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Original Research Article

To compare peripapillary retinal nerve fibre layer thickness in diabetes mellitus type ii with and without diabetic retinopathy with normal healthy individual

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Abstract

Background: The diabetic retina undergoes significant degenerative changes, particularly in the retinal nerve fibre layer (RNFL), alongside notable vascular alterations. These changes include the loss of RNFL and modifications within the inner retina. Researchers have extensively studied the association between these retinal alterations and metabolic control in diabetic patients, yielding varied results.

Aim: To evaluate the thickness of the peripapillary retinal nerve fibre layer (RNFL) in individuals with Type II diabetes mellitus, both with and without diabetic retinopathy, and to compare these findings with those of healthy individuals.

Materials and Methods: 120 patients were enrolled in the study, divided into three groups: 40 healthy controls, 40 patients with diabetes without retinopathy, and 40 patients with diabetic retinopathy. Optical coherence tomography (OCT) scans were performed on both eyes of all participants to assess the RNFL and ganglion cell complex (GCC). The parameters obtained were then analysed in relation to the patient's metabolic control.

Results: Significant RNFL thinning was observed in the superior temporal (ST) ($p = 0.036$), superior nasal (SN) ($p = 0.028$), nasal upper (NU) ($p = 0.04$), and nasal lower (NL) ($p = 0.029$) quadrants around the optic disc in the diabetic retinopathy group. Additionally, HbA1c levels demonstrated a weak negative correlation with RNFL thickness.

Conclusion: This study shows that neurodegeneration is an early component of diabetic retinopathy.

Keywords: Diabetes mellitus, Retinal nerve fibre layer thickness, Optical coherence tomography, Ganglion cell complex, HBA1c.

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1. Introduction

Diabetic Macular Edema (DME) is the leading cause of legal blindness worldwide.[1-3] It has been attributed to the microvascular theory.[4,5] This theory suggests increased capillary permeability and a breakdown of the blood-retinal barrier in diabetic patients as the cause of macular oedema.[2-4] The current treatment option for varying grades of Diabetic Retinopathy (DR) and DME consists mainly of photocoagulation, which destroys the diseased tissue so that unaffected retinal areas can be saved.[1,4] Much before the onset of microvascular changes, functional changes occur in a diabetic retina.[5,6] Various studies using electroretinography, colour vision, contrast sensitivity, and dark adaptation have concluded that neuronal loss occurs much earlier than microvascular abnormalities.[7-9] Any loss of neuronal tissue will lead to a decrease in retinal thickness.[10] Optical Coherence Tomography (OCT) is the most precise measure of retinal thickness in vivo.[5] It is an advantageous tool that helps acquire data quickly, reconstruct it in a three-dimensional form, and shows the different retinal layers.[5] Fourier-domain OCT offers high-resolution imaging (5μ) and a faster scan rate. The RTVue-100 OCT (Optovue, Inc., Fremont, CA) is one of the latest commercially available Fourier-domain OCT instruments. The study was undertaken to map the retinal nerve fibre layer thickness variation in patients with Type II Diabetes Mellitus (DM) and compare them with age-matched healthy controls.

2. Materials and Methods

120 patients attending the Ophthalmology outpatient department of a tertiary hospital over 18 months (February

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2023 – June 2024) were included in the study after obtaining written and informed consent. The participants were divided into three groups: 40 diabetic patients without diabetic retinopathy (Non-DR Group), 40 patients with mild to moderate nonproliferative diabetic retinopathy (DR Group), and 40 healthy control subjects. Inclusion criteria encompassed healthy individuals and Type II diabetic patients without and with mild to moderate no proliferative diabetic retinopathy.[12]

Patients were excluded if they had a history of Type I diabetes mellitus (DM), diabetic macular oedema (DME), proliferative diabetic retinopathy (DR), pre-existing glaucoma, intraocular inflammation, optic nerve pathology, vitreous haemorrhage, previous retinal laser treatment, previous intraocular surgery or procedures, media opacities such as dense cataracts or corneal opacities, or if they were uncooperative. (**Figure 1**)

Prior approval from the Ethical Committee was also obtained. (SMC/UECM/2023/509/257)

All patients underwent a comprehensive ophthalmological examination following a standardized protocol. Intraocular pressure was recorded using noncontact tonometry. Optical coherence tomography (OCT) was performed using the Optovue RTVue 100 three-dimensional Fourier-domain OCT, with all scans conducted by a single operator. After pupil dilation, both eyes of each subject underwent the following scans:

