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Original Research Article

Analysis of Retinal Nerve Fiber Layer Thickness in Patients of Primary Open Angle Glaucoma Compared To Patients of Primary Open Angle Glaucoma with Type 2 Diabetes Mellitus

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Abstract

Retinal nerve fiber layer thickness is affected in several ocular and systemic conditions, most commonly glaucoma and diabetic retinopathy. The present cross sectional study was conducted to compare the retinal nerve fiber layer thickness in patients of primary open angle glaucoma and patients of primary angle glaucoma suffering from type 2 diabetes mellitus. A total of 120 consecutive eyes of 60 patients were assigned to 2 groups of 30 patients each of primary open angle glaucoma and patients of primary open angle glaucoma having type 2 diabetes mellitus. Retinal nerve fiber layer thickness was measured with spectral-domain optical coherence tomography. Readings from all the areas of retina (superior nasal, inferior nasal, inferior temporal, superior temporal, nasal upper, nasal lower, temporal lower, temporal upper) were measured in both eyes. The presence of type 2 diabetes mellitus in patients of primary open angle glaucoma significantly affected the thickness of retinal nerve fiber layer specially in superonasal and inferotemporal quadrants as compared to patients of primary open angle glaucoma. Retinal nerve fiber layer thickness is negatively correlated with the duration of glaucoma, duration of diabetes and HBA1c levels. Hence, care should be taken in interpreting optical coherence tomography readings in patients of primary open angle glaucoma having diabetes mellitus, and such patients should not be over treated. The changes in retinal nerve fiber layer thickness can be used to monitor the progression or regression of diseases affecting nerve fiber layer and efficacy of treatment modalities in individual cases.

Keywords: Applanation tonometry, diabetic retinopathy, electroretinography, HbA1c levels, intraocular pressure, optical coherence tomography, optic nerve head changes, retinal ganglion cells, scanning laser polarimetry.

INTRODUCTION

Normal vision depends on the proper functioning of the retinal neurons in order to produce a good quality of image. Retinal nerve fiber layer (RNFL) is an important structure in the retina, which is affected, in several ocular and systemic conditions, most commonly glaucoma and diabetic mellitus. The RNFL comprises of retinal ganglion cell (RGC) axons, neuroglia and astrocyte. The RNFL thickness (RNFLT) evaluation as a mean of assessing optic nerve health has been a well-established clinical and investigational tool [1].

Glaucoma is an optic neuropathy, which is characterized by ganglion cell death, which presents clinically as characteristic optic nerve head (ONH) and/or RNFLT changes with correlating visual field defects. Primary open angle glaucoma is the most common form of glaucoma. Soliman *et al*. found that retinal nerve fiber loss precedes measurable ONH changes, visual field defects, and is observed in 60% patients, approximately six years before any detectable visual field defects in glaucoma [2]. Examination of the ONH and its surrounding RNFL is considered essential in the diagnosis as well as monitoring of glaucoma. Damage to the optic disc is associated with an abnormal appearance of RNFL.

There are various techniques, as suggested by Greaney *et al*., such as confocal scanning laser polarimetry (GDX with variable corneal compensation) and Optical coherence tomography (OCT), which helps in quantitative, reproducible and objective measurement of ONH and RNFLT [3].

Diabetes mellitus is a metabolic disorder. Type 2 DM is more common than type 1. Diabetic

complications include microvascular and macrovascular. As observed by Lin *et al.*, Abscouwer *et al.* and Sahin *et al*., in addition to vascular changes, the earlier stages of diabetic retinopathy (DR) causes neurodegenerative changes such as loss of RGC, glial cell reactivity and thinning of RNFL [4-6]. In recent clinical and experimental studies it has been observed that these neurodegenerative changes cause abnormalities in the electroretinogram (ERG), contrast sensitivity, dark adaptation and microperimetry [7]. Demir *et al.* and Takis *et al*. on the basis of histological and immunohistochemical studies have reported that DR affects retinal ganglion cells, horizontal cells, amacrine cells and photoreceptor in the neural retina and results in significant decrease in RNFLT [8, 9]. Baumann *et al*. used Spectral-domain OCT (SD-OCT) to show that RNFL thinning in DR is due to RGC loss [10].

