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ORIGINAL ARTICLE

# Correlation of Ganglion Cell Complex and Retinal Nerve Fiber Layer Thickness in Relation to Glycemic Control and Lipid Profile in Diabetics and Age-Matched Normal

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**Keywords:**

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## ABSTRACT

**Purpose:** The purpose of the study was to evaluate the thickness of ganglion cell complex (GCC) layer and retinal nerve fiber layer (RNFL) in diabetics with respect to the duration of diabetes, glycated hemoglobin (HbA1c) level, and lipid profile in comparison to age-matched normal.

**Methods:** Prospective study of 150 eyes of 150 patients. Patients were divided into 50 controls, 50 diabetics with diabetic retinopathy (DR), and 50 diabetics with no DR changes. All the patients were evaluated using a standard spectral-domain optical coherence tomography oct. Biochemical parameters – HbA1c and lipid profile were also evaluated.

**Results:** Our study showed significant GCC thinning in diabetes which is mainly focal than diffuse and non-significant loss of RNFL. As the duration of diabetes increased, there was a significant loss of gcc and rnfl. Increased hba1c levels lead to non-significant thinning of gcC and RNFL. There was no significant correlation between altered lipid profile and OCT parameters.

**Conclusion:** The GCC and RNFL loss in diabetics could be an early indicator of neuronal loss. Hence, OCT can be a useful non-invasive tool for early detection of neuronal loss even before retinopathy changes are seen.

## Introduction

Diabetic retinopathy (DR) is one of the leading causes of blindness according to vision 2020 protocol.[1] Due to the large number of diabetic subjects, DR is likely to pose a public health burden in India. CURES eye study showed that the major systemic risk factors for onset and progression of DR are duration of diabetes, degree of glycemic control, and hyperlipidemia.[2] Early detection of DR is particularly essential for patients with diabetes mellitus because advanced diabetic eye disease is refractory. With advanced technologies, various phenomena that relate to retinal changes at retinal microvascular level have been reported in cases with no DR changes.

The retinal nerve fiber layer (RNFL) forms the innermost neural layer of the retina and is composed of the large unmyelinated axons of ganglion cells. RNFL fibers originate from different locations of the retina and converge together in a unique pattern to form the optic nerve. The ganglion cell complex (GCC) is defined as the three innermost retinal layers: The nerve fiber layer, the ganglion cell layer, and the inner plexiform layer (IPL).[3] The GCC and RNFL loss in diabetics could be an early indicator of neuronal loss and optical coherence tomography (OCT) can be a useful non-invasive tool for early detection of neuronal loss even before retinopathy changes are seen. Understanding of these retinal structural changes in early stages of DR may provide information regarding progression [Figure 1].

Optical properties of the intraretinal layers may provide useful information to differentiate pathological from healthy eyes. It is known that diabetes leads to thinning of the retina preceding the onset of severe DR, which is most possibly attributed to neurodegeneration.[4] Hence, we decide to do this