1. Optic Nerve Head (ONH) Scan: Utilized the ONH protocol with a 3.45 mm diameter circle centred around the optic nerve head. This scan included 13 circular scans with diameters ranging from 1.3 to 4.9 mm and 12 radial lines, each 3.7 mm long. The retinal nerve fibre layer (RNFL) thickness was analyzed in eight sectors: Superotemporal (ST), Superonasal (SN), Inferotemporal (IT), Inferonasal (IN), Nasal Upper (NU), Nasal Lower (NL), Temporal Upper (TU), and Temporal Lower (TL). (**Figure 2**)
2. Ganglion Cell Complex (GCC) Scan: Centered 1 mm temporal to the foveal centre, this scan comprised 15 vertical line scans covering a 7 mm square region.(**Figure 3**)

Metabolic control of diabetes was evaluated using glycosylated haemoglobin (HbA1c) and serum creatinine reports available at the time of examination. HbA1c was measured by high-performance liquid chromatography with the Biorad D-10 machine, while serum creatinine was measured by the alkaline picrate method using the Unicel DXC 800 instrument.

2.1. Statistical analysis

Data collected were organized and tabulated in an Excel spreadsheet under the guidance of a statistician. Statistical analysis was performed using SPSS version 22.0 for Windows (SPSS Inc., Chicago, USA). The means and standard deviations of measurements for each group were calculated. Differences between groups were assessed using one-way ANOVA, with post-hoc analysis applied where significant differences were observed. Pearson's correlation coefficients were calculated to evaluate the relationship between RNFL thickness, HbA1c levels, and the duration of diabetes. The level of significance was set at $p < 0.05$.

3. Results

The study included 48 males (40%) and 72 females (60%), with a predominance of females in all groups. Out of the 120 patients enrolled, 80 (66.67%) were diabetic, distributed between the diabetic retinopathy (DR) and non-diabetic retinopathy (non-DR) groups. The mean age of the healthy control subjects was 51.62 ± 9.02 years.

Table 1 displays the baseline characteristics of diabetic patients in both groups. **Table 2** illustrates the RNFL measurements across eight sectors in the study groups. **Table 3** represents the comparison of GCC among the study subjects.

RNFL was thinner in diabetic patients compared to healthy controls, with significant differences observed in the Superior Temporal (ST) (p = 0.036), Superior Nasal (SN) (p = 0.028), Nasal Upper (NU) (p = 0.04), and Nasal Lower (NL) (p = 0.029) sectors. However, the Ganglion Cell Complex (GCC) did not show significant differences among the three groups (p = 0.66).

Pearson's correlation coefficients indicated a weak negative correlation between the duration of diabetes and RNFL thickness. In the diabetic retinopathy group, the correlation was -0.038 (p = 0.815), indicating no significant correlation. For the diabetic group without retinopathy, the correlation was 0.067 (p = 0.709), and in the healthy control group, it was -0.078 (p = 0.631), all indicating no significant correlation.

Metabolic control was worse in patients with diabetic retinopathy. Pearson's coefficient of correlation was calculated to assess the relationship between RNFL thickness and metabolic control parameters. No correlation was seen between RNFL thickness and HbA1c.