The OCT is a non-invasive tool for objective, real-time, quantitative, high resolution (approximately up to 10μ) measurement and cross sectional imaging of retina with high reproducibility, reliability. Huang *et al*., noted that from OCT images RNFLT could be calculated by using low- coherence interferometry [11]. The OCT uses a computer fed algorithm to calculate RNFLT. Presence of conditions like hazy media, high astigmatism, dense cataract, asteroid hyalosis and poor fixation can compromise the quality of tomogram.

Attempts have been made by Demir *et al*., to find the correlations between thinning of RNFL and age, sex, duration of POAG, status of intraocular pressure control, duration of diabetes, disease stage and glycemic control [8].

Till now, researchers have been evaluating RNFLT in patients with glaucoma (both POAG and normal tension glaucoma) and patients of T2 DM separately. To the best of our knowledge no study has been conducted to compare changes in RNFLT in patients of POAG and patients of POAG with T2 DM. Hence, this study was carried out to evaluate the effect of POAG on RNFLT and compare it with RNFLT in patients of POAG with T2 DM.

MATERIALS AND METHODS

The present cross sectional study was carried out on 60 patients in a tertiary care eye institute in northern India. A total of 60 patients were divided in two groups of thirty patients each having POAG and patients of POAG with T2 DM respectively. Patients of both sexes, and age group of 30 to 70 years attending glaucoma and diabetes clinic were enrolled in this study. All patients had best corrected visual acuity (BCVA) of 20/40 (6/12) or better, and open anterior chamber angles. The patients were divided into two groups and the following inclusion and exclusion criteria were applied respectively:

In group I, 30 patients of POAG having any two of the following characteristics for 1-3 year were included in the study: i) intraocular pressure (IOP) > 21mmHg (without any treatment for raised IOP), or < 21mmHg (on anti-glaucoma treatment), ii) glaucomatous field defects or iii) glaucomatous ONH changes. Patients having history of diabetes mellitus were not included in this group.

In group II, patients of POAG with T 2 DM having any two of the following characteristic for 1-3 years were included: i) IOP > 21mmHg (without on anti-glaucoma treatment) or < 21mmHg (on anti-glaucoma treatment), ii) glaucomatous field defects iii) glaucomatous disc changes. And all patients having the following characteristics for more than 5 years were also included: Blood glucose levels ≥ 126 mg/dl (fasting) or ≥ 200 mg/dl (post prandial) according to ADA.

The following exclusion criteria were applied to all the patients in this study: anterior chamber angle abnormalities on gonioscopy, any other intraocular disease except those mentioned in the inclusion criteria, secondary causes of IOP increase (pseudoexfoliation, corticosteroid use, iridocyclitis, trauma), any kind of laser fundus photocoagulation in the past, retinal disease, such as branch or central vein occlusion, central retinal artery occlusion, age related macular degeneration, macular hole or epiretinal membrane, high myopia, previous refractory surgeries, history of major intraocular surgery, corneal opacity or dense cataract.

An informed consent was taken in all cases. A detailed history regarding demographic features, predisposing factors, associated ocular conditions, systemic diseases like hypertension, cardiovascular diseases (e.g., stroke, coronary artery disease, peripheral artery disease), any kind of medications (systemic or topical) was taken. Best corrected visual acuity (BCVA), slit lamp examination, applanation tonometry, gonioscopy, visual field analysis using Humphry visual field analyser and detailed fundus examination using direct and indirect ophthalmoscopy and slit lamp biomicroscopy using +78 D lens was done.