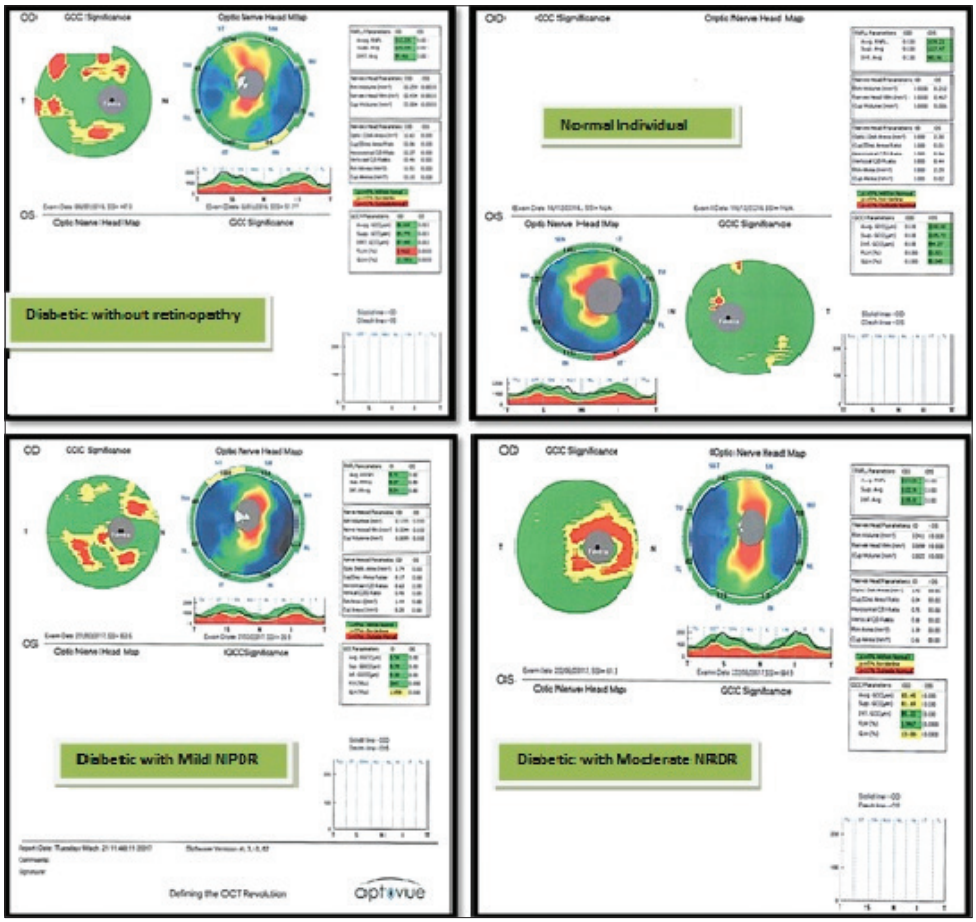


**Figure 1:** Ganglion cell complex in diabetic patients with and without retinopathy

study to detect changes in the ganglion cell layer and RNFL of retina in diabetic and normal healthy subjects using spectral-domain OCT.

## Methods

Prospective study of 150 eyes of 150 patients aged ≥18 years (Group 1; 50 control, Group 2; 50 diabetic with DR, and Group 3; 50 diabetic with no DR) which were included in the study. The study was approved by the Institutional Review Board. Patients with glaucoma or those with intraocular pressure (IOP) >21 mmhg in either eye and those showing evidence of visual field defects in either eye as detected using Humphrey visual field analyzer, hypertension, diabetic macular edema, high myopia, severe ocular trauma, refractive surgery, and any high-risk proliferative DR condition altering the OCT examination (i.e. pre-retinal hemorrhages and vitreous traction retinal detachment/combined retinal detachment), any other retinal disorders affecting RNFL and GCC layers were excluded from the study. Informed consent was obtained from all the patients. Each patient was subjected to detailed history taking, followed by complete ophthalmic evaluation including best-corrected vision assessment; IOP, slit-lamp examination, fundus evaluation using slit-lamp biomicroscopy, and indirect ophthalmoscope. One eye of each patient either OD/OS was included in the study.

Gcc and RNFL analysis were done using optovue (RTVue100) OCT with software version 6.3.0.62. It was performed through dilated pupil and external fixation was used. ONH/GCC symmetry analysis was obtained. OCT was repeated when the obtained scans were not appropriate due to poor focusing or inadequate centration. The patient was excluded if repeat scans were unsatisfactory. Finally, the selected OCT scans were analyzed, then retinal nerve fiber layer, GCC, focal loss volume (FLV), and global loss volume (GLV) thickness values were obtained. Five milliliters of blood sample were obtained from all patients for investigations (glycemic status and lipid profile)

## Results

Mean age was 57.3 ± 12.7 in Group 1, 58.6 ± 12.1 in Group 2, and 60.9 ± 8.6 in Group 3. The mean ratio between males to females is 19/31 in Group 1, 27/23 in Group 2, and 29/21 in Group 3. Mean glycated hemoglobin (HbA1c) range was

