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Original Research Article

Association of Gamma-glutamyl transferase with severity of hypertensive retinopathy in the Indian population

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ABSTRACT

Background: Hypertension is the condition of elevated blood pressure and is a serious medical condition that significantly increases risk of diseases associated with the heart, brain, kidney, eyes, etc. and its most common ocular presentation is Hypertensive retinopathy (HR). Oxidative stress has been extensively studied for its role in the pathophysiology of Hypertensive retinopathy. Through this study, we want to establish an association between the severity of Hypertensive retinopathy and Gamma-glutamyl transferase (GGT).

Materials and Methods: After obtaining clearance from the ethics committee, an analytical study was carried out comprising 100 individuals having Hypertensive retinopathy. Patients were divided into four groups according to the Keith Wagener classification. The patients underwent thorough clinical examinations. The ocular examination included visual acuity evaluation, IOP measurement by Goldmann tonometry, and fundoscopy. Biochemical investigation of Serum Gamma-glutamyl transferase was done using a CORAL Colorimetric assay kit and SPSS Version 21.0 was used for statistical analysis.

Result: The majority of Grade I HR people belonged to either normal or prehypertensive group, while the majority of Grade IV, II & III were from the Stage I hypertensives group, followed by Grade II and Grade III hypertension. Statistically, a significant association between the increasing severity of retinopathy and the rise in BP was observed. Most patients with Grade I retinopathy (66.7%) had GGT levels < 40 U/l, while all the patients in Grade II, III & IV (100.0% each) had GGT >40 U/L. Statistically, it was also noted that the GGT levels increased with increasing grades in HR.

1. Introduction

Hypertension is the condition of elevated blood pressure and is a serious medical condition that significantly increases the risk of diseases associated with the heart, brain, kidneys, eyes, etc. The World Health Organization defines hypertension as a systolic pressure greater than 140 mmHg and/or a diastolic pressure greater than 90 mmHg.[1] Due to unhealthy diets and lack of physical activity,[2] the prevalence of hypertension has been on a rise globally. In 2010, about 1.39 billion adults worldwide had hypertension and by the year 2025, a 30% increase in this prevalence is estimated, exposing nearly two billion individuals to risk of hypertension and associated comorbidities.[3]

The most common ocular presentation of hypertension is Hypertensive retinopathy (HR). HR occurs when the retinal vessels get damaged due to elevated blood pressure.[4]

As the pathophysiological mechanism of Hypertensive retinopathy (HR) is not fully established, in recent years, an association between oxidative stress has been extensively studied to evaluate its role and explore other pathogenic mechanisms that might be involved.[5]

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Gamma-glutamyl transferase (GGT) is a plasma membrane enzyme with a central role in glutathione homeostasis, which is important in maintaining adequate concentrations of intracellular glutathione to protect cells against oxidants. Elevated serum GGT activity is a sensitive marker of oxidative stress.[6]

Therefore, in this study, we want to establish a relationship between the severity of hypertensive retinopathy and GGT.

2. Materials and Methods

An analytical study was carried out in a tertiary care in North India, which comprised 100 individuals having hypertensive above the age of 40 years. Clearance for carrying out the study was obtained from the Institutional Ethical Committee. Informed consent was obtained, and the study was in accordance with the ICMR's ethical guidelines for biomedical and health research on human participants (2017).

Patients were divided into 4 groups according to the Keith Wagener classification of Hypertensive retinopathy. 33 patients with Grade I HR were classified as Group 1, 35 patients with Grade II HR as Group 2, 27 patients with Grade III HR as Group 3, and 5 patients with Grade IV HR as Group 4. The exclusion criteria included any ocular media opacity, history of anti-epileptic drug intake, age< 40 years, Diabetes mellitus, smoking, and alcohol intake more than 30 g/day, Hepatitis B or C infection or other known liver diseases, use of hepatotoxic drugs, cardiac, renal, cerebral or other systemic diseases, recent major surgery or illness.

The patients underwent thorough ophthalmological clinical examination and a detailed history including ocular symptoms of hypertension, duration and treatment of hypertension, other associated illnesses, etc. was taken. Systemic examination was also carried out and baseline biochemical investigations were done.

2.1. Measurement of BP

A mercury sphygmomanometer was used for the measurement of arterial BP in a sitting position. An average of three readings was recorded in 5 mins for each subject. The subjects were divided into 4 groups as per the eighth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines (JNC 8): Normal <120/80mmHg; Prehypertensive- SBP 120-139mmHg and DBP 80; Stage 1 HTN- SBP 140-159mmHg and DBP 90-99mmHg; Stage 2 HTN- SBP>160mmHg and DBP>100mmHg.

2.2. Ocular examination

Visual acuity was evaluated by using Snellen's chart, and intraocular pressure by using the Goldmann Applanation tonometer. Fundoscopy was done by direct ophthalmoscopy and indirect ophthalmoscopy. Fundoscopy was performed by a single-blinded observer, after which grading for Hypertensive retinopathy was done by using Keith-Wagener-Barker (KWB) classification. The participants were classified as Grade I, Grade II, Grade III, and Grade IV.

