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# PERIPAPILLARY RETINAL NERVE FIBRE LAYER THICKNESS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS.

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**ABSTRACT** **Context:** Recent literature shows that Diabetic retinopathy is studied as a neuronal degeneration, which is said to precede retinal microvascular changes. Diabetic retinal neurodegeneration can be detected by measuring peripapillary retinal nerve fibre layer thickness by Optical coherence tomography.Thus can be used an early diagnostic tool to diagnostic tool to predict the onset of diabetic retinopathy. **Aims:** To compare the peripapillary retinal nerve fibre layer thickness(peripapillary RNFL thickness) in type 2 Diabetics with healthy subjects and correlate with severity of Diabetic retinopathy(DR) **Settings and Design:** Cross-sectional analytical study **Methods and Material:** Type2 DM patients above 40 years of age were categorised into 2 groups subgroup (SG)1 with glycosylated haemoglobin (HbA1c) <7% and SG2 with HbA1c >7% .The peripapillary RNFL thickness of both these groups of patients were compared with non-diabetic normal subjects.The peripapillary RNFL thickness was correlated with severity of DR. **Results:** We studied 210 eyes of 70 diabetics and 35 normal subjects.In both eyes of diabetic subjects ,there was a thinning of global and quadrant wise peripapillary RNFL thickness compared to normal subjects in well controlled and superiorly in uncontrolled DM. However,in patients with uncontrolled DM ,the global peripapillary RNFL thickness was higher than patients with well controlled DM . The peripapillary RNFL thickness progressively increased with the increasing severity of DR and was found to be higher than in patients without DR. **Conclusions:** Thinning of peripapillary RNFL occurs in patients with type 2 DM due to retinal neurodegeneration. Peripapillary RNFL changes is seen with increasing DM duration and severity of DR.

**KEYWORDS :** Peripapillary retinal nerve fibre layer thickness, retinal neurodegeneration

## INTRODUCTION

DR which is a microvascular complication of DM, is one of the leading causes of visual impairment and preventable blindness in the world.[1] In 2019,the prevalence of DR worldwide was 27%,in India it was 16.9%.[2,3] The prevalence of DR leading to blindness globally was 0.05%(above the age of 50 years) and in India it was 6%.[4,5]

DR is a growing health problem that affects the young working age population,eventually leading to blindness especially in developing countries.[6]

Over the past decade, a new pathological model has been accepted which has emphasized neurodegeneration as an early component of DR, even before the clinically detectable retinal changes.These changes may be picked up on Optical Coherence Tomography(OCT) and thus may pave way for early detection of DR prior to appearance of ophthalmoscopic signs.

Retinal neurodegenerative changes in DR have been shown to precede microvascular changes in previous studies and hence measurement of peripapillary retinal nerve fibre layer (RNFL) thickness may help us in early detection prior to occurrence of clinically detectable signs and prevention of vision loss by initiating appropriate therapeutic approach.

Some of the previous studies have observed increased peripapillary RNFL thickness in DM with any stage of DR,[7]and some have observed reduced peripapillary RNFL thickness in DM with/without DR compared to normal subjects.[8]Few other studies even reported no significant difference in peripapillary RNFL thickness in patients with DM compared to normal subjects.[9,10]

In a study by Hyung Bin Lim et al,[11]there was a progressive thinning of peripapillary RNFL in the NPDR group in comparison to non-DR group in the longitudinal follow up study ,where as in a study by Sindi Dwijayanthi et al there was increase in the peripapillary RNFL thickness in the advanced DR stages in comparison with normal subjects.Hence this study was planned to address the descripencies in the existing literature about the association of peripapillary RNFL thickness in patients with type 2 DM and its association with severity of DR.

### Subjects and Methods

This cross-sectional study was carried out between February 2021 and august 2022,after approval from institutional ethical committee and taking written informed consent from patients.Patients of either gender aged 40-60 years,either normal individuals or with the diagnosis of type2 DM were included.

