Retinal Nerve Fibre Layer and Ganglion Cell Complex Thickness in Diabetes Mellitus without Diabetic Retinopathy

Annadurai Rajeshwari,[1] Sharmila Sundaresan,[1] Malathi Vasuki Krishnan,[1] Ramya Chelliah,[1] Suma Elangovan[1]

[1]Department of Ophthalmology, Employees' State Insurance Corporation Medical College and Hospital, Ashok Pillar Road, Kalaignar Karunanidhi Nagar, Chennai, Tamil Nadu, India

ABSTRACT

Introduction: Diabetic retinopathy is on the rise and understanding mechanisms of retinal neurodegeneration in diabetes mellitus will help in halting retinopathy.

Objective: The study was done to assess the retinal nerve fibre layer and ganglion cell complex thickness in type two diabetes mellitus without clinically evident vascular retinopathy and compare them with the normal population to understand the early neurodegenerative changes.

Methodology: This was a hospital-based, prospective, observational study conducted in South India from 2022 May to 2023 March. This study included one hundred and seventeen eyes with type two diabetes mellitus without clinical diabetic retinopathy and 115 normal age-matched controls after ethical approval using a consecutive sampling technique. Participants with other systemic co-morbidities and retinal pathology were excluded. Average, superior, and inferior retinal nerve fibre layer thickness and average, superior, inferior, inferonasal, superonasal, superotemporal, and inferotemporal macular ganglion cell complex thickness were measured using spectral-domain optical coherence tomography. A student's unpaired t-test was used for comparing the thickness between cases and controls, and analysed using SPSS Statistics version 26.

Result: The retinal nerve fibre layer thickness was significantly reduced in all quadrants in type two diabetes mellitus without diabetic retinopathy when compared to normal controls ($p < 0.001$), with the mean nerve fibre layer thickness of 100.3µm ± 12.5µm in cases and 110.9µm ± 8.7µm in controls. The mean macular ganglion cell complex thickness was also significantly decreased in diabetes without retinopathy ($p < 0.001$), with values of 99.9µm ± 8.1µm in diabetics and 109.3µm ± 4.9µm in controls. In diabetics, increased glycosylated haemoglobin correlated negatively with the nerve fibre layer and ganglion cell complex thickness.

Conclusion: Neurodegeneration of the retinal nerve fibre layer and ganglion cell complex in diabetics occurs before clinically visible vascular changes appear. Higher glycosylated haemoglobin is a risk factor for early neurodegeneration.

Key words: Diabetes mellitus; ganglion cell complex; neurodegeneration; optical coherence tomography; retinal nerve fibre layer; vasculopathy.

Financial Interest : Nil
Conflict of Interest : Nil

Received : 08.02.2025
Accepted : 27.02.2026
Published : 03.04.2026

Corresponding Author
Dr. Suma Elangovan,
Professor, Department of Ophthalmology,
Employees' State Insurance Corporation Medical College and Hospital,
Ashok Pillar Road, Kalaignar Karunanidhi Nagar,
Chennai, Tamil Nadu, India.
E-mail address: elangovansuma@hotmail.com

Access this article online
Website: www.nepjol.info/index.php/NEPJOPH
DOI: https://doi.org/10.3126/nepjoph.v18i35.75209

ISSN: 2072-6805, **E-ISSN:** 2091-0320

INTRODUCTION

The worldwide prevalence of diabetes in adults aged eighteen years and older is estimated to be 828 million in 2022, an increase of 630 million from 1990 (Lancet, 2024). Vision loss is a debilitating complication of diabetes (Mounirou et al., 2022; Stewart, 2016). Diabetic retinopathy though considered primarily of vascular aetiology, recent evidence shows that neurodegeneration occurs much earlier and possibly is a primary pathogenic event rather than a result of vascular pathology (Barber et al., 2017; Sohn et al., 2016; Pillar et al, 2020). All current treatments available primarily address vascular pathology (Mounirou et al., 2022; Stewart et al., 2016). Retinal neuronal apoptosis occurs very early in the disease course, causing a reduction in the thickness of inner retinal layers and of the retinal nerve fibre layer (RNFL) (Sachdeva, 2021; Bianco et al., 2022; Ola et al., 2013; Deng et al., 2022). So in this study ganglion cell complex thickness (GCC) and peripapillary RNFL thickness in diabetic patients without diabetic retinopathy was compared with age-matched individuals without diabetes to understand and evaluate the early neurodegeneration using spectral domain optical coherence tomography (SD-OCT).