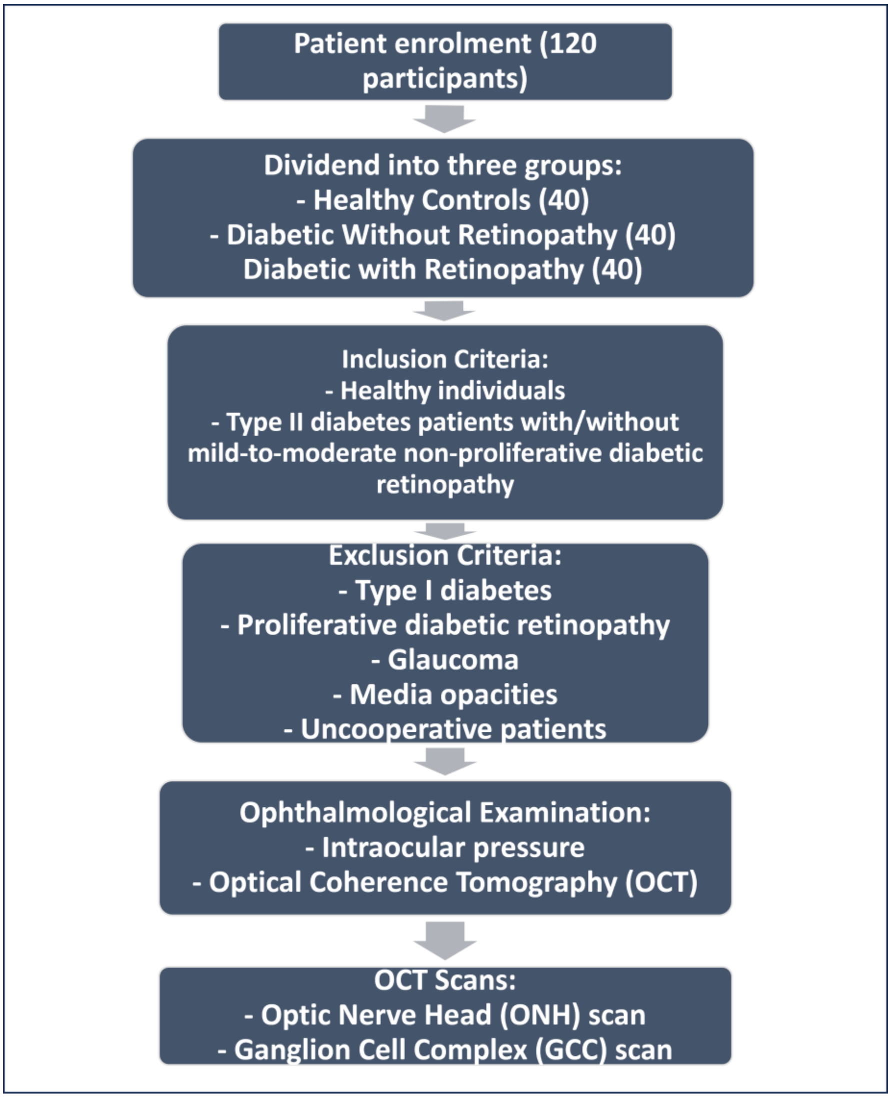

Figure 1: Process flow

Table 1: Baseline characteristics of diabetic patients

Baseline Characteristics	**Non-DR Group**	**DR Group**
Mean age	51.59±10.72	55.75±10.24
Insulin	1	2
OHA	39	38
HbA1c (%)	8.2±1.22	9.6±2.04
Creatinine (mg/dl)	0.95±0.20	1.28±0.65

DR: Diabetic Retinopathy; OHA; Oral Hypoglycemic Drug

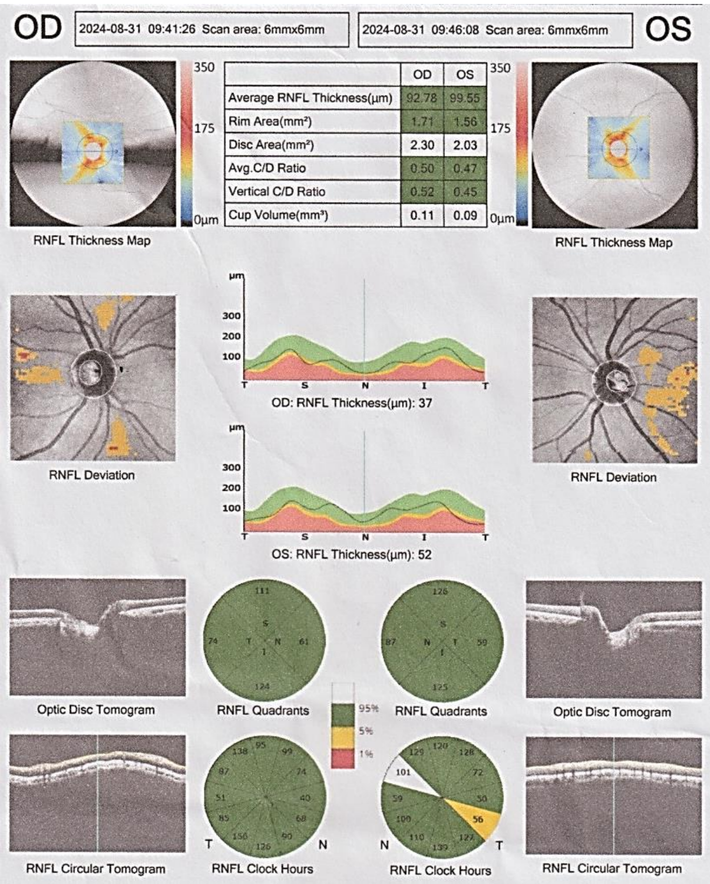

Figure 2: Optical coherence tomography (OCT) image showing the retinal nerve fiber layer (RNFL) thickness