Optical coherence tomography was done on spectral-domain OCT machine (RTVue, model-RT100 of OPTOVUE Inc. FREEMONT, CALIFORNIA, USA), software version 5.0. After dilating the pupil, multiple scans were taken. The RNFLT was calculated using glaucoma protocol. Three circular scans, each 3.4 mm in diameter centered on the optic disc, were obtained in each patient. The best quality and properly aligned scans were used for analysis. The RNFLT was calculated globally and separately for superior, inferior, temporal and nasal quadrants. We also calculated the RNFLT for all 16 sectors of RNFL.

The data was entered in Microsoft excel spreadsheet and statistical analysis was performed by using SPSS (Statistical Package for the Social Sciences) software version 21.0 (SPSS Inc., Chicago, IL). Clinical data were expressed as mean ± standard deviation (SD) and percentage (%). The difference was considered significant when the p value was < 0.05 (two sided).

RESULTS AND DISCUSSION

In the present study age distribution of the groups was as shown in Table-1.

Table-1: Age Distribution in the two groups

Age range (years)	Group I (POAG) (n=30)	Group II (POAG+T2DM) (n=30)
<30	1	0
31-40	2	0
41-50	6	4
51-60	8	10
>60	13	16
Range	30-70	42-70
Mean ± SD	56.56 ± 11.47	61.13 ± 8.27

On statistical analysis, the comparison between the two groups was not significant.

The sex distribution in two groups was as shown in Table-2.

Table-2: Sex distribution of cases in two groups

Sex	Group I (POAG) n (%)	Group II (POAG+T2DM)n (%)
Male	14 (46.70)	15 (50)
Female	16 (53.30)	15 (50)

On statistical analysis sex distribution was not significant between the groups.

The mean duration of POAG in groups I and II was as shown in Table-3.

Table-3: Mean duration of POAG in group I and II

Duration	Group I (POAG)	Group II (POAG+T2DM)	p value
Mean ± SD (years)	2.14 ± 0.75	2.03 ± 0.85	0.636 NS

NS= Not significant

Duration of glaucoma was not statistically significant between group I and II

The mean duration of DM in group II was 9.40± 4.47 years.

The routine laboratory investigations to check the status of DM were done.

Table-4: Routine laboratory investigations for POAG with Type 2 DM

Investigations	Group II (POAG+ T2DM) (mean ± SD)
Fasting plasma glucose (mg/dl)	166 ± 40.81
Post prandial plasma glucose (mg/dl)	255.03 ± 72.96
HBA1c (%)	8.22 ± 1.52
S. creatinine (mg/dl)	1.84 ± 0.67

The various microvascular complications of DM include DR, diabetic nephropathy and diabetic neuropathy and macrovascular complications such as stroke, coronary artery disease and peripheral arterial disease were noted in group II.

Retinal nerve fiber layer thickness of RE in different areas was as showen (Table-5).

Table-5: Mean superior nasal RNFLT of RE

Parameter	Group I (POAG)	Group II (T2DM + POAG)	p value I vs. II
Superior nasal RNFLT (mean±SD) (µm)	99.86±17.52	96.16±16.33	0.401 NS

vs.= versus, µm= micrometer

On statistical analysis, the difference between groups I and II was found to be insignificant.

Table-6: Mean nasal upper RNFLT of RE of two groups

Parameter	**Group I (POAG)**	**Group II (T2DM + POAG**	**p value I vs. II**
Nasal upper RNFLT (mean±SD) (µm)	72.86±15.24	64.03±16.45	0.003 Sig.

Sig.= Significant

On statistical analysis, the difference between group I and II was significant.

Table-7: Mean nasal lower RNFLT of RE in group I and II

Parameter (mean±SD) (µm)	**Group I (POAG)**	**Group II (T2DM + POAG**	**p value I vs. II**
Inferior nasal RNFLT (mean±SD) (µm)	101.63±22.57	110.13±29.67	0.216 NS

On statistical analysis, the difference between groups I and II was not significant.