METHODOLOGY

This was a hospital-based, prospective, observational study conducted in the department of ophthalmology in a tertiary care hospital in South India from 2022 May to 2023 March 2023. The study commenced after institutional ethics committee clearance (Reference number: IEC/2022/1/33; Dated: 2022 May 03), and it was conducted as per the Declaration of Helsinki.

Every type two diabetic patient without retinopathy (cases) and controls without diabetes fitting into the inclusion criteria presented during the study period were included in the study till the desired sample size was attained using consecutive sampling technique. One hundred and twenty seven eyes of cases and 115 eyes of controls were included. The following were the inclusion criteria for cases: 1) Age more than 20 years 2) Absence of evident clinical diabetic retinopathy 3) No other systemic comorbidities. Exclusion criteria for cases included: the presence of systemic comorbidities other than diabetes, any pre-existing retinal or optic nerve head pathology, media opacities, pregnancy, refractive error $\geq \pm 3$Diopter, and previous trauma or surgeries. Controls were age-matched people without any systemic comorbidities, any pre-existing retinal or optic nerve head pathology, media opacities, pregnancy, refractive error $\geq \pm 3$Diopter, previous trauma, or surgeries.

An informed written consent form was obtained from the eligible participants before recruitment in a language they would understand. One eye of each participant was included. All participants underwent a complete ophthalmological examination, including visual acuity, intraocular pressure assessment, anterior segment examination with slit lamp biomicroscopy, and retinal evaluation with indirect ophthalmoscopy after dilatation with tropicamide and phenylephrine eye drops. Data, including the patient's name, age, duration of diabetes, and value of glycosylated haemoglobin

(HbA1c) done within the last three months, were recorded.

Retinal nerve fibre layer thickness and Ganglion cell complex thickness of all participants were measured using SD-OCT Topcon Maestro. In OCT 3D wide mode, a 12*9 mm wide area of macula was used to scan the thickness of the GCC layer, which includes the macular ganglion cell layer (m-GCL) and inner plexiform layer (m-IPL).

The thickness of average RNFL (avg. RNFL), superior RNFL, and inferior RNFL was measured. The values of the thickness of average GCC (avg. GCC), superior GCC, inferior GCC, inferonasal GCC, superonasal GCC, superotemporal GCC, and inferotemporal GCC were measured.

Data was entered into MS Excel, cleaned, and imported to IBM SPSS Statistics version 26 (IBM Corp., Armonk, N.Y., USA) for further analysis. Baseline characteristics were described as mean for continuous data and as frequency and percentage for categorical data. Normality was checked visually by histogram and quantile-quantile plot and statistically confirmed using the Shapiro-Wilk test. A student's unpaired t-test was used for comparing RNFL and GCC thickness between cases and controls. The difference in proportions for categorical variables between the two groups was tested by the chi-square test. Descriptive statistics were reported as mentioned above. To look for an association between RNFL, GCC thickness, and the other factors in the diabetic group, logistic regression was done. The p-value of <0.05 was considered significant.

RESULT

A total of 117 eyes were included as cases, and 115 eyes were included as controls. The mean age of cases was 51.46 ± 8.48 years in the diabetic group, and the mean age in the control group was 48.78 ± 6.73 years (Table 1).

The mean duration of diabetes in cases was 5.8 ± 4.24 years. The mean HbA1c was 8.10 ± 1.94 among cases, and 61% of cases had HbA1c >7.

The mean average GCC thickness was 99.9 ± 8.1µm in diabetic eyes and 109.3 ± 4.9µm in the controls (p <0.001). The mean average RNFL thickness was 100.3 ± 12.5µm in the diabetic group and 110.9 ± 8.7µm in the control group (p <0.001). The GCC thickness (Table 2) and RNFL thickness (Table 3) were lower in cases in all quadrants compared to controls and were statistically significant.