5.37 ± 0.42 in Group 1, 9.36 ± 2.27 in Group 2, and 9.40 ± 2.08 in Group 3. On statistical analysis, F (one-way ANOVA) = 48.25 and $P < 0.001$ were obtained, suggesting a statistically highly significant correlation. The mean triglyceride values were 183.6 ± 97.5 in Group 1, 235.3 ± 131.0 in Group 2, and 189.1 ± 111.3 in Group 3. On statistical analysis, F (one-way ANOVA) = 3.10 and $P = 0.05$ were obtained, suggesting a statistically significant correlation. A non-significant correlation was seen with F (one-way ANOVA) = 2.45 and $P = 0.09$, for high-density lipoprotein (hdl) values in all the three groups. Overall, low-density lipoprotein (ldl) values in the three groups on statistical analysis obtained an F = 6.95 and $P = 0.001$, suggesting a statistically significant correlation. However, total cholesterol (TC) mean values were 189.9 ± 4.46 in Group 1, 206.1 ± 43.2 in Group 2, and 170.2 ± 41.9 in Group 3. On statistical analysis, F = 8.67 and $P = 0.00$ were obtained, suggesting a statistically significant correlation. The mean values of very LDL and TC/HDL in all three groups on statistical analysis obtained a statistically significant correlation with $P < 0.05$. GCC and RNFL thickness measurements in all three groups are shown in Table 1.

For the two diabetic groups, further subanalysis was done to analyze the relation between HbA1c range and oct parameters. In Group 2, average GCC (AGCC) mean values obtained with respective to HbA1c range <6.0 was 91.9 ± 3.1, 6.1–8.0 was 91.3 ± 9.8, 8.1–10.0 was 92.3 ± 8.4, and >10.0 was 92.6 ± 10.1. On statistical analysis, F = 0.05 and $P = 0.98$ were obtained suggesting a non-significant correlation. In Group 3, AGCC mean values obtained with respective to HbA1c range <6.0 was 87.0 ± 4.2, 6.1–8.0 was 89.5 ± 7.5, 8.1–10.0 was 91.8 ± 4.6, and >10.0 was 91.6 ± 7.1. On statistical analysis, F = 0.66 and $P = 0.59$ were obtained suggesting a non-significant correlation. For FLV in Groups 2 and 3 with respect to HbA1c range, F = 1.34, $P = 0.27$ and F = 0.81, $P = 0.50$ were obtained suggesting a non-significant correlation. GLV in both the diabetic groups with respective to HbA1c range obtained F = 0.46, $P = 0.46$ in Group 2 and F = 0.0.81, $P = 0.81$ in Group 3 suggesting a non-significant correlation. The relation between Hb A1C and AGCC is shown in Figure 2. The average RNFL (ARNFL) mean values with respective to HbA1c range in Group 2 obtained F = 0.08 and $P = 0.97$ suggesting a non-significant correlation. However, in Group 3 on statistical analysis, F = 5.26 and $P = 0.003$ were obtained suggesting a significant correlation.

The relationship between triglycerides and OCT findings was as follows: For AGCC with respect to TG range, mean values for Group 1 were 96.0 ± 4.9 for <150, 89.5 ± 7.9 for 150–199, and 95.3 ± 6.9 for >200. On statistical analysis, F = 4.05 and $P = 0.02$ were obtained suggesting a significant correlation. However, for the diabetic groups, a non-significant correlation was obtained for the same with $P > 0.05$. In all the three groups, FLV with respect to TG range showed a non-significant correlation with $P > 0.05$. GLV with respect to TG range for Group 1 was 4.52 ± 3.79 for <150, 9.40 ± 6.52 for 150–199, and 5.26 ± 4.37 for >200. On statistical analysis, ANOVA F = 4.12 and $P = 0.02$ were obtained suggesting a significant correlation. However, the diabetic groups showed a non-significant correlation with $P > 0.05$. The mean values for ARNFL with respect to TG range in Group 1 were 110.6 ± 10.2 for <150, 100.1 ± 11.7 for 150–199, and 107.7 ± 11.4 for >200. On statistical analysis, ANOVA F = 3.30 and $P = 0.05$ were obtained suggesting a significant correlation. However, the same relation in diabetics group was not significant ($P > 0.05$).