2.3. Biochemical investigation

2ml of blood sample was obtained from the antecubital vein without the use of a tourniquet, between 09.00 and 10.00 hours, of overnight fasting patients to avoid the differences of diurnal variation under aseptic conditions. Serum estimation of Gamma-glutamyl transferase was measured colorimetrically using a CORAL Colorimetric assay kit.

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 21.0 Statistical analysis software. Gamma-glutamyl transferase values across groups were compared with a one-way analysis of variance (ANOVA). Summary data for GGT and other continuous variables was expressed as mean SD. Statistical significance was defined as $P<0.05$.

3. Result

The majority of Grade 1 HR people belonged to either normal or prehypertensive group, while the majority of Grade IV, II & III were from the Stage I hypertensive group, followed by Grade II and Grade III hypertension. Statistically, a significant association between the increasing severity of retinopathy and the rise in BP was observed. (Table 1)

Of patients with Grade I HR, 36.4% belonged to the age group of 50-59 years. In Grade III HR, the maximum number of people belonged to the age group 50-59 years i.e., around 37% of the total. In patients with Grade II HR and Grade IV HR, a maximum number of people belonged to the age group of 40-49 years (40%). On comparing statistically, age among the retinopathy Grades was found to be comparable. The ratio of females having HR was found to be more than that of males. On comparing statistically, gender among the retinopathy grades was found to be comparable. Statistically, family history of hypertension and ongoing treatment were comparable among retinopathy grades. In 88.6% of patients with Grade II HR, there was a positive family history of hypertension and 85.7% of them were on treatment. Longest duration of hypertension was found in Grade III (63.4±48.4 months), followed by Grade I (55.6±31.5 months), Grade II (39.2±20.4 months), Grade IV (29.8±13.1 months) respectively. Statistically, a significant association was observed between the duration of hypertension with grades of retinopathy. (Table 2)

Table 1: Blood pressure distribution according to JNC 8 guidelines in different grades of hypertensive retinopathy

S.No.	Blood Pressure category (mmHg)	Grade I		Grade II		Grade III		Grade IV	
		No.	%	No.	%	No.	%	No.	%
1	Normal (<120 and <80) (n=14)	12	36.4	2	5.7	0	0.0	0	0.0
2	Prehypertension (SBP 120-139) (n=17) (DBP 80-89)	11	33.3	5	14.3	1	3.7	0	0.0
3	High blood pressure (Hypertension) Stage 1 (SBP -140-159) (DBP-90-99) (n=51)	9	27.3	23	65.7	14	51.9	3	60.0
4	High blood pressure (Hypertension) Stage 2 (SBP- >=160) (DBP->=100) (n=20)	1	3.0	5	14.3	12	44.4	2	40.0
χ^2=46.706; p<0.001									

Table 2: Demographic distribution in different grades of hypertensive retinopathy according to JNC 8 guidelines (n=100)

Parameter	Subtype	Total	Grade I (n=33)		Grade II (n=35)		Grade III (n=27)		Grade IV (n=5)		P Value
			No.	%	No.	%	No.	%	No.	%	
Age group	40-49 years	28	6	18.2	14	40.0	6	22.2	2	40.0	χ^2=7.097 (df=9); p=0.627
	50-59 years	32	12	36.4	9	25.7	10	37.0	1	20.0	
	60-69 years	26	9	27.3	7	20.0	9	33.3	1	20.0	
	≥70 years	14	6	18.2	5	14.3	2	7.4	1	20.0	
Gender	Female	55	18	54.5	20	57.1	14	51.9	3	60.0	χ^2=0.226 (df=3); p=0.973
	Male	45	15	45.5	15	42.9	13	48.1	2	40.0	
Family H/o		83	26	78.8	31	88.6	22	81.5	4	80.0	χ^2=1.261 'p'=0.738
Ongoing Treatment		78	27	81.8	30	85.7	17	63.0	4	80.0	χ^2=5.064 'p'=0.167
Duration (months)	Mean±SD		55.6±31.5		39.2±20.4		63.4±48.4		29.8±13.1		**'p'=0.017**

Table 3: Blood pressure distribution in 4 Grades of retinopathy

S. No	Blood pressure	Grade I (n=33)		Grade II (n=35)		Grade III (n=27)		Grade IV (n=5)		ANOVA	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	'p'
1	SBP	127.09	12.55	140.35	12.96	153.70	17.35	156.0	16.73	19.1999	<0.001
2	DBP	82.06	6.26	88.80	5.54	97.78	13.61	98.00	13.04	16.651	<0.001
3	MAP	97.07	7.64	106.78	6.87	116.42	13.93	117.33	13.82	21.207	<0.001