Among cases, mean average GCC thickness and mean average RNFL thickness were thinner in participants with HbA1c >7 when compared to HbA1c <7, with HbA1c levels negatively correlating with GCC (p = 0.03) and RNFL thickness (p = 0.002) (Table 4).

Age (p = 0.021) and higher HbA1c (p = 0.004) were independently related to reduction of average RNFL thickness on multivariable logistic regression analysis. Age (p = 0.003) and HbA1c (p = 0.026) were again independent risk factors for thinner average GCC thickness on regression analysis. The multivariable linear regression analysis of the independent relationships of systemic parameters with average GCC and RNFL thickness were summarised in (Table 5).

Table 1: Demographic characteristics and systemic characteristics.

	Cases	Controls
Age (mean ±SD*)	51.5 ± 8.5 years	48.8 ± 6.7 years
Sex (male/female)	51/66	50/65
Vision	6/6	6/6
IOP†	14 mmHg	15 mmHg
Hypertension	-	-
Heart disease	-	-
HbA1c§ (mean)	8.1±1.9	5.7±1.01

*SD: standard deviation; †IOP: intraocular pressure; ‡mmHg: millimeters of mercury; §HbA1c: glycosylated haemoglobin.

Table 2: Comparison of ganglion cell layer–inner plexiform layer thickness.

	Cases (mean ± SD*) μm	Controls (mean ± SD) μm	p-value
average GCC†	99.9 ± 8.1	109.3 ± 4.9	<0.001
Superior GCC	99.9 ± 8.7	109 ± 4.8	
Inferior GCC	99.92 ± 8.2	109.3 ± 5.5	
Inferonasal GCC	107.7 ± 10.9	117.3 ± 7.3	
Superonasal GCC	108.06 ± 11.5	117.4 ± 6.8	
Superotemporal GCC	108.05 ± 11.5	117.4 ± 6.8	
Inferotemporal GCC	107.9 ± 11.5	117.4 ± 7.3	

*SD: standard deviation; †GCC: ganglion cell layer–inner plexiform layer thickness.

Table 3: Comparison of retinal nerve fibre layer thickness.

	Cases (mean ± SD*) μm	Controls (mean ± SD) μm	p-value
average RNFL†	100.3 ± 12.5	110.9 ± 8.7	<0.001
Superior RNFL	128.3 ± 18.3	137.4 ± 10.8	0.002
Inferior RNFL	125.9 ± 19.1	142.2 ± 15.3	<0.001

*SD: standard deviation; †RNFL: retinal nerve fibre layer.

Table 4: Influence of demographic and systemic factors on retinal nerve fibre layer and ganglion cell layer–inner plexiform layer thickness.

Variable	Subgroup	GCC thickness (Mean ± SD)	p-value	RNFL thickness (Mean ± SD)	p-value
HbA1c (§)	<7	103.1 ± 9.3	0.03	107.4 ± 8.7	0.002
	>7	99.1 ± 7.6		98.5 ± 11.9	
Diabetes Duration	<5 years	101.25 ± 6.87	0.29	102.62 ± 8.93	0.96
	5–10 years	99.08 ± 7.97		103.04 ± 15.67	
	>10 years	95.32 ± 6.61		104.16 ± 20.67	
Age (Cases)	<40	106.85 ± 8.09	0.05	108.57 ± 12.81	0.05
	40–50	100.15 ± 8.12		102.2 ± 13.25	
	>50	99.19 ± 7.86		98.35 ± 11.76	
Age (Controls)	<40	113 ± 7.82	0.16	112.45 ± 3.11	0.04
	40–50	111.11 ± 8.07		108.37 ± 5.35	
	>50	103.5 ± 12.87		107.25 ± 0.5	

*SD: standard deviation; †GCC: ganglion cell layer–inner plexiform layer thickness; ‡RNFL: retinal nerve fibre layer; §HbA1c: glycated haemoglobin.