The relationship between TC and OCT findings was as follows. The mean values of AGCC with respect to TC range in Group 1 were 95.8 ± 6.6 for <200, 90.1 ± 7.5 for 200–239, and 95.3 ± 4.2 for >240. On statistical analysis, ANOVA F = 3.04 was obtained and $P = 0.04$ which suggested a significant correlation. However, the diabetic groups showed a non-significant correlation with $P > 0.05$. The mean values of FLV with respect to TC range in Group 1 were 0.97 ± 1.23 for <200, 2.76 ± 2.60 for 200–239, and 1.56 ± 1.99 for >240. On statistical

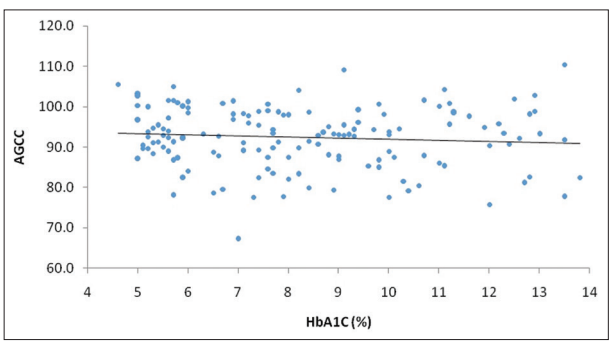


**Figure 2:** The relation between glycated hemoglobin and average ganglion cell complex

**Table 1:** GCC and RNFL measurements in all three groups

| Groups | AGCC | SGCC | IGCC | FLV | GLV | ARNFL | SRNFL | IRNFL |
|---|---|---|---|---|---|---|---|---|
| 1 | 94.3±6.8 | 94.6±7.4 | 94.0±7.4 | 1.51±1.89 | 5.87±4.99 | 107.2±11.5 | 111.4±13.4 | 102.3±11.5 |
| 2 | 92.2±8.8 | 91.9±8.5 | 92.5±9.5 | 1.91±2.09 | 7.24±6.58 | 103.8±11.8 | 107.2±13.5 | 100.7±11.2 |
| 3 | 90.8±6.5 | 89.4±7.6 | 92.2±8.6 | 3.32±2.61 | 8.08±5.27 | 103.5±21.2 | 106.7±19.9 | 100.8±23.4 |
| ANOVA F | 2.93 | 5.39 | 0.67 | 9.17 | 1.90 | 0.91 | 1.34 | 0.15 |
| *P* value | 0.05* | 0.006* | 0.51, NS | 0.00** | 0.15, NS | 0.41, NS | 0.27, NS | 0.85, NS |

AGCC: Average GCC, SGCC: Superior GCC, IGCC: Inferior GCC, FLV: Focal loss volume, GLV: Global loss volume, ARNFL: Average RNFL, SRNFL: Superior RNFL, IRNFL: Inferior RNFL, NS: Not significant, GCC: Ganglion cell complex, rnfl: Retinal nerve fiber layer

**Table 2:** Relationship between duration of diabetes and OCT findings

| Duration (years) | AGCC | | FLV | | GLV | | ARNFL | |
|---|---|---|---|---|---|---|---|---|
| | G2 | G3 | G2 | G3 | G2 | G3 | G2 | G3 |
| <5 | 92.3±6.9 | 93.8±6.7 | 1.57±1.40 | 1.48±1.34 | 6.90±4.92 | 4.11±3.23 | 106.9±10.5 | 107.9±15.4 |
| 5–10 | 92.2±9.8 | 91.2±6.5 | 1.32±1.71 | 3.68±.48 | 6.90±8.06 | 8.13±4.32 | 102.6±14.5 | 108.0±25.7 |
| >10 | 91.8±11.7 | 89.1±6.0 | 3.43±3.10 | 3.85±2.86 | 8.43±8.21 | 9.84±5.88 | 98.1±9.4 | 97.8±18.6 |
| ANOVA F | 0.02 | 1.99 | 4.32 | 3.41 | 0.22 | 4.66 | 2.38 | 1.43 |
| *P* value | 0.98, NS | 0.15, NS | 0.02*, S | 0.04* S | 0.80, NS | 0.02*, S | 0.10, NS | 0.25, S |