Table 4: Distribution of GGT levels and mean GGT levels in Grades of retinopathy

S.No.	GGT levels	Total	Grade I (n=33)		Grade II (n=35)		Grade III (n=27)		Grade IV (n=5)		
			No.	%	No.	%	No.	%	No.	%	
1	<=40	11	11	33.3	0	0.0	0	0.0	0	0.0	χ^2=25.094; p<0.001
2	>40	89	32	66.7	35	100.0	27	100.0	5	100.0	
	mean GGT levels		41.85±3.27		45.63±2.67		49.81±4.35		66.20±5.26		**<0.001**

Most elevation of SBP, DBP, and MAP was seen in Grade IV retinopathy and there was a significant association between elevated blood pressure parameters with retinopathy grades with p<0.001. (Table 3)

Most patients with Grade I retinopathy (66.7%) had GGT levels < 40 U/L, while all the patients in Grade II, III & IV (100.0% each) had GGT levels>40 U/L. Statistically, a significant difference was found among the retinopathy grades and mean for GGT levels, and it was also noted that the GGT levels increased with increasing grades of HR. (Table 4)

4. Discussion

Hypertension is characterized by persistently high blood pressure (BP) in the systemic arteries. Several etiologies can underlie hypertension and it is the most common preventable risk factor for cardiovascular disease, chronic kidney disease, etc. Elevated BP alone does not fully account for the extent of retinopathy, other pathogenic mechanisms may be involved, such as, increased oxidative stress.

Gamma-glutamyl transferase (GGT) is a plasma membrane enzyme with a central role in glutathione homeostasis, which is important in maintaining adequate concentrations of intracellular glutathione to protect cells against oxidants. Hence, this study was done to find a correlation between GGT and Grades of Hypertensive retinopathy in the North Indian population.

In our study, we observed that most people with Grade I and Grade III HR belonged to the age group of 50-59 yrs, and most people with Grade II and Grade IV HR belonged to the age group 40-49 yrs. These findings were similar to the study of Omotoso et al. (2016),[7] in which they concluded that retinopathy was found to be significantly associated with older age and longer duration of hypertension. Besharati et al. (2006),[8] in their study, observed that 55.4% of hypertensive patients were females which was similar to our result in which 55% were females, while in a study by Shah et al. (2013)[9] and Mondal et al. (2017),[10] majority of the hypertensive patients enrolled were males.

Cheung et al. (2011)[7] found that only GGT, significantly and independently predicted a new onset of hypertension. In another study, Jung et al. (2011)[8] reportedGGT to have strong and positive correlation with systolic blood pressure and diastolic blood pressure. Elahiekh et al. (2014)[9] concluded that patients with metabolic disorders have significantly elevated GGT levels and hs-CRP, except for hypertensive.

Kim et al. (2012)[10] reported that GGT levels were within the normal range but had a positive association with an increased risk of incident hypertension, particularly in drinkers and overweight individuals.

In the present study, levels of GGT showed a significant difference in different Grades of retinopathy. Serum GGT levels were observed to be highest in Grade IV Hypertensive retinopathy (66.20±5.26 U/L), followed by Grade III (49.81±4.35 U/L) than Grade II (45.63±2.67 U/L) and then Grade I hypertensive retinopathy (41.85±3.27 U/L). Karaca et al. (2013),[11] in their study compared GGT levels among Grade I & Grade II Hypertensive retinopathy and normotensive and reported a similar finding of an increasing trend of GGT levels among the three groups. In their study, the level of GGT in Group 2 was significantly higher than in Group 1 (30.57 6.01 U/L vs. 26.57 6.25 U/L, P $\frac{1}{4}$ .004) and Normotensive control group (30.57 6.01 U/L vs. 23.27 3.94 U/L, P $\frac{1}{4}$ .001); it was also higher in Group I than in Normotensive control group (26.57 6.25 U/L vs. 23.27 3.94 U/L, P $\frac{1}{4}$ .025). In addition, GGT showed a positive correlation with the degree of HR in the hypertensive group (r $\frac{1}{4}$ 0.309, P$\frac{1}{4}$ .004). Divya et al. (2019)[20] also reported significantly elevated GGT in patients with retinopathy as compared to those without retinopathy.

The findings of the present study were interesting and were able to document a relationship between GGT and the Grades of retinopathy. However, further studies are required to find and prove this association between GGT and the severity of Hypertensive retinopathy.

5. Conclusion

In the present study, all four Grades of Hypertensive retinopathy were included and serum GGT levels were evaluated, and it was observed that GGT was directly proportional to the severity of Hypertensive retinopathy. So GGT, which is a marker of oxidative stress, shows an increasing trend with increasing grades of Hypertensive retinopathy.

A small sample size, an open analytical approach, and the probability of higher incidental findings are certain limitations of the study. Keeping in mind the above limitations, further studies are required to establish a relationship between GGT and the severity of Hypertensive retinopathy.

6. Conflict of Interest

None.

7. Source of Funding

None.

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