Table 5: Multivariable Regression Analysis on the associations between Ocular and Systemic Parameters with average ganglion cell-inner plexiform layer thickness and retinal nerve fibre layer thickness.

Average RNFL*					
	β§	**Standard error**	β'‖	**95% Confidence Interval**	**p-value**
HbA1c† (%)	-2.284	0.767	-0.358	-3.822 to -0.746	0.004
Age	-0.406	0.171	-0.286	-0.749 to -0.063	0.021
Diabetes duration	0.126	0.354	0.041	-0.584 to 0.836	0.723
Average GCC‡					
HbA1c (%)	-1.121	0.488	-0.27	-2.1 to -0.141	0.026
Age	-0.341	0.109	-0.368	-0.56 to -0.123	0.003
Diabetes duration	-0.352	0.226	-0.177	-0.805 to 0.1	0.124

*RNFL: retinal nerve fibre layer; †HbA1c: glycated haemoglobin; ‡GCC: ganglion cell layer–inner plexiform layer thickness; §β: denotes the change in GC-IPL and RNFL thickness (μm) per unit change in predictor variables; ‖β': represents a standardized coefficient.

DISCUSSION

Diabetic retinopathy, being a vision-threatening condition and a serious challenge to treat, mandates the ned to identify the retinal disease onset as early as possible (Stewart et al., 2016). So, in this case-control study using SD-OCT, the GCC and RNFL thickness were evaluated in diabetes mellitus without clinical retinopathy and healthy controls to quantify and confirm the neurodegenerative pathogenesis of diabetic retinopathy.

Age with average RNFL and average GCC thickness showed a negative correlation in the current study. Various studies have shown that there is an age-related loss of retinal axonal cells even in the normal population (Deng et al., 2022; Vilasboas-Campos et al., 2024; Patel et al., 2014). As cases and controls were age-matched in this study, the confounding effect of age on RNFL and GCC thickness was negated in the current study.

In the present study, peripapillary average RNFL thickness and thickness in superior and inferior quadrants were significantly lesser in type 2 diabetes mellitus without clinical retinopathy when compared to non-diabetics. The current study findings were similar to the findings of Baskaran et al., (2023); Rodrigues et al., (2015) and Carpineto et al., (2016). Also, the current study findings were in contrast to the studies by Demir et al., (2014) and Pekel et al., (2017), where there was no difference in RNFL thickness between diabetics and non-diabetics. A point to note is that this study had a larger sample size compared to the other studies and excluded patients with other systemic comorbidities, including hypertension and heart disease, which can be confounding factors.

Similarly, in the current study, GCC thickness was reduced in all sectors in diabetics compared to non-diabetics. Present study findings were similar to other studies by Chhablani et al., (2015); Li et al., (2017) and Lim et al., (2020), whereas in the study by Demir et al., (2014), there was no significant difference between diabetics and non-diabetics GCC thickness.

A within-group analysis of type 2 diabetes mellitus showed that HbA1c is negatively correlated with both average RNFL and average GCC thickness, indicating patients having higher HbA1c (>7) are having thinning of both RNFL and GCC thickness. Current study findings were similar to the studies by Nor-Sharina et al., (2013) and Mikhail et al., (2021) showing the importance of strict disease control to delay the process of neurodegeneration.

The current study proves that neurodegeneration of the nerve fibre layer and inner retinal layers occurs even before evident clinical changes appear and can be used as an early biomarker for ongoing retinal damage to help patients be aware and vigilant of the disease and to delay further damage. Spectral-domain optical coherence tomography can be a helpful tool in the future to assess RNFL thickness and GCC thickness to start neuroprotective measures if available in the future.

The strengths of this study were larger sample size, age-matched controls, and exclusion of participants with other systemic comorbidities, including hypertension (Akay et al., 2016; Lee

et al., 2021; White et al., 2016) and heart disease (White et al., 2016; Majithia et al., 2023; Ural et al., 2023) which could be influencing the RNFL and GCC thickness and confounding the results.