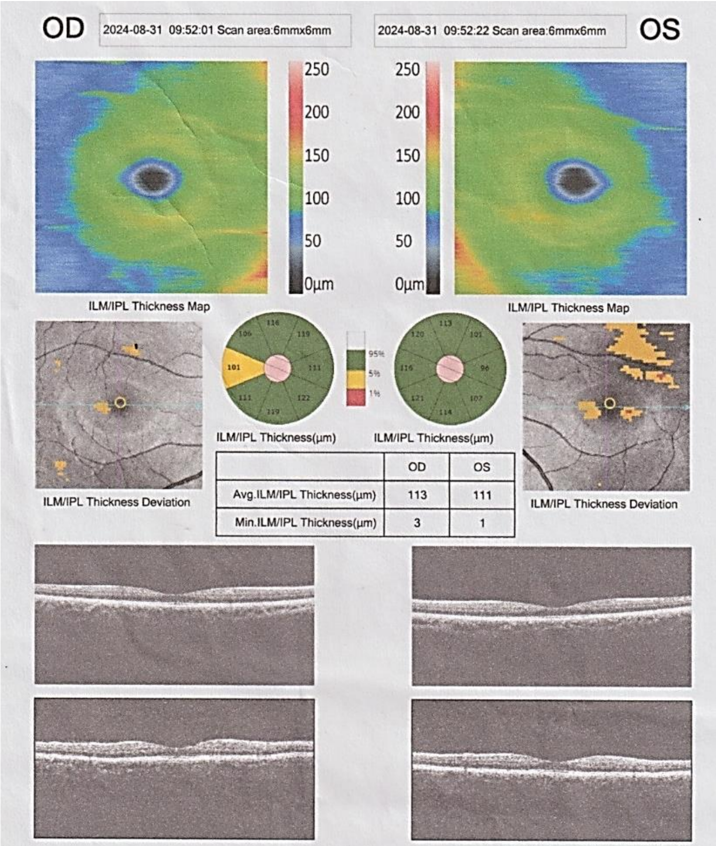

Figure 3: Ganglion cell complex scan

Table 2: Comparison of retinal nerve fibre layer in the study subjects

Variables	DR		Non-DR		Control		p-value*		
	Mean	SD	Mean	SD	Mean	SD	DR vs. non-DR	DR vs. Control	Non-DR vs. Control
Mean RNFL Thickness	97.74	17.44	102.96	10.35	104.365	11.535	0.59	0.25	0.37
ST	123.84	34.485	129.03	15.655	124.3	24.415	0.047**	0.043**	0.036*
SN	115.63	30.385	116.15	20.59	126.69	24.785	0.77	0.031*	0.028**
IT	118.37	31.32	122.72	23.17	122.28	27.47	0.19	0.16	0.78
IN	115.12	31.88	114.89	19.42	116.51	26.68	0.67	0.62	0.43
NU	83.92	26.15	89.135	15.44	96.71	20.125	0.049**	0.006**	0.04**
NL	72.2	20.845	80.82	15.79	88.665	23.175	0.025**	<0.01**	0.029**
TU	71.39	21.805	84.44	13.47	79.39	17.61	0.015**	0.06	0.053
TL	66.65	20.055	70.625	14.985	71.6	18.79	0.11	0.048**	0.32

ST: Supero-temporal; SN: Supero-nasal; IT: Inferio-temporal; IN: Infero-nasal; NU: Nasal upper NL: Nasal lower; TU: Temporal upper; TL: Temporal lower; DR: Diabetic Retinopathy
*One-way ANOVA** P <0.05 Significant

Table 3: Comparison of GCC among the study subjects

Groups	GCC	
	Mean	SD
With Diabetic Retinopathy	102.11	20.585
Without Diabetic Retinopathy	102.965	10.72
Control	101.35	14.665
p-value*		
With vs. Without Diabetic Retinopathy	0.73	
Diabetic Retinopathy vs Control	0.64	
Without Diabetic Retinopathy vs Control	0.66	

GCC: Ganglion Cell Complex; SD: Standard Deviation
* One-way ANOVA (P <0.05 Significant)

4. Discussion

One of the leading causes of eyesight loss in the globe is diabetic retinopathy (DR).

Psychophysical and functional visual tests have demonstrated retinal dysfunction before the appearance of clinically detectable retinal vascular changes.[13,14] Specifically, the implicit time of first- and second-order multifocal electroretinograms (mfERGs) is delayed in diabetic patients without diabetic retinopathy (DR). Additionally, the amplitudes of the second-order component are reduced.[15]

It is commonly recognized that neurodegeneration plays a significant role in retinal illnesses like retinitis pigmentosa and glaucoma. On the other hand, little attention has been paid to how neurodegeneration affects diabetes. In the absence of glaucoma and other disorders of the optic nerve, RNFL may also thin in diabetes mellitus. Neurodegenerative changes in DR include increased apoptosis, glial reactivity, microglia, and altered glutamatergic pathways.[16]

Because glaucoma damage directly affects the GCC, which comprises the RNFL, ganglion cell layer, and inner plexiform layer, it can help diagnose glaucoma.[17] An objective assessment of GCC in DR is crucial since its quantification aids in the early diagnosis of the condition and the provision of neuroprotective therapies.[18] To enable a preventive rather than an interventional therapy approach in the future, it is imperative to investigate the neurodegenerative element of diabetic retinopathy (DR).