Table-8: Mean inferior temporal RNFLT of RE in two groups

Parameter (mean±SD) (µm)	**Group I (POAG)**	**Group II (T2DM + POAG**	**p value I vs. II**
Inferior temporal RNFLT	126.6±32.75	126.5±32.89	0.990 NS

On statistical analysis, the difference between group I and II was not significant.

Table-9: Mean temporal lower RNFLT of RE in group I and II

Parameter (mean±SD) (µm)	**Group I (POAG)**	**Group II (T2DM + POAG)**	**p value I vs. II**
Temporal lower RNFLT	75.56±18.11	70.06±17.75	0.230 NS

On statistical analysis the difference between the two groups was insignificant.

Table-10: Mean temporal upper RNFLT of RE in the two groups

Parameter (mean±SD) (µm)	**Group I (POAG)**	**Group II (T2DM +POAG)**	**p value I vs. II**
Temporal upper RNFLT	77.33±18.44	76.43±21.27	0.861 NS

On statistical analysis the difference between the two groups was insignificant.

Table-11: Mean superior temporal RNFLT of RE in group I and II

Parameter (mean±SD) (µm)	**Group I (POAG)**	**Group II (T2DM + POAG)**	**p value I vs. II**
Superior temporal RNFLT	120.23±22.55	115.53±21.65	0.413 NS

On statistical analysis, the difference between group I and II was insignificant.

Table-12: Mean superior nasal RNFLT of LE in group I and II

Parameter (mean±SD) (µm)	Group I (POAG)	Group II (T2DM + POAG)	p value I vs. II
Superior nasal RNFLT	106.80±27.57	102.63±20.97	0.512 NS

On statistical analysis, the difference between group I and II was insignificant.

Table-13: Mean nasal upper RNFLT of left eye in group I and II

Parameter (mean±SD) (µm)	Group I (POAG)	Group II (T2DM + POAG)	p value I vs. II
Nasal upper RNFLT	75.93±24.48	74.20±18.30	0.757 NS

On statistical analysis the difference between the groups was found to be comparable and thus insignificant.

Table-14: Mean nasal lower RNFLT of LE in the two groups

Parameter (mean±SD) (µm)	Group I (POAG)	Group II (T2DM + POAG)	p value I vs. II
Nasal lower RNFLT	69.36±19.51	69.43±19.82	0.989 NS

On statistical analysis the difference between the groups was found to be insignificant.

Table-15: Mean inferior nasal RNFLT of LE in the two groups

Parameter (mean±SD) (µm)	Group I (POAG)	Group II (T2DM + POAG)	p value I vs. II
Inferior nasal RNFLT	116.86±31.55	121.60±32.78	0.571 NS

On statistical analysis, the difference between groups I and II was insignificant.

Table-16: Mean inferior temporal RNFLT of LE in the two groups

Parameter (mean±SD) (µm)	Group I (POAG)	Group II (T2DM + POAG)	p value I vs. II
Inferior temporal RNFLT	119.70±33.76	117.00±26.83	0.739 NS

On statistical analysis, the difference between group I and II was insignificant.

Table-17: Mean temporal lower RNFLT of LE in group I and II

Parameter (mean±SD)	Group I (POAG)	Group II (T2DM + POAG)	p value I vs. II
Temporal lower RNFLT	65.76±15.83	64.00±12.92	0.637 NS

On statistical analysis the difference between group I and II was insignificant.

Table-18: Mean temporal upper RNFLT of LE in the two groups

Parameter (mean±SD) (µm)	Group I (POAG)	Group II (T2DM + POAG)	p value I vs. II
Temporal upper RNFLT	71.30±20.54	73.26±16.19	0.682

On analysis the difference between the groups was found to be insignificant.

