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Original Research Article

Comparative Analysis of Retinal Nerve Fiber Layer Thickness in Patients of Primary Open Angle Glaucoma and Type 2 Diabetes Mellitus

Dhull V K[1]*, Bishnoi Marisha[2], Sachdeva Sumit[1], Aggrawal Sameer[3]
[1]Professor, RIO, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, SH 16A, Haryana 124001, India
[2]Resident, RIO, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, SH 16A, Haryana 124001, India
[3]Professor, Department of Medicine, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, SH 16A, Haryana 124001, India

***Corresponding author:** Dhull V K
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Abstract

Retinal nerve fiber layer thickness is affected in several ocular and systemic conditions, most commonly glaucoma and diabetes mellitus. 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 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 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. Retina nerve fiber layer thickness was 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 and diabetes mellitus. 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, electroretinography, HbA1c levels, intraocular pressure, optical coherence tomography, Optic nerve head changes, Retinal ganglion cells, Scanning laser polarimetry.

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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 (POAG) 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 DM. Hence, this study was carried out to evaluate the effect of POAG on RNFLT and compare it with RNFLT in patients of type 2 DM.

MATERIALS AND METHODS

The present cross sectional study was carried out on 60 patients in a tertiary eye care institute in northern India. A total of 60 patients were divided in 2 groups of thirty patients each having POAG and T2 DM respectively. The 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 6/12 (20/40) 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) > 21 mmHg (without any treatment for raised IOP), or < 21 mmHg (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, 30 patients of type 2 Diabetes mellitus (T 2 DM) having the following characteristics for more than 5 years were included: blood glucose levels ≥ 126 mg/dl (fasting) or ≥ 200 mg/dl (post prandial) according to ADA. The patients having intraocular pressure > 21 mmHg (without any treatment) or <21 mmHg (on anti-glaucoma treatment), glaucomatous field changes and glaucomatous disc changes were excluded from this group

The following exclusion criteria were applied to both the groups: 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 ± SD (standard deviation) and percentage (%). The difference was considered significant when the p value was < 0.005.

RESULTS AND DISCUSSION

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

Table-1: Age Distribution of cases

Age (years)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)
<30	1	0
31-40	2	4
41-50	6	7
51-60	8	11
>60	13	8
Range	30-70	31-70
Mean ± SD	56.56 ± 11.47	54.06 ± 9.84

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

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

Table-2: Sex distribution of cases

Sex	Group I (POAG) (n=30)	Group II (T2DM) (n=30)
Male	14 (46.70%)	16 (53.30%)
Female	16 (53.30%)	14 (46.70%)

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

The mean duration of POAG in groups I was 2.14±0.75 years and the mean duration of DM in group II was 9.47±4.47 years

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

Table-3: Routine laboratory investigations for Type 2 DM

Investigations	Group II (T2 DM) (mean ± SD)
Fasting plasma glucose (mg/dl)	147.96 ± 34.90
Post prandial plasma glucose (mg/dl)	220 ± 72.31
HBA1c (%)	7.54 ± 1.65
S. creatinine (mg/dl)	1.65 ± 0.82

The various microvascular complications of DM include diabetic retinopathy (DR), nephropathy and neuropathy and macrovascular complications stroke (CVA), coronary artery disease (CAD) and peripheral arterial disease were noted (Table-4).

Table-4: Various diabetic complications in group II

Complications of DM	Group II (T2DM)
Microvascular	23 (76.70%)
Macrovascular	9 (30%)

Microvascular and macrovascuar complications of diabetes were present in large number of cases in group II.

Retinal nerve fiber layer thickness of right eye in different areas was as shown in table 5.

Table-5: Mean superior nasal RNFL thickness of RE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs II
Superior nasal RNFLT	99.86±17.52	113.1±21.53	0.01 Sig.

µm= micrometer; vs.= versus; Sig.= Significant; NS= not significant

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

Table-6: Mean nasal upper RNFLT of RE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs. II
Nasal upper RNFLT	72.86±15.24	76.96±12.82	0.264 NS

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

Table-7: Mean nasal lower RNFLT of RE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs. II
Inferior nasal RNFLT	101.63±22.57	124.33±21.68	0.002 Sig.

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

Table-8: Mean inferior temporal RNFLT of RE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs. II
Inferior temporal RNFLT	126.6±32.75	143.9±27.04	0.02 Sig.

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

Table-9: Mean temporal lower RNFLT of RE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs. II
Temporal lower RNFLT	75.56±18.11	77.53±14.35	0.642 NS

On statistical analysis the difference was found to be insignificant.

Table-10: Mean temporal upper RNFLT of RE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs. II
Temporal upper RNFLT	77.33±18.44	84.36±18.76	0.148 NS

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

Table-11: Mean superior temporal RNFLT of RE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs. I
Superior temporal RNFLT	120.23±22.55	131.86±20.04	0.03 Sig.