The present study explored the demographic characteristics, treatment modalities, and various clinical and ocular parameters among three groups: individuals with diabetic retinopathy, those without diabetic retinopathy, and a control group without diabetes. This comprehensive investigation sheds light on the complex interplay between diabetes and its ocular complications, providing valuable insights into the mechanisms and risk factors associated with diabetic retinopathy.

In our study, we saw RNFL was thinner in diabetic patients compared to healthy controls, with significant differences observed in the Superior Temporal (ST) (p = 0.036), Superior Nasal (SN) (p = 0.028), Nasal Upper (NU) (p = 0.04), and Nasal Lower (NL) (p = 0.029) sectors. However, the Ganglion Cell Complex (GCC) did not show significant differences among the three groups (p = 0.66).

A similar study was conducted by Jay Chhablani et al.[19] in 2015 to assess changes in the neural retina in eyes with different stages of diabetic retinopathy (DR) in comparison to age-matched healthy subjects, which showed the RNFL thickness was lower in diabetics compared with controls ($P<0.05$).

Another study was conducted by Anand et al.[20] in 2019. They also observed that diabetes was strongly associated with a decreased level of retinal nerve fibre layer thickness. This decrease was statistically significant in several areas: overall retinal nerve fibre layer thickness ($p < 0.001$), superior retinal nerve fibre layer thickness ($p < 0.001$), nasal retinal fibre layer thickness ($p < 0.001$), inferior retinal layer thickness ($p < 0.001$), and temporal nerve fibre layer thickness ($p < 0.001$).

Mohammad A.M. EI-Hifnaway et al.[21] also observed in 2016 that the superior and temporal RNFL thickness in diabetic patients with and without DR was significantly less than that of the control group.

The current study also highlights the impact of diabetes duration and glycemic control on retinal nerve fibre layer (RNFL) thickness. Our findings indicate that while there is a weak negative correlation between the duration of diabetes and RNFL thickness across different groups, the correlation is not statistically significant (p-values > 0.05). This suggests that longer durations of diabetes do not linearly correlate with more severe RNFL thinning within the study's timeframe.

Moreover, the correlation between HbA1c levels and RNFL thickness was similarly weak and non-significant. This weak correlation might be indicative of the multifactorial nature of retinal neurodegeneration in diabetic patients, where factors beyond glycaemic control and disease duration, such as blood pressure and lipid levels, could play crucial roles. This finding aligns with the studies by other researchers, which reported that the relationship between metabolic control and retinal health might not be straightforward and could involve other systemic and local retinal factors.

5. Limitations

The current study has several limitations. First, it employed a non-randomized cross-sectional observational design. The participants were of North Indian origin, which restricts the applicability of the findings to the global population. Additionally, many participants could only provide an approximate duration of their diabetes, which may affect the accuracy of the data. The study utilized only one type of OCT device, which could limit the generalizability of our results, as different devices may produce slightly different outcomes. Although we controlled for several confounding variables, we could not account for other unknown factors that may influence retinal nerve fibre layer (RNFL) thickness, such as undiagnosed ocular conditions.

6. Conclusion

This study highlights the impact of Type II Diabetes Mellitus on the thickness of the peripapillary retinal nerve fibre layer (RNFL). It shows significant thinning in individuals with diabetic retinopathy compared to those without the condition and in healthy controls. These findings suggest that neurodegeneration may serve as an early indicator of diabetic retinopathy, as changes in RNFL thickness can occur before any vascular symptoms become noticeable. The weak correlation between HbA1c levels and RNFL thickness indicates that various factors, including the duration of diabetes and overall systemic health, influence ocular changes in diabetic patients. This complexity calls for a comprehensive management approach that combines strict glycemic control with regular eye assessments to effectively monitor and reduce the progression of diabetic retinopathy. Our research advocates for further investigation into the multiple factors affecting RNFL thickness to better understand the neurodegenerative aspects of diabetic eye disease. The goal is to enhance early diagnosis and preventive strategies for diabetic retinopathy.

7. Source of Funding

None.

8. Conflict of Interest

None.

9. Ethical

Ethical No. SMC/UECM/2023/509/257.

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