 study groups. The odds ratio was 0.945 between Group 1 and Group 2 and 1.388 between Group 1 and Group 3. The odds ratio significantly increased between Group 1 and Group 3. This quantified a strong association between UACR >300 mg/g and Primary Open-Angle Glaucoma.

Table 1: Mean, SD, and P-Value of Age, FBS, and HbA1c, Urinary Albumin and Urinary Creatinine.

		Number	Mean	Std. Deviation	P-value
AGE	Group 1	151	49.77	5.241	0.946
	Group 2	19	50.21	6.277	
	Group 3	32	49.88	6.236	
	Total	202	49.83	5.481	
FBS	Group 1	151	93.19	9.806	0.832
	Group 2	19	92.05	10.485	
	Group 3	32	93.78	9.644	
	Total	202	93.17	9.805	
HbA1c	Group 1	151	5.038	.2847	0.803
	Group 2	19	5.079	.3066	
	Group 3	32	5.025	.2929	
	Total	202	5.040	.2869	
Urine Albumin	Group 1	151	14.70	4.989	0.000**
	Group 2	19	45.53	10.564	
	Group 3	32	377.19	85.882	
	Total	202	75.02	136.082	
Urine Creatinine	Group 1	151	.7097	.08841	0.665
	Group 2	19	.7084	.06735	
	Group 3	32	.7247	.09112	
	Total	202	.7119	.08690	

FBS – Fasting Blood Sugar, HbA1C – Glycated Hemoglobin, Std: Standard; P<0.05 was considered significant, P- 0.000** is considered highly significant; Table is Original.

Table 2: Mean, SD, and P-Value of Urinary Albumin-Creatinine Ratio (UACR) in 3 groups.

	Number	Mean	Std. Deviation	P-value
Group 1	151	20.320	5.2408	0.000
Group 2	19	64.542	14.4813	
Group 3	32	519.247	86.6435	
Total	202	103.517	184.5428	

Std: Standard; P- 0.00 was considered highly significant; Table is Original.

Table 3: Mean Difference and P-Value of Urinary Albumin-Creatinine Ratio (UACR) between 3 groups.

(I) group	(J) group	Mean Difference (I-J)	Standard Error	P-value
Group 1	Group 2	-44.2222*	8.4644	.000
	Group 3	-498.9270*	6.7670	.000
Group 2	Group 1	44.2222*	8.4644	.000
	Group 3	-454.7048*	10.0709	.000
Group 3	Group 1	498.9270*	6.7670	.000
	Group 2	454.7048*	10.0709	.000

P- 0.00 was considered highly significant; the Table is Original

Table 4: Post HOC analysis between different variables.

	(I) group	(J) group	Mean Difference (I-J)	Standard Error	P-value
AGE	Group 1	Group 2	-.442	1.341	.742
		Group 3	-.107	1.072	.921
	Group 2	Group 1	.442	1.341	.742
		Group 3	.336	1.595	.834
	Group 3	Group 1	.107	1.072	.921
		Group 2	-.336	1.595	.834
FBS	Group 1	Group 2	1.133	2.396	.637
		Group 3	-.596	1.916	.756
	Group 2	Group 1	-1.133	2.396	.637
		Group 3	-1.729	2.851	.545
	Group 3	Group 1	.596	1.916	.756
		Group 2	1.729	2.851	.545
HbA1c	Group 1	Group 2	-.0405	.0701	.564
		Group 3	.0134	.0561	.811
	Group 2	Group 1	.0405	.0701	.564
		Group 3	.0539	.0834	.519
	Group 3	Group 1	-.0134	.0561	.811
		Group 2	-.0539	.0834	.519
Urine Albumin	Group 1	Group 2	-30.831*	8.354	.000**
		Group 3	-362.492*	6.679	.000**
	Group 2	Group 1	30.831*	8.354	.000**
		Group 3	-331.661*	9.940	.000**
	Group 3	Group 1	362.492*	6.679	.000**
		Group 2	331.661*	9.940	.000**
Urine Creatinine	Group 1	Group 2	.00125	.02121	.953
		Group 3	-.01502	.01696	.377
	Group 2	Group 1	-.00125	.02121	.953
		Group 3	-.01627	.02524	.520
	Group 3	Group 1	.01502	.01696	.377
		Group 2	.01627	.02524	.520

FBS – Fasting Blood Sugar, HbA1C – Glycated Hemoglobin, Std: Standard; P<0.05 was considered significant, P- 0.000** was considered highly significant; Table is Original.