One-way ANOVA, *$P$<0.05, S, P>0.05, NS: not sig, s: Significant, NS: Not significant. AGCC: Average GCC, FLV: Focal loss volume, GLV: Global loss volume, ARNFL: Average RNFL, GCC: Ganglion cell complex, rnfl: Retinal nerve fiber layer

analysis, ANOVA F = 4.27 was obtained and $P$ = 0.02 which suggested a significant correlation. However, in Groups 2 and 3, the correlation was non-significant ($P$ > 0.05). The mean values of GLV with respect to TC range in all the groups had a non-significant correlation ($P$ > 0.05). The mean values of ARNFL with respect to TC range in Group 1 were 110.4 ± 9.5 for <200, 101.3 ± 14.3 for 200–239, and 104.9 ± 10.8 for >240. On statistical analysis, ANOVA F = 3.10 and $P$ = 0.05 were obtained which suggested a significant correlation. However, in diabetic groups, it showed a non-significant correlation ($P$ > 0.05).

The relationship between LDL and OCT findings was as follows: Overall, AGCC with respect to LDL range in all three groups suggested a non-significant correlation ($P$ > 0.05). For FLV with respect to LDL range, mean values in Group 1 were 1.03 ± 1.20 for <100, 1.04 ± 1.44 for 100–129, 1.05 ± 0.91 for 130–150, and 3.37 ± 2.99 for >150. On statistical analysis, F = 5.02 and $P$ = 0.004 were obtained, which suggested a significant correlation. However, among diabetic groups (2 and 3), non-significant correlation was obtained ($P$ > 0.05). GLV and ARNFL with respect to LDL range in all three groups showed a non-significant correlation with $P$ > 0.05.

Relationship between duration of diabetes and OCT findings is shown in Table 2. Correlation analysis was done to access the relationship between OCT findings and selected biochemical parameters shown in Table 3. There was an inverse relationship between HbA1c and AGCC/ARNFL layers showing as there is increase in HbA1c, there will be decrease in the layer. However, this relationship was not significant. Positive relationship was found between HbA1C and FLV/GLV showing as there is an increase in HbA1c, there is an increase in FLV/GLV. No significant correlation was found between lipid profile and OCT parameters. Similar to HbA1c results, duration of diabetes also found to be inversely related to AGCC and ARNFL and a positive relationship was present with respect to FLV/GLV. Relation between duration of diabetes and AGCC is shown in Figure 3.

**Table 3:** Correlation analysis between OCT findings and selected biochemical parameters and duration of diabetes

| Relationship with | AGCC | FLV | GLV | ARNFL |
|---|---|---|---|---|
| HbA1C | | | | |
| *r* | −0.09 | 0.25 | 0.14 | −0.01 |
| *P* | 0.28 | 0.003* | 0.09 | 0.95 |
| TGL | | | | |
| *r* | −0.02 | −0.13 | −0.02 | 0.09 |
| *P* | 0.79 | 0.11 | 0.83 | 0.26 |
| TC | | | | |
| *r* | 0.03 | −0.07 | −0.03 | 0.07 |
| *P* | 0.74 | 0.37 | 0.7 | 0.38 |
| LDL | | | | |
| *r* | 0.06 | −0.05 | 0.01 | 0.05 |
| *P* | 0.49 | 0.56 | 0.95 | 0.52 |
| Duration of diabetes (years) | | | | |
| *r* | −0.18 | 0.31 | 0.23 | −0.38 |
| *P* | 0.06* | 0.002* | 0.02* | 0.00** |

r: Pearson's correlation coefficient (−ve sign indicates inverse relationship). *$P$<0.05, Sig. **$P$<0.001, HS, $P$>0.05, NS. AGCC: Average GCC, FLV: Focal loss volume, GLV: Global loss volume, ARNFL: Average RNFL, NS: Not significant, GCC: Ganglion cell complex, rnfl: Retinal nerve fiber layer

## Discussion

Multiple studies have indicated that neuronal and vascular abnormalities are associated with the pathogenesis of early DR.[5-9] Barber *et al.*[6] showed retinal neuronal damage accompanies microvascular damage in patients with type 2 diabetes. Oshitari *et al.*[8] in their immunohistochemical studies of cross-sections of human retinas demonstrated an increase in expression of Bax, caspase-3, and caspase-9 in RGCs from diabetic patients, thus suggesting loss of some retinal ganglion cells through apoptosis. It is becoming increasingly evident that neuronal cells of the retina also are affected by diabetes, resulting in neuronal dysfunction and even degeneration of some neuronal cells. Retinal ganglion cells have been implicated in this pathology.[2]