The limitations are the cross-sectional nature of the study, and longitudinal studies with larger sample sizes are needed to assess the trend of decline in RNFL and GCC thickness over the years as the disease progresses.

CONCLUSION

The study shows that degeneration of the retinal nerve fibre layer and ganglion cell complex in diabetics occurs before clinical vascular changes appear. Higher glycosylated haemoglobin is a risk factor for early neurodegeneration. Picking up neurodegeneration early can be a great tool for preventing or delaying vascular-related diabetic retinopathy complications in the eye and can be vision-saving when early treatment modalities are available for neurodegeneration in the future.

REFERENCES

Akay F, Gundogan FC, Yolcu U, et al., (2016) 'Retinal structural changes in systemic arterial hypertension: An OCT study', European Journal of Ophthalmology, 26(5), 436–441. DOI: 10.5301/ejo.5000740. PMID: 26868661.

Barber A.J. and Baccouche B. (2017) 'Neurodegeneration in diabetic retinopathy: Potential for novel therapies', Vision Research, 139, 82–92. doi: 10.1016/j.visres.2017.06.014. PMID: 28669830.

Bhaskaran A, Jeganathan J, Chidambaram S, et al., (2023) 'Study of retinal nerve fibre layer thickness in diabetic patients using optical coherence tomography', Indian Journal of Ophthalmology, 71(3), 920–926. DOI: 10.4103/ijo.IJO_1918_22. PMID: 36840916.

Bianco L, Mutti A, Quarantotti, M, et al., (2022) 'Neuroinflammation and neurodegeneration in diabetic retinopathy', Frontiers in Aging Neuroscience, 14, 937999. doi: 10.3389/fnagi.2022.937999. PMID: 36159516.

Carpineto P, Toto L, Aloia R, et al., (2016) 'Neuroretinal alterations in the early stages of diabetic retinopathy in patients with type 2 diabetes mellitus', Eye, 30(5), 673–679. DOI: 10.1038/eye.2016.13. PMID: 26869151.

Chhablani J, Sharma A, Goud A, et al., (2015) 'Neurodegeneration in type 2 diabetes: Evidence from spectral-domain optical coherence tomography', Investigative Ophthalmology & Visual Science, 56(11), 6333–6338. DOI: 10.1167/iovs.15-17334. PMID: 26431484.

Demir M, Oba E, Sensoz, H, et al., (2014) 'Retinal nerve fibre layer and ganglion cell complex thickness in patients with type 2 diabetes mellitus', Indian Journal of Ophthalmology, 62(6), 719–720. DOI: 10.4103/0301-4738.136234. PMID: 25005199.

Deng Y, Xu H, Wang J, et al., (2022) 'Age-related focal thinning of the ganglion cell-inner plexiform layer in a healthy population', Quantitative Imaging in Medicine and Surgery, 12(6), 3034–3048. doi: 10.21037/qims-21-860. PMID: 35694294.

Lee MW, Chung MY, Kim TY, et al., (2021) 'Effect of systemic hypertension on peripapillary RNFL thickness in patients with diabetes without diabetic retinopathy', Diabetes, 70(11), 2663–2667. DOI: 10.2337/db21-0491. PMID: 34413158.

Li ST, Guo J, Fan WJ, et al., (2017) 'Comparison of spectral-domain optical coherence tomography for intra-retinal layers thickness measurements between healthy and diabetic eyes among Chinese adults', PLoS ONE, 12(5), e0177515. DOI: 10.1371/journal.pone.0177515. PMID: 28542247.

Lim HB, Shin YI, Cho M, et al., (2020) 'Ganglion cell-inner plexiform layer damage in diabetic patients: 3-year prospective study', Scientific Reports, 10(1), 1470. DOI: 10.1038/s41598-020-58465-x. PMID: 32001740.

Majithia S, Tham YC, Gan A. et al., (2023) 'Cardiovascular disease and thinning of retinal nerve fibre layer in a multi-ethnic Asian population', Frontiers in Medicine, 10, 1235309. DOI: 10.3389/fmed.2023.1235309. PMID: 37554907.