Table 5: P-Value and Odds Ratio between 3 study groups.

			Odds ratio
Group 2	Intercept	.000	
	[SEX=Female]	.891	.945
	[SEX=Male]	.	.
Group 3	[SEX=Female]	0.0345	1.388
	[SEX=Male]	.	.

P<0.05 was considered significant, P- 0.000** was considered highly significant; Table is Original.

Discussion

This was one of the first Cross-sectional study to show the association between albuminuria and POAG in India in nondiabetic patients. Even though many studies were done before, it was done in Diabetic patients. Our cross-sectional study showed statistically significant (P-Value 0.000**) Albuminuria in Group 3 Patients compared to Group 1 and Group 2. Urine albumin also had a highly statistically significant (P-Value 0.00) association with the Urine Albumin-Creatinine ratio. UACR was seen to be highly increased (Group 1 < Group 2 << Group 3) in group 3 compared to other groups. The odds ratio significantly increased between Group 1 and Group 3. This quantified a strong association between UACR >300 mg/g and Primary Open-Angle Glaucoma. This association was also seen in a study conducted by Lim ZW et al (2021)[8]. The study proved albuminuria was independently associated with POAG. It's regarded as a risk factor and also an Indicator of the possibility of POAG in patients. The same findings were also seen in the study by Wei Liu et al (2022) [9], and Choi JA et al (2015) [10].

Glaucoma is one of the most common reasons for Blindness in India and the world. Two major types of Glaucoma are Primary Open-Angle Glaucoma (POAG) and Primary Closed-angle Glaucoma (PCAG). The etiology of both types of Glaucoma are different and POAG has more systemic connection than PCAG. Eye and Kidney have common Embryonic and genetic development. Glomerulus and Choroid have similar vascularity [11,12]. The Choroid and Glomerulus have similar filtration barriers with the Renin-Angiotensin-Aldosterone System (RAAS) regulating both of them. Due to this both Choroid and Glomerulus get affected in Vascular systemic diseases. Several earlier studies investigated Ocular factors with Urinary Albumin excretion among non-Glaucomatous Diabetes patients [10]. The study by Lim ZW et al (2021)[8], and Choi JA et al (2015) [10] showed Urinary albumin excretion was associated with high Intra Ocular pressure. Albuminuria was an independent risk factor for the development of POAG. An article by Wei Liu et al (2022) [9] showed Macroalbuminuria as an independent risk factor for POAG and microalbuminuria as not a risk factor.

In recent times Albuminuria is considered an independent predictor for cardiovascular events like Myocardial Infarction, Stroke, and Death in both Non-diabetic and Diabetic subjects [13,14]. Albumin leak from Glomerulus reflects widespread capillary vasculopathy mediated by atherosclerosis. There will be endothelial dysfunction which causes endothelial-dependent vasodilatation [15]. It causes an increased risk of cardiovascular diseases in long term [16]. Insufficient ocular blood supply is one of the factors for the pathogenesis of Glaucoma [17]. Various systemic factors influence and compromise ocular blood flow in Glaucoma patients. Some of them are blood pressure behavior [18,19], vascular endothelial dysfunction [20,21,22,] and autonomic dysfunction. These facts establish a common angiopathic link between Albuminuria and POAG. It is also noteworthy that association between POAG and albuminuria via angiopathic mechanism is also possible in low-grade albuminuria, as early as the

association between cardiovascular disease and albuminuria in the general population [23,24,25].

Conclusion:

Our study proved a strong Statistically significant association between High-grade Albuminuria recognized by high UACR and POAG. Even though the association was strong in UACR <300 mg/g, it's highly significant in UACR > 300 mg/g. Patients with High-grade albuminuria can be checked for possible Primary Open-angle Glaucoma. POAG is a silent killer. Symptoms appear in POAG patients months after irreversible damage to the optic nerve. So, considering High-grade albuminuria as a sign, early detection of POAG is possible which will decrease visual loss.

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