Demir *et al.*[10] studied the RNFL and GCC thickness in patients with no DR, mild non-proliferative (NPDR) and moderate NPDR, and healthy participants and concluded that there is a non-significant loss of RNFL and GCC in patients with type 2 diabetes. Wei *et al.*[11] concluded that thickness values of GCL + IPL and OPL showed a significant decrease in DR eyes

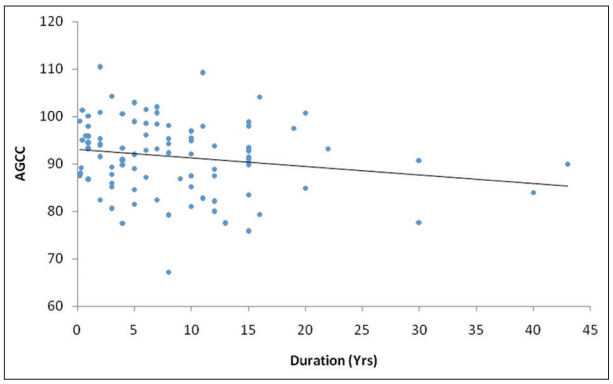


**Figure 3:** Relation between duration of diabetes and average ganglion cell complex

compared to controls. Dorothy *et al.*[12] examined the association of diabetes and DR with retinal ganglion cell loss in Type 2 diabetes and age-gender-matched controls without diabetes. They concluded that RGC loss is present in subjects with diabetes and no DR, and is progressive in moderate or severe DR. RGC neuronal damage in diabetes and DR can be clinically detected using OCT.

Asnaghi *et al.*[13] concluded that the RNFL defect is common in patients with early DR. Chhablani *et al.*[9] concluded that average and minimum ganglion cell-inner plexiform layer (GCIPL) showed significant thinning in diabetic subjects compared with controls in all stages of DR, especially involving the papillomacular bundle. GCIPL thickness was similar between the diabetic groups. No relationship between GCIPL, RNFL thicknesses, and duration of diabetes was present. Araszkiewicz *et al.*,[14] subjects with retinopathy had thinner parafoveal retina, reduced mean RNFL thickness, reduced inferior and nasal RNFL thickness, and reduced superior and inferior GCL. Significant correlations were found between duration of diabetes and nasal RNFL thickness and parafoveal retinal thickness. They noted significant RNFL thinning with increase in duration of diabetes mellitus. Asefzadeh *et al.*[15] concluded that in subjects with no or mild DR, macular and foveal thickness is significantly thinner with longer duration of disease. They concluded that this may reflect neurodegenerative changes in the diabetic retina. Araszkiewicz *et al.*,[14] significant correlations were found between duration of diabetes and nasal RNFL thickness and parafoveal retinal thickness. They noted significant RNFL thinning with increase in duration of diabetes mellitus. Asefzadeh *et al.*[15] also concluded that there was a significant negative correlation between retinal thickness and diabetes duration in all macular quadrants. In our study, duration of diabetes was found to be inversely related to AGCC and ARNFL and a positive relationship was present with respect to FLV/GLV.

Zhu *et al.*,[16] macular GCC reduction occurred much earlier than peripapillary RNFL thinning in diabetic patients without retinopathy. Ng *et al.*,[12] RGC loss is present in subjects with diabetes and no DR, and is progressive in moderate or severe DR. RGC neuronal damage in diabetes and DR can be clinically detected using OCT. Salvi *et al.*[17] concluded that the GCC is significantly affected in patients with type 2 diabetes and SD-OCT might represent a useful tool to detect diabetic polyneuropathy, but not DR in these individuals but in our study, we did not evaluate for polyneuropathy. Dhasmana *et al.*,[18] neurodegeneration is seen as an early component of DR. They also evaluated GCC and it showed statistically significant in diabetic patients creatinine levels showed a week negative correlation to the RNFL; however, in our study, we did not evaluate creatinine levels.