Table-19: Mean superior temporal RNFLT of LE in group I and II

Parameter (mean±SD) (µm)	Group I (POAG)	Group II (T2DM + POAG)	p value I vs. II
Superior temporal RNFLT	115.26±30.79	117.16±24.67	0.792 NS

On statistical analysis, the difference between group I and was insignificant.

Table-20: Correlation between duration of glaucoma and RNFL thickness of RE and LE in group I

	RE			LE		
Parameter	**R value**	**p value**	**Statistical significance**	**R value**	**p value**	**Statistical Significance**
Superior nasal RNFLT	0.191	<0.05	Sig.	-0.339	>0.05	NS
Nasal upper RNFLT	0.042	<0.05	Sig.	-0.179	>0.05	NS
Nasal lower RNFLT	-0.025	<0.05	Sig.	-0.160	>0.05	NS
Inferior nasal RNFLT	-0.198	>0.05	NS	-0.347	>0.05	NS
Inferior temporal	-0.253	>0.05	NS	-0.494	<0.01	Sig.
Temporal lower RNFLT	-0.087	>0.05	NS	-0.480	<0.01	Sig.
Temporal upper RNFLT	-0.141	>0.05	NS	-0.450	<0.05	Sig.
Superior temporal RNFLT	0.028	>0.05	NS	-0.436	<0.05	Sig.

Sig. = Significant, NS= Not significant

When correlated, the duration of glaucoma with RNFLT of the RE in group I, all the sectors of RNFLT except superior nasal, nasal upper and superior temporal were negatively correlated but statistically insignificant (p>0.05). When compared in the LE, inferior temporal, temporal lower, temporal upper and superior temporal RNFLT was found to be negatively correlated and statistically significant (p <0.05)

Table-21: Correlation between duration of glaucoma and RNFLT of RE and LE of group II

	RE			LE		
Parameter	**R value**	**p value**	**Statistical Significance**	**R value**	**p value**	**Statistical Significance**
Superior nasal RNFLT	0.370	<0.05	Sig.	-0.123	>0.05	NS
Nasal upper RNFLT	0.345	>0.05	NS	-0.271	>0.05	NS
Nasal lower RNFLT	-0.416	<0.05	Sig.	-0.179	>0.05	NS
Inferior nasal RNFLT	-0.213	>0.05	NS	-0.700	>0.05	NS
Inferior temporal RNFLT	-0.375	<0.05	Sig.	-0.178	>0.05	NS
Temporal lower RNFLT	-0.261	>0.05	NS	-0.251	>0.05	NS
Temporal upper RNFLT	-0.435	<0.05	Sig.	-0.426	<0.05	Sig.
Superior temporal RNFLT	-0.484	<0.01	Sig.	-0.423	<0.05	Sig.

When correlated, duration of glaucoma with RNFLT of RE in group II, nasal lower, inferior temporal, temporal upper and superior temporal were negatively correlated and statistically significant (p <0.05. When compared with LE, only temporal upper superior temporal were negatively correlated and statistically significant (<0.05)

Table-22: Correlation between HbA1c and RNFL thickness of RE and LE of group II

	RE			LE		
Parameter	**R value**	**p value**	**Statistical significance**	**R value**	**p value**	**Statistical Significance**
Superior nasal RNFLT	-0.169	>0.05	NS	-0.365	<0.05	Sig.
Nasal upper RNFLT	-0.243	>0.05	NS	-0.287	>0.05	NS
Nasal lower RNFLT	0.070	>0.05	NS	-0.366	<0.05	Sig.
Inferior nasal RNFLT	-0.100	>0.05	NS	-0.345	>0.05	NS
Inferior temporal RNFLT	-0.470	>0.05	NS	-0.207	>0.05	NS
Temporal lower RNFLT	-0.047	<0.01	Sig.	0.070	>0.05	NS
Temporal upper RNFLT	-0.430	<0.01	Sig.	-0.183	>0.05	NS
Superior temporal RNFLT	-0.614	<0.01	Sig.	-0.310	>0.05	NS

When correlated, HbA1c with the RNFLT of the RE in group II, temporal lower, temporal upper and superior temporal RNFLT was negatively correlated and statistically significant ($p<0.01$). When similar comparison was made with LE, superior nasal and nasal lower RNFLT was negatively correlated and statistically significant ($p <0.05$).

