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Research Article

Effect of Glaucoma on Development of Diabetic Retinopathy in Long Standing Diabetics

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Abstract

Aim: To compare the prevalence and severity of diabetic retinopathy in patients with glaucoma and compare it with patients without any evidence of glaucoma.

Methods and materials: In this retrospective observational study, a total of 70 diabetics with a history of diabetes since a minimum of ten years and under regular treatment presenting to the ophthalmology OPD were taken for the study. The right eye was taken into the study. These 70 eyes of 70 patients underwent detailed ophthalmic examination and the presence or absence of retinopathy (as per Modified Airlie House classification of diabetic retinopathy) as well as severity of retinopathy and glaucoma was noted.

Results: Mean age of the patients was 60.39+/- 10 years. Males were predominant in the study. 38 eyes were diagnosed with glaucoma. The mean duration of diabetes was similar in both glaucomatous and non-glaucomatous patients (12.2 yrs vs. 12.7 yrs). Most patients (63%) with glaucoma had no retinopathy changes and none of these patients had severe retinopathy. On the other hand, most patients without any signs of glaucoma were found to have some retinopathy changes (72%) with nearly half of them having severe retinopathy changes. This was statistically highly significant ($p<0.0001$). The Intraocular pressure was found to be lower in patients with retinopathy changes. Odds ratio of 4.38 was calculated.

Conclusion: It was found that both Normal tensive glaucoma and primary open angle glaucoma had a suppressive effect on both onset and progression of diabetic retinopathy.

Keywords: Normal tension glaucoma; Primary open angle glaucoma; Diabetic retinopathy

Introduction

Diabetes mellitus is the latest epidemic of our times with a near quadrupling in its worldwide prevalence since 1980. Diabetic patients require more outpatient visits, chronic medications, and are at risk for a number of systemic microvascular complications [1].

Primary Open Angle Glaucoma (POAG) is the most common form of glaucoma and is associated with a number of risk factors such as family history, African ancestry, and elevated Intraocular Pressure (IOP). Of these, IOP is the only modifiable and effective target of therapy [2].

Though the pathophysiology of glaucoma is not completely understood, both diabetes and glaucoma appear to share some common risk factors and pathophysiologic similarities with studies also reporting that elevated fasting glucose levels are associated with elevated intraocular pressure - the primary risk factor for glaucomatous optic neuropathy [3]. On the other front, there is a special entity called as Normal Tension Glaucoma (NTG). It is a variety of POAG that features an IOP within the normal range, and visual field damage despite pressures that have never been documented above 21 mmHg. On an average 20% to 30% of glaucoma patients fall into this category [4].

Even with the recent advances of the 21st century, there is no clear consensus on the association between Diabetes Mellitus (DM) and glaucoma. There have been several population-based studies that have shown a positive association, [5-12] between glaucoma and diabetes mellitus while some have shown a negative association [13-15].

This study tries to evaluate the prevalence of glaucoma both high tension and normal tension in patients with type 2 diabetes and compare it with retinopathy changes.

Materials and Methods

This retrospective observational study was done in a tertiary hospital in southern India. All the diabetic patients attending ophthalmology OPD over six months fulfilling the inclusion and exclusion criteria were taken for the study. Patients were divided into groups such as diabetics without glaucoma, diabetics with POAG and diabetics with NTG.

A written informed consent was taken from all the patients. The tenets of Helsinki declaration of 1975 and modified in 2000 and 2008 were adhered to.

Inclusion criteria were all patients with diabetes more than ten years history and on regular follow up with the endocrinologist. This was done to remove any bias towards uncontrolled diabetes and its related complications as well as to give diabetes its sufficient time period for its association with glaucoma as well as retinopathy to occur. These patients were then checked for glaucoma changes. Type 1 diabetics were excluded from the study. Patients with known atherosclerosis and ocular abnormalities such as but not limited to optic nerve disease, retinal vein occlusions, macular oedema were

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excluded from the study.

All patients underwent detailed visual acuity testing using Snellen's visual acuity chart. Stereoscopic funds examination using 90D after dilatation of pupil was done and detailed assessment of disc were noted. Indirect ophthalmoscopy was done to observe the peripheral retina for any abnormality. IOP was measured using Goldmann Applanation Tonometer (GAT). Gonioscopy was done using four mirror Gonio lens and Shaffer's grading was used to grade the angles. Visual fields using Carl Zeiss, USA, and Humphrey field analyser 3 (30-2) was done.