In our study, we found that with respect to AGCC, mean values in Group 1, Group 2, and Group 3 were 94.3 ± 6.8, 92.2 ± 8.8, and 90.8 ± 6.5, and on statistical analysis, F (one-way ANOVA) = 2.93 and $P = 0.05$ were obtained, suggesting a statistically significant correlation. The ARNFL mean values in Group 1, Group 2, and Group 3 were 107.2 ± 11.5, 103.8 ± 11.8, and 106.7 ± 19.9, and on statistical analysis, F (one-way ANOVA) = 0.91 and $P = 0.91$ were obtained, suggesting a statistically non-significant correlation.

Hegazy *et al.*,[19] FLV% was negatively correlated to the refraction and level of HbA1c ($P = 0.019$ and 0.013, respectively) and positively correlated to BCVA in log MAR in diabetic group ($P = 0.004$). They concluded that significant GCC thinning in diabetes predates retinal vasculopathy, which is mainly focal rather than diffuse. It has no preference to either the superior or inferior halves of the macula. Increase of myopic error is significantly accompanied with increased focal GCC loss. GCC loss is accompanied with increased C/D ratio in diabetic eyes. However, we did not include high myopia in this study.

Srinivasan *et al.*,[20] diabetic peripheral neuropathy is associated with abnormal GCC FLV at the macula, which is independent of DR, age, sex, type of diabetes, duration of diabetes, and HbA1c levels. An abnormality in GCC FLV is an independent predictor of diabetic peripheral neuropathy. However, in our study, we found that with respect to FLV, mean values in Group 1, Group 2, and Group 3 were 1.51 ± 1.89, 1.91 ± 2.09, and 3.32 ± 2.6, respectively. On statistical analysis, F (one-way ANOVA) = 9.17 and $P = 0.00$ were obtained, suggesting a statistically significant correlation.

Pekel *et al.*,[21] diabetic patients without retinopathy have more binocular RNFL thickness asymmetry, higher cup to disc ratio, and thinner sectoral macular GCL+IPL when compared to healthy control and support the statement that DM causes inner retinal neurodegenerative changes. However, in our study, we did not include ONH parameters.

Debadatta *et al.*[22] aimed to study any correlation of RNFLT with blood glucose parameters. RNFLT showed significant negative correlation with blood glucose parameters. Especially for HbA1C, this correlation was high in all quadrants around optic nerve head. Further studies will be needed to elucidate the relation of other blood parameters such as cholesterol with retinal thickness in diabetes. In our study, lipid profile was done and compared to the retinal thickness. In our study, no correlation was found between oct parameters and lipid profile. In our study, in Groups 2 and 3, the AGCC with respect to

HbA1c range obtained F = 0.05, *P* = 0.98 and F = 0.66, *P* = 0.59, respectively, suggesting a non-significant correlation. However, the ARNFL values with respective to HbA1c range in Group 2 obtained F = 0.08 and *P* = 0.97 suggesting a non-significant correlation. However, in Group 3 on statistical analysis for the same relation, F = 5.26 and *P* = 0.003 were obtained suggesting a significant correlation.

Gundogan *et al*.,[23] Type 1 diabetic patients without clinically diagnosed DR had neurodegeneration in the inner retinal layers compared with healthy controls. we did not consider type 1 diabetes in our study. El-Fayoumi *et al*.[24] concluded that thinning of the RNFL and GCC in children with T1DM with no DR compared to healthy controls suggests that neurodegenerative changes occur in the absence of vascular changes. It also shows that neurodegeneration is not related to disease duration, onset, or control.

## Conclusion

As the duration of diabetes increases, there was a significant loss of gcc and rnfl. With poor glycemic controls (increased hba1c), thinning of gcc was non-significant and the loss was more focal (FLV) than diffuse (GLV). With poor glycemic control, decrease in RNFL thickness was non-significant. There was no significant correlation between altered lipid profile with respect to gcc and rnfl. The results of our study are similar to earlier studies. However, unlike other studies, we did not evaluate the correlation between higher grades of retinopathy, that is, severe NPDR and PDR, increased axial length, and certain systemic correlates such as diabetic neuropathy and diabetic nephropathy. The GCC and RNFL loss in diabetics could be an early indicator of neuronal loss. Hence, OCT can be a useful non-invasive tool for early detection of neuronal loss even before retinopathy changes are seen. Multiple studies with larger population and longer follow-ups are needed to assess the efficacy and importance of this outcome.

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