Patients with glaucoma,proliferative DR(PDR), congenital optic disc anomalies,optic neuropathies, oculr trauma,previous retinal laser photocoagulation, media opacities, high refractive errors >±6D, and poor OCT strength <6 were excluded.Demographic data of study population was acquired.Patients fulfilling the above criteria were categorized into the following groups.

**Group A:** 35 Normal subjects (without DM)
**Group B:** 35 Type 2 diabetics with HbA1c levels <7 g/dl (well-controlled diabetics)
**Group C:** 35 Type 2 diabetics with HbA1c levels >7 g/dl (impaired glycaemic control)

All patients underwent a comprehensive ophthal examination with measurement of best corrected visual acuity (BCVA), anterior and posterior segment examination with staging of DR(according to ETDRS classification).[12]Peripapillary RNFL thickness measuements were taken using Cirrhus HD OCT (Carl Zeiss Meditec) after pupillary dilatation with 0.8%Tropicamide + 5%phenylephrine eye drops .Global as well as mean peripapillary RNFL thickness of all four quadrants was taken.

SPSS (version 17,IBM) was used for statistical analysis.Descriptive statistics (mean±SD) for quantitative values (age,RNFL) and frequencies with % for qualitative variables were used to describe the data.Quantitative variables were compared between the groups using one way ANOVA test.A p value of ≤0.05 was considered statistical significant.

## RESULTS

### Patient Characteristics

Two hundred and ten eyes of 105 patients fulfilling the inclusion criteria were analysed. Mean age of the study population was 54.38±6.12 years (range 41-60 years). 46 ( 43.8 %) subjects were males, while 59( 56.2%) were females.

There was no statistically significant difference in both groups in terms of age and gender(p 0.1,0.15) respectively(table 1).

Best corrected visual acuity (BCVA) of normal subjects and diabetics were recorded.There was a statistical significant($p<0.001$) reduction in BCVA in uncontrolled DM in comparison to controlled DM and normal subjects.

Mean of the global peripapillary RNFL thickness along with peripapillary RNFL thickness of superior,inferior,nasal and temporal quadrants of normal subjects was compared with both the diabetic subgroups (tables2,3).

**1) Peripapillary RNFL Thickness Among the 3 Groups:** In the right eye of patients, there was a reduction in the global and quadrant-wise peripapillary RNFL thickness in Group B.However,in Group C we found the peripapillary RNFL thickness was higher in global and all quadrants except the superior,nasal quadrants.This was not statistically significant(table 2).

As depicted in table 3,in the left eye of the patients,the global,inferior and temporal quadrant peripapillary RNFL thickness was significantly reduced compared to normal subjects in Group B ( p 0.045,0.011 and 0.019 respectively). In Group C, the global and quadrant-wise peripapillary RNFL thickness was higher in all quadrants except superior compared to other 2 groups,but was statistically significant only in global (p 0.04) and inferior, temporal quadrants (p 0.011,0.019).

**2) Peripapillary RNFL Thickness and Severity of DR :** As depicted in table 4, in the right eyes of diabetics, we found increase in the peripapillary RNFL thickness in patients with clinically detectable DR (greater in severe NPDR group) compared to no DR , in the global(p 0.001) and all quadrants except superior,nasal quadrants in mild –moderate NPDR and it reached statistical significance.

As depicted in table 5, in left eye there was increase in the peripapillary RNFL globally and all quadrants with increasing DR severity compared to no DR, where it reached statistical significance only in nasal quadrant (p 0.04).Except in the nasal quadrant where there was significant(p 0.04) thinning in mild –moderate NPDR group.

**3) Peripapillary RNFL Thickness and Duration of DM:** In Group B (well controlled diabetics),the global peripapillary RNFl thickness in both eyes was lesser in patients with duration of DM >10 years.In Group C (impaired glycaemic control),the global peripapillary RNFL thickness was higher in patients with >10 years duration of DM .However,this difference did not reach statistical significance.