Seventy cases were selected according to the inclusion and exclusion criteria. Only the right eye was taken for evaluation of all the patients to prevent any bias but both eyes were evaluated in detail specially to help in diagnosing glaucoma patients (being an asymmetric disease). Any patient having asymmetric retinopathy between the eyes was excluded to remove any bias. Patients with suspected glaucoma as well as patients with high IOP levels underwent detailed glaucoma assessment including field testing, diurnal variation, gonioscopy and fundoscopy. All patients underwent Retinal Nerve Fiber Layer (RNFL) analysis using a Spectral Domain Optical Coherence tomography (SD-OCT; Zeiss Cirrus 6000; USA).

All patients' glaucoma status was compared with severity of Diabetic Retinopathy (DR). The retinopathy was also compared with the IOP levels.

Differential statistics was done to determine the mean, median and standard deviation. Inferential statistics was done by using following statistical tests chi-square test and independent t test. All calculations are done by using SPSS software version 22.0. $p<0.05$ was considered as statistically significant. Tables were created using Microsoft Excel 2017.

Results

A total of 70 eyes of 70 diabetic patients who came to the Ophthalmology OPD and fulfilled the inclusion and exclusion criteria were studied. Among these, 38 eyes were found to have optic disc signs of glaucoma associated with correlating visual field defects thus were diagnosed with glaucoma. Out of these 38, 25 were found to have high intraocular pressure and were labeled as primary open angle glaucoma while 13 had normal intraocular pressure and were labeled as normotensive glaucoma. The remaining 32 eyes did not show any signs of glaucoma. Among the two groups severity of retinopathy was studied. The mean age of patients studied was 60.39+/-10 years.

Males were predominant in our study being 71.9% in non-glaucomatous group while 89.5% in glaucoma group. Mean duration of diabetes was 12.2 years in non-glaucomatous group while it was 12.7 years in glaucomatous group.

Amongst the patients with glaucoma (both primary open angle glaucoma and normal tensive glaucoma together) it was observed that most of the patients (63.2%; n=24) had no retinopathy changes and no patient was found to have severe stages of diabetic retinopathy. On the other hand, it was seen that patients with no evidence of glaucoma, most patients (72.1%, n=23) had retinopathy changes with 36.6% (n=16) having severe retinopathy changes (Table 1). This was found to be highly statistically significant with a p value of <0.0001 on chi square test. An odds ratio of 4.38 was calculated thus inferring that diabetic patients with no glaucomatous changes were 4 times more likely to have retinopathy (p=0.04).

On further evaluation it was observed that the same also remains true with primary open angle glaucoma group as well as with patients of normal tension glaucoma with a p value of 0.03 on chi square test in both (Table 2 and 3)

The Mean IOP was found to be significantly lower in patients with retinopathy changes with a p value of 0.0001 on chi square test (Table 4) signifying that high IOP was protective for diabetic retinopathy development.

Discussion

Abnormalities of blood flow to the posterior segment of the eye in POAG have been shown by using colour Doppler imaging, Fluorescein angiography, Laser Doppler flowmetry and Pulsatile ocular blood flow measurements [16]. Patients with POAG have also been found to have altered autoregulation of blood flow in the optic nerve and retinal circulation [17]. On the other hand, blood flow to the retina is significantly increased in patients with diabetic retinopathy probably due to the increased demand of the ischemic retina and high endothelial growth factors in circulation [18].

Any significant rise in IOP causes a decrease in the blood flow by a compressive effect on the vessels at the level of lamina [19].

Table 1: Comparison of Diabetic retinopathy severity between eyes with glaucoma and no glaucoma.

		Glaucoma		Non-glaucoma	
		No of eyes (n)	No of eyes (%)	No of eyes (n)	No of eyes (%)
Severity of retinopathy	No retinopathy	24	63.2	9	28.1
	Mild NPDR	10	26.3	4	12.5
	Moderate NPDR	4	10.5	7	21.9
	Severe NPDR	0	0	6	18.8
	Proliferative retinopathy	0	0	6	18.8

*NPDR: Non Proliferative Diabetic Retinopathy

Table 2: Comparison of Diabetic retinopathy severity between eyes with Primary Open angle glaucoma and those without glaucoma.