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

Table-12: Mean superior nasal RNFLT of LE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs. II
Superior nasal RNFLT	106.80±27.57	123.23±16.82	0.007 Sig.

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

Table-13: Mean nasal upper RNFLT of LE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs. II
Nasal upper RNFLT	75.93±24.48	80.20±15.84	0.426 NS

On statistical analysis the difference between the groups was insignificant.

Table-14: Mean nasal lower RNFLT of left eye

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs. II
Nasal lower RNFLT	69.36±19.51	74.96±13.32	0.199 NS

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

Table 15: Mean inferior nasal RNFLT of LE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs. II
Inferior nasal RNFLT	116.86±31.55	134.16±22.22	0.01 Sig.

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

Table-16: Mean inferior temporal RNFLT of LE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	value I vs. II
Inferior Temporal RNFLT	119.70±33.76	132.66±20.11	0.070

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

Table-17: Mean temporal lower RNFLT of LE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs. II
Temporal lower RNFLT	65.76±15.83	66.96±10.28	0.729 NS

On statistical analysis the difference between the groups was insignificant.

Table-18: Mean temporal upper RNFLT of LE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs. II
Temporal upper RNFLT	71.30±20.54	78.03±15.37	0.156 NS

On statistical analysis the difference between the groups was insignificant

Table-19: Mean superior temporal RNFLT of LE

Parameter (mean±SD) (µm)	Group I (POAG) (n=30)	Group II (T2DM) (n=30)	p value I vs. II
Superior temporal RNFLT	115.26±30.79	132.76±19.82	0.01 Sig.

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

Table-20: Correlation between duration of glaucoma and RNFL 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 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 with the LE, inferior temporal, temporal lower, temporal upper and superior temporal RNFLT were found to be negatively correlated and statistically significant (p <0.05).

The correlation between duration of DM and RNFLT of RE and LE of group II was analysed using Pearson's coefficient of correlation.

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

	RE			LE		
Parameter	**R value**	**p value**	**Statistical Significance**	**R value**	**p value**	**Statistical significance**
Superior nasal RNFLT	-0.255	>0.05	NS	-0.623	<0.01	Sig.
Nasal upper RNFLT	-0.326	>0.05	NS	-0.554	<0.01	Sig.
Nasal lower RNFLT	-0.287	>0.05	NS	-0.435	<0.05	Sig.
Inferior nasal RNFLT	-0.332	>0.05	NS	-0.224	>0.05	NS
Inferior temporal RNFLT	-0.280	>0.05	NS	-0.292	>0.05	NS
Temporal lower RNFLT	-0.253	>0.05	NS	-0.243	>0.05	NS
Temporal upper RNFLT	-0.263	>0.05	NS	-0.202	>0.05	NS
Superior temporal RNFLT	-0.202	>0.05	NS	-0.358	>0.05	NS

*Sig, = Significant, NS= Not significant

When correlated, duration of diabetes with RNFLT of LE in group II in superior nasal, nasal upper, nasal lower quadrant was found to be negatively correlated and statistically significant (p <0.05). But, with regard to the RE, all of the sectors of RNFLT were found to be negatively correlated but statistically insignificant (p> 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

In group II, when correlated HbA1c with the RNFLT of the 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 value<0.05).

Retinal nerve fiber layer thickness was measured in all areas of RE. Except inferior nasal, all areas showed more thinning of RNFL in patients of POAG > T 2DM group. 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> T2 DM group. Rest of the areas showed RNFL thinning in the order POAG> T2 DM.

Various studies have reported significant loss of RNFL in patients of POAG as well as in patients of type 2 DM. In the present study we evaluated the magnitude of decrease in RNFLT in patients of POAG, type 2 DM and compared the two groups.

In the present study, mean age of the patients was 55.31 years. 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*. and Ramakrishanan *et al*. [8, 12].

The mean duration of POAG in this study was 2.14 years. We found a negative correlation between duration of glaucoma and RNFLT. Studies carried out by various investigators support our finding that in glaucomatous eyes RNFL thickness decreases with duration of glaucoma [13-17].

Mean duration of diabetes in-group II was 9.40±4.47 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 [17, 18]. Literature search showed that no study in the past has evaluated the effect duration of DM and plasma glucose levels on RNFLT.

We also found a negative correlation between HbA1c and RNFLT. One study go against our findings by revealing that there was a worsening of RNFLT after good glycemic control [19]. Nor- Shaina *et al*., conducted a cross sectional study and observed a positive correlation between HbA1c and RNFL thickness [20]. 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 type 2 diabetes mellitus cause retinal nerve fiber layer thinning. 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 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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