**4) Association of Peripapillary RNFL Thickness with DM Treatment:** In Group B ,none of the patients were on Insulin.

In Group C,24 patients were on OHA and 11 on Insulin.We found the global peripapillary RNFL thickness to be higher in the both eye of patients on Insulin and this was statistically significant only in right eyes(p 0.014).

## DISCUSSION

Loss of peripapillary RNFL and its association with metabolic control and severity of DR has been studied with varying results in diabetic patients.In our study,we found that periapapillary RNFL thickness was thinner in diabetics as compared to healthy normal subjects,but was thicker in patients with poor metabolic control of DM when compared with well controlled type 2 diabetics.

Our study population age group ranged from 41 to 60 years . The study included 46 males and 59 females. There were 10 patients in the age group 41-50 years ,5 patients each in 46-50 years,8 patients in 51-55 years and 12 patients in 56-60 years in Group A,B and C respectively.

As per the Barbados Eye Study[13]most of the diabetic patients were in the age group of 50-64 years,which is similar to our study.Similarly, in the previous study by Rania et al[14] majority of the DM patients were in the age group of 40-59 years.The prevalence of vision threatening DR were most among the age group of 50-64 years as well.

Among the 70 diabetic patients ,35 were females and 35 were males.

As per the previous studies such as Barbados Eye Study,Barbados [13] and in the study by Irini Chatzivalli et al, [8]a female preponderence for diabetes was found. Where as in the study conducted by Rania et al [14] males were more in number. However, in our study we had equal number of males and females in the DM group.

We compared the BCVA in log MAR among the DM with the normal subjects and found a significant reduction of BCVA in Group C compared to the Group A in both the eyes.Our study results were similar to the study by Jin li et al.[15]Reduction of BCVA is correlated to the microvascular ischaemia and retinal neurodegeneration in DR, greater levels of DR severity corresponded to worse vision .

We evaluated the global and quadrant –wise (superior,inferior,nasal and temporal quadrants) peripapillary RNFL thickness in both the eyes among the 3 study groups.

In both the eyes of the diabetic subjects, there was thinning of the global and quadrant-wise peripapillary RNFL in all the quadrants in comparison with normal subjects.In exception in group C there was increase in the peripapillary RNFL in the global and quadrant-wise except superior and nasal quadrants in both eyes and in superior quadrant in left eyes.It reached statistical significance only in left eyes.

Our results are similar to the studies by Irini Chatzivalli et al,[8] Hyung Bin Lim et al,[11] where thinning of peripapillary RNFL was detected in DM subjects with or without DR in comparison to normal subjects. Early DRN can be attributed to various factors resulting in neuronal degeneration from metabolic derangements , reactive gliosis , glutamate excitotoxicity and nerve fibre layer and ganglion cell apoptosis , which results in thinning of peripapillary RNFL thickness.

In the study by Rania et al [14] and Irini Chatzivalli et al [8] they found significant thinning of superior and inferior quadrant peripapillary RNFL in uncontrolled DM (HbA1c >/=7%),in contradiction to our study ,suggesting progressive retinal neurodegenerative changes as DR severity increases.

However,in a study by Sindi Dwijayanti et al [16] there was no significant difference of the global peripapillary RNFL thickness in DR compared to healthy subjects.But,there was a significant increase in peripapillary RNFL thickness at the nasal quadrant in advanced DR compared to normal subjects similar to our study results.They suggested intra-retinal edema caused due to neuronal inflammation and exudates and damage to BRB as the possible mechanism.

Previous studies by Jay Chhablani et al [17]Mohammad AM et al[9] found no statistically significant difference in the peripapillary RNFL thickness in DM with or without DR in comparison to normal subjects in contradiction to our study.