		POAG eyes		Non-glaucomatous	
		No of eyes (n)	No of eyes (%)	No of eyes (n)	No of eyes (%)
Severity of retinopathy	No retinopathy	20	80	9	28.1
	Mild NPDR	4	16	4	12.5
	Moderate NPDR	1	4	7	21.9
	Severe NPDR	0	0	6	18.8
	Proliferative retinopathy	0	0	6	18.8

*POAG: Primary Open Angle Glaucoma; NPDR: Non-Proliferative Diabetic Retinopathy

Table 3: Comparison of Diabetic retinopathy severity between eyes with Normal tension glaucoma and those without glaucoma.

		NTG eyes		Normal eyes	
		No of eyes (n)	No of eyes (%)	No of eyes (n)	No of eyes (%)
Severity of retinopathy	No retinopathy	4	30.8	9	28.1
	Mild NPDR	6	46.2	4	12.5
	Moderate NPDR	3	23.1	7	21.9
	Severe NPDR	0	0	6	18.8
	Proliferative retinopathy	0	0	6	18.8

*NTG: Normotensive Glaucoma; NPDR: Non-Proliferative Diabetic Retinopathy

Table 4: Mean IOP among eyes with diabetic retinopathy and those without retinopathy changes.

IOP	No retinopathy		Retinopathy	
	Mean	SD	Mean	SD
	20.73	8.32	14.30	4.10

*SD: Standard Deviation; IOP: Intraocular Pressure

This decreased blood flow may be a hindrance for development and progression of diabetic retinopathy as seen in other ocular ischemic conditions such as ocular ischemic syndrome secondary to carotid artery stenosis.

Similar to our study, study done Williams et al on 75 patients suggested a suppressive effect of glaucoma on DR. As these results were not repeated in patients with ocular hypertension, they postulated that the reduced number ganglion cells found in glaucoma led to a decreased ischemic response and thus prevent development of DR. They also found that patients with POAG ($p<0.002$) were significantly different in the severity of retinopathy than normal patients similar to our study [20].

Another hypothesis to explain our results can be the fact that higher levels of Vascular Endothelial Growth Factor (VEGF) are present in eyes with DM, and the same VEGF is also involved in neuroprotection of RGCs [21].

A very recent study by Hou et al. [22] on 197 eyes found that POAG patients with treated type 2 DM had significantly slower rates of RNFL thinning compared to those without diagnosed DM. It has to be taken into note that both their study and ours took only diabetics who had good sugar control. It's a well-documented fact that for every 10 mg/dL increase in fasting serum glucose, IOP increases by 0.09 mmHg in men and 0.11 mmHg in women [23].

Choroidal circulation is compromised in POAG, which is supported by electroretinographic data demonstrating outer retinal layer damage in eyes with glaucoma [24].

In our study, it was observed that mean duration of diabetes with early Non proliferative changes was maximum in patients POAG (15.8 years), followed by NTG (14.0 years) followed by13.3 years in Non-Glaucomatous group thus suggesting that glaucoma delayed the onset of DR. Thus, patients with NTG were less protected as compared to POAG. This is a novel finding of our study that previous studies have not researched upon.

We also observed that advanced stages of DR changes were seen mainly in the group without glaucoma thus suggesting that glaucoma had an effect in delaying the progression of retinopathy similar to the study of Williams et al. [20].

Thus, to conclude, Glaucoma is protective in development as well as progression of diabetic retinopathy. Also, the effects are seen more with patients with high tension glaucoma as compared to patients with normal tension glaucoma.

Small sample size was a major limitation of our study. Another limitation was the cross-sectional nature of the study. Utmost care was taken to remove any bias of control of diabetes such as poor/ tight diabetic control by choosing all patients who were under the treatment of same endocrinologist and had history of being diabetic since over ten years. Still a bias of control of diabetes cannot be ruled out. A prospective study following diabetic glaucoma cases for changes in diabetic retinopathy maybe more helpful in giving significance to our hypothesis.

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