Mikhail MEA, Sharaf MH, El-Hifnawy MA, et al., (2021) 'Correlation of retinal nerve fibre layer and ganglion cell complex thickness with glycosylated haemoglobin in diabetic patients', Delta Journal of Ophthalmology, 22(1), 34–41. DOI: 10.4103/DJO.DJO_57_20.

Mounirou BAM, Adam ND, Yakoura AKH et al., (2022) 'Diabetic Retinopathy: An Overview of Treatments', *Indian Journal of Endocrinology and Metabolism, 26(2),* 111–118. doi: 10.4103/ijem.ijem_480_21. PMID: 35873941.

NCD Risk Factor Collaboration (NCD-RisC) (2024) 'Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants', The Lancet, 404(10467), 2077–2093. doi: 10.1016/S0140-6736(24)02317-1. PMID: 39549716.

Nor-Sharina Y, Mohamad MS, Sharanjeet-Kaur S, et al., (2013) 'Correlation of retinal nerve fibre layer thickness with HbA1c and oxidised LDL in non-proliferative diabetic retinopathy', Journal of Diabetes & Metabolism, 4, 274. DOI: 10.4172/2155-6156.1000274.

Ola MS, Nawaz MI, Khan AA, et al., (2013) 'Neurodegeneration and neuroprotection in diabetic retinopathy', International Journal of Molecular Sciences, 14(2), 2559–2572. doi: 10.3390/ijms14022559. PMID: 23358257.

Patel NB, Xie S, Thompson H, et al., (2014) 'Age-associated changes in the retinal nerve fibre layer and optic nerve head', Investigative Ophthalmology & Visual Science, 55(8), 5134–5143. DOI: 10.1167/iovs.14-14303. PMID: 25034600.

Pekel E, Altınbay D, Başıpak S, et al., (2017) 'Assessment of optic disc and ganglion cell layer in diabetes mellitus type 2', Medicine (Baltimore), 96(29), e7556. DOI: 10.1097/MD.0000000000007556. PMID: 28723788.

Pillar S, Vujosevic S, Simó R. et al., (2020) 'Recent developments in diabetic retinal neurodegeneration: A literature review', Journal of Diabetes Research, 2020, 5728674. doi: 10.1155/2020/5728674. PMID: 32509930.

Rodrigues EB, Urias MG, Penha FM et al., (2015) 'Diabetes induces changes in neuroretina before retinal vessels: a spectral-domain optical coherence tomography study', International Journal of Retina and Vitreous, 1, 4. DOI: 10.1186/s40942-015-0001-z. PMID: 27847587.

Sachdeva, M.M. (2021) 'Retinal neurodegeneration in diabetes: an emerging concept in diabetic retinopathy', Current Diabetes Reports, 21(12), p. 65. doi: 10.1007/s11892-021-01428-x. PMID: 34741215.

Sohn EH, van Dijk HW, Jiao C, et al., (2016) 'Retinal neurodegeneration may precede microvascular changes characteristic of diabetic retinopathy in diabetes mellitus', *Proceedings of the National Academy of Sciences*, 113(19), 655–664. doi: 10.1073/pnas.1522014113. PMID: 27114552.

Stewart, M.W. (2016) 'Treatment of diabetic retinopathy: Recent advances and unresolved challenges', World Journal of Diabetes, 7(16), 333–341. doi: 10.4239/wjd.v7.i16.333. PMID: 27625747

Ural Fatihoglu O and Fatihoglu, SG. (2023) 'Ganglion cell complex damage in coronary artery disease', Photodiagnosis and Photodynamic Therapy, 44, 103789. DOI: 10.1016/j.pdpdt.2023.103789. PMID: 37659546.

Vilasboas-Campos V, Geyman LS, Wang H, et al., (2024) 'Estimated rates of retinal ganglion cell loss with aging', Ophthalmology Science, 5(1), 100616. DOI: 10.1016/j.xops.2024.100616. PMID: 39309405.

White R, Goudreault N, Shaukat A. et al., (2016) 'Association of retinal nerve fibre layer thickness and systemic hypertension', Investigative Ophthalmology & Visual Science, 57(12), p. 2040.