In our study,in Group B (HbA1c<7%) ,thinning of peripapillary RNFL in both the eyes was found in patients with DM duration of >10 years and also in left eyes of SG2.However in right eyes in Group C (HbA1c>/=7%) we found thickening in global peripapillary RNFL in both eyes in patients with DM of duration >10 years but was not significant.Increased thickness may be associated with damage to BRB as a result of chronic low-grade inflammation of longer duration >10 years ,causing intraretinal edema.[16]

In the study by Rania et al [14] and Irini Chatzivalli et al [8] there was an inverse relation between longer DM duration and thinning of peripapillary RNFL in contradiction to our study results .They suggested that the DM duration had an inverse relation with peripapillary RNFL thickness, where in although longer DM duration leads to increase in DR severity, the peripapillary RNFL got characteristically thinner.

In both the eyes of diabetics, we found increase in the peripapillary RNFL thickness in clinically detectable DR (greater in severe NPDR group) compared to no DR,in the global and all quadrants in right eyes which was statistically significant and global and all quadrants of left eye , however it did not reach statistical significance.Except we found significant thinning nasally in both eyes and superiorly in right eyes of mild-moderate NPDR.

Our results are similar to the results of the study by Sindi Dwijayanthi et al, where they found increase in thickness in the nasal quadrant when compared to normal subjects in advanced DR. Increase in peripapillary RNFL thickness is due to low –grade chronic inflammation,hyperglycaemia causing damage to the inner BRB resulting in edema in the extracellular spaces in early stages of DR and damage to outer blood-retinal barrier (BRB) at the level of retinal pigment epithelium (RPE),thus resulting in the diffuse edema in advanced DR.

Rania et al [16] and Irini Chatzivalli et al, [12] where they found thinning in the peripapillary RNFL thickness in the clinically detectable DR compared to no DR patients,explained by the neurodegenerative changes in DR. Neuronal degeneration from metabolic derangements , reactive gliosis, glutamate excitotoxicity and nerve fibre layer and ganglion cell apoptosis, which results in thinning of peripapillary RNFL thickness, which is in contradiction to our study.

We looked into the association between peripapillary RNFL thickness and treatment of DM by comparing the peripapillary RNFL values of patients on oral hypoglycaemic agents(OHA) and those on Insulin. There was an increase in the global peripapillary RNFL in both eyes of patients on Insulin.Increase in the peripapillary RNFL thickness in patients on Insulin is due to its association with advanced DR in our study.

In a study by Rania et al , [14] thinning of the peripapillary RNFL thickness in patients who are on insulin was detected which is in contradiction to our study results,which is explained by the good glycaemic control from the insulin usage.

**Table 1 – Age and Gender Distribution of Patients**

| Parameters | Study population(105) | Group A(35) | Group B(35) | Group C(35) |
|---|---|---|---|---|
| 1.Age (years)<br>Mean ±SD | 54.38±6.12 | 57±6.42 | 51.65±6.35 | 51.88±5.97 |
| 2.Gender<br>Male | 46 (43%) | 11 (31%) | 16 (45%) | 19 (54%) |
| Female | 59 (56%) | 24 (68%) | 19 (54%) | 16 (45%) |
| 3.DM duration<br><10 years<br>>10 years | - | - | <br>28<br>7 | <br>15<br>20 |

**Table 2: Comparison of Peripapillary RNFL Thickness Among Groups in Right Eye**

| Parameters | Group A | | Group B (HbA1c< 7%) | | Group C (HbA1c≥7%) | | Significance | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | F | P |
| Global RNFL | 93.06 | 5.60 | 88.60 | 7.11 | 94.46 | 18.10 | 0.85 | 0.43 |
| SUPERIOR | 116.69 | 10.63 | 114.97 | 12.93 | 110.46 | 29.37 | 0.38 | 0.69 |
| NASAL | 74.34 | 15.02 | 73.34 | 9.08 | 72.0 | 21.23 | 0.06 | 0.94 |
| INFERIOR | 115.74 | 9.21 | 107.57 | 15.83 | 119.03 | 21.25 | 2.10 | 0.13 |
| TEMPORAL | 64.06 | 11.35 | 58.11 | 10.62 | 74.31 | 26.64 | 4.78 | 0.120 |