Retinal nerve fiber layer thickness was measured in all the areas of RE eye. Except for inferior nasal, all areas showed more thinning of RNFL in patients of POAG with DM > T2 DM. This difference was statistically significant in all areas except for temporal upper and temporal lower. In the LE, superior nasal, nasal upper, inferior temporal and temporal lower areas showed more thinning of RNFL in patients of POAG with DM > T2 DM. Rest of the areas showed RNFL thinning in the order of POAG with T2DM> T2 DM.

Various studies have reported significant loss of RNFL in patients of POAG as well as in patients of type 2 DM, but none have studied it in patients of POAG having Type 2 DM. In the present study, we evaluated the magnitude of decrease in RNFLT in patients of POAG and patients of POAG with type 2 DM and compared the two groups.

The mean age in the present study was 58.85 years. The age difference between the two groups was not statistically significant. Mean age in the present study was close to that reported by Demir *et al*. and Takis *et al*. [8, 9].

The sex distribution in the present study was comparable in the two groups. It was similar to the studies conducted by. Demir *et al.*, Ramakrishanan *et al*. and Sari *et al.* [8, 12, 13].

The mean duration of POAG in this study was 2.03 years and it was comparable in the two groups. Studies carried out by various investigators support our finding that in glaucomatous eyes RNFL thickness decreases with duration of glaucoma [14-18].

Mean duration of diabetes in the present study was 9.40 years. We found a negative correlation between duration of DM and RNFLT. Two studies in the past found that RNFL thinning was seen in early stages and accelerated by the progression of diabetic retinopathy [18, 19]. Literature search showed that no study in the past has evaluated the effect duration of DM and plasma glucose levels on RNFLT.

In the present study we observed that patients having POAG with T2 DM had statistically significant RNFL damage compared to those having POAG. The damage was more pronounced in superior quadrant. The study conducted by Sari *et al*., who found that the RNFL was thinner in patients of POAG with T2 DM compared to POAG patients. Particularly, the superior quadrant was affected the most as in the present study [13]. Several other studies conducted in the past comparing RNFL thinning individually in the above two groups compared to the normal support the findings of the present study [9, 14-16, 20-22].

In this study, we also found a negative correlation between HbA1c and RNFLT. One study by Funatsu *et al.* go against our findings by reporting that there was a worsening of RNFLT after good glycemic control [23]. Nor-Sharina *et al.* conducted a cross sectional study and observed a positive correlation between HbA1c and RNFL thickness [24]. More studies are needed to find the effect of glycemic control on RNFLT.

Limitations of the present study are a smaller sample size, single centre study and being a cross

sectional study no follow-up was done. So, a multicentric study with a larger sample size and subsequent follow up of the patients to monitor the effects glaucoma and glycemic control is required to generalize the results.

CONCLUSION

We conclude that primary open angle glaucoma (POAG) and POAG with type 2 diabetes mellitus cause retinal nerve fiber layer thinning. Further, the presence of type 2 DM in patients of POAG significantly affects the thickness of RNFL specially in superonasal and inferotemporal quadrants as compared to patients of POAG or DM individually. Retinal nerve fiber layer is negatively correlated with the duration of glaucoma, duration of diabetes and HbA1c levels. Hence, care should be taken in interpreting OCT findings in patients of POAG having T2 DM, and such patients should not be over treated. The limitations of this study are small sample size, single centre research and lack of follow up of the study population. Hence, a multicentric, longitudinal study with larger sample size will be better able to corroborate our findings.

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