**Table 3: Comparison of Peripapillary RNFL Thickness Among Groups in Left Eye**

| Parameters | Group A | | Group B (HbA1c< 7%) | | Group C (HbA1c≥7%) | | Significance | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | F | P |
| Global RNFL | 94.31 | 6.49 | 86.80 | 4.89 | 95.09 | 24.92 | 3.20 | 0.045* |
| SUPERIOR | 120.17 | 11.86 | 115.34 | 14.54 | 114.46 | 36.12 | 0.60 | 0.55 |
| NASAL | 67.20 | 12.73 | 67.03 | 14.84 | 68.14 | 19.90 | 0.98 | 0.38 |
| INFERIOR | 113.83 | 14.68 | 104.00 | 15.99 | 116.29 | 21.86 | 4.68 | 0.011* |
| TEMPORAL | 67.00 | 12.51 | 60.34 | 9.47 | 68.71 | 15.97 | 4.10 | 0.019* |

**Table 4 : Comparison of Peripapillary RNFL Thickness Among Groups in Right Eye With Dr Staging**

| Parameters | No DR(37) | | Mild to Moderate NPDR(24) | | Severe NPDR(9) | | Significance | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | F | P |
| Global RNFL | 87.73 | 10.54 | 91.13 | 12.45 | 108.22 | 18.85 | 9.81 | < 0.001*S |
| SUPERIOR | 113.54 | 20.40 | 108.33 | 24.71 | 121.00 | 25.58 | 1.08 | 0.35 |
| NASAL | 72.59 | 11.86 | 67.88 | 14.18 | 85.78 | 28.23 | 4.38 | 0.02*, S |
| INFERIOR | 106.76 | 18.60 | 117.92 | 17.82 | 127.89 | 17.28 | 6.07 | 0.004*, S |
| TEMPORAL | 58.19 | 10.30 | 67.42 | 19.20 | 96.00 | 35.11 | 15.72 | < 0.001 *S |

**Table 5 : Comparison of Peripapillary RNFL Thickness Among Groups in Left Eye With Dr Staging**

| Parameters | No DR(37) | | Mild to Moderate NPDR (24) | | Severe NPDR(9) | | Significance | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | F | P |
| Global RNFL | 87.49 | 7.67 | 93.88 | 23.64 | 97.33 | 29.87 | 1.54 | 0.22 |
| SUPERIOR | 113.03 | 18.10 | 118.21 | 30.74 | 113.78 | 46.93 | 0.26 | 0.77 |
| NASAL | 71.03 | 14.50 | 62.58 | 11.70 | 78.44 | 32.32 | 3.41 | 0.04*, S |
| INFERIOR | 106.24 | 17.45 | 112.58 | 22.26 | 119.67 | 21.49 | 1.96 | 0.15 |
| TEMPORAL | 61.00 | 10.18 | 69.00 | 17.97 | 67.11 | 9.93 | 2.81 | 0.07 |

## CONCLUSION

- Thinning of peripapillary RNFL occurs in patients with type 2 DM, possibly due to retinal neurodegeneration.The peripapillary RNFL thickness progressively increased with the increasing severity of DR and was found to be higher than in patients without DR.
- Peripapillary RNFL thickness was higher in patients with uncontrolled DM compared to patients with well controlled DM.Thinning of peripapillary RNFL occurs with increasing duration of DM.OCT can thus be used to detect retinal neurodegeneration in patients with DM.

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18) RE Right eye, LE Left eye, DR Diabetic retinopathy, NPDR Non proliferative diabetic retinopathy, RNFL Retinal nerve fibre layer, HbA1c Glycosylated haemoglobin, SD Standard deviation, $p<0.05$ significant