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PERIPAPILLARY RETINAL NERVE FIBRE LAYER THICKNESS IN DIABETICS AND IT'S CORRELATION WITH GLYCOSYLATED HAEMOGLOBIN.

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ABSTRACT **Context:** To correlate the peripapillary retinal nerve fibre layer thickness in patients with type2 diabetes mellitus with glycaemic control. **Aims:** To compare the peripapillary retinal nerve fibre layer thickness in type 2 diabetics with healthy subjects and correlate with glycaemic index. **Settings and Design:** Cross-sectional analytical study **Methods and Material:** Type2 diabetes mellitus patients above 40 years of age were categorised into 2 groups subgroup1 with glycosylated haemoglobin <7% and subgroup2 with >7% .The peripapillary retinal nerve fibre layer thickness of both these groups of patients were compared with non-diabetic normal subjects.The peripapillary retinal nerve fibre layer thickness was correlated with glycosylated haemoglobin. **Results:** We studied 150 eyes of 50 diabetics and 25 normal subjects.In both eyes of diabetic subjects ,there was a thinning of global and quadrant wise peripapillary retinal nerve fibre layer thickness compared to normal subjects. However,in patients with uncontrolled diabetes ,the global peripapillary retinal nerve fibre layer thickness was higher than patients with well controlled diabetics.The peripapillary retinal nerve fibre layer thickness progressively increased with impaired glycaemic control. **Conclusions:** Thinning of peripapillary retinal nerve fibre layer occurs in patients with type 2 diabetes mellitus due to retinal neurodegeneration. Peripapillary retinal nerve fibre layer changes is seen with increasing diabetes duration,glycaemic control,severity of diabetic retinopathy.

KEYWORDS : glycosylated haemoglobin,peripapillary retinal nerve fibre layer thickness,retinal neurodegeneration

INTRODUCTION:

Diabetic retinopathy (DR) which is a microvascular complication of Diabetes mellitus (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] Delayed detection of DR may be attributed to the lack of awareness in people about DR,inadequate screening for the disease and the fact that it remains largely asymptomatic in its early stages.

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 thickness (peripapillary 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.

Previous literature states that HbA1c levels can be used as an indirect marker of the retinal endothelial dysfunction, where poor glycaemic control indicated by raised HbA1c is associated with severe retinal vascular endothelial dysfunction which results in reduced peripapillary RNFL thickness.[15]Many studies have detected an inverse association of HbA1c levels to the reduced peripapillary RNFL thickness ,[16] and some studies have observed no association between peripapillary RNFL thickness to HbA1c levels.[17]

Hence this study was planned to address the descripancies in the existing literature about the association of peripapillary RNFL thickness in patients with DM and glycaemic control.

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. 25 Normal subjects (without DM)

Sub group SG1: 25 Type 2 diabetics with HbA1c levels <7 g/dl (well-controlled diabetics)
SG2: 25 Type 2 diabetics with HbA1c levels >7 g/dl (impaired glycaemic control)

All patients underwent a comprehensive ophthalmic 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 measurements 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.

One hundred and fifty eyes of 75 patients fulfilling the inclusion criteria were analysed.Mean age of the study population was 54.38±6.12 years(range 41-60 years).40 (46.6 %) subjects were males ,while 35(53.3%) were females.

There was no statistically significant difference in both groups in terms

of age and gender(p 0.1,0.15)respectively(graphs 1,2).

Best corrected visual acuity (BCVA) of normal subjects and diabetics were recorded.There was a statistical significant($p<0.001$) reduction in DM groups compared to normal subjects,worse in SG2.

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(graphs 5,6).

Peripapillary RNFL thickness among the 3 groups:
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.

As depicted in graph 5,in the right eye of the subjects,the global and quadrant-wise peripapillary RNFL thickness in all the 4 quadrants was lesser in both the diabetic sub-groups in comparison with normal subjects,but this thinning of peripapillary RNFL in the diabetic groups was non significant.

In the left eye of the study subjects,we found a reduction in the global and quadrant-wise peripapillary RNFL thickness in both the diabetic sub-groups in comparison with the normal subjects.The reduction in the global (0.03),superior(0.05) and inferior quadrant(0.056) peripapillary RNFL thickness was statistically significant compared to normal subjects as shown in graph 6.

In the SG2, the peripapillary RNFL in the inferior and temporal quadrant was thicker than that in the SG1 group,but this difference did not reach statistical significance.

Correlation of HbA1c levels with peripapillary RNFL thickness
As depicted in table 1,in SG1, we found a negative correlation between the HbA1c levels and peripapillary RNFL thickness in both the eyes.However,this correlation did not reach statistical significance.

In SG2 (HbA1c >/=7%) we found a positive correlation between HbA1c levels and peripapillary RNFL thickness(global as well as quadrant-wise values) in both the eyes.This correlation reached statistical significance in all except superior and inferior quadrants in right eye and only in the temporal quadrant (0.033)of left eyes,in table 2.

Peripapillary RNFL thickness and duration of DM:
In SG1(well controlled diabetics),the global peripapillary RNFL thickness in both eyes was lesser in patients with duration of DM >10 years.In SG2 (impaired glycaemic control),the global peripapillary RNFL thickness was higher in patients with >10 years duration of DM ,as depicted in graphs 3,4.However,this difference did not reach statistical significance.

Association of peripapillary RNFL thickness with DM treatment:
In SG1 ,none of the patients were on Insulin. In SG2,24 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 0.015) as depicted in table 3.

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 35 males and 40 females. There were 10 patients in the age group 46-50 years ,51-55 and 56-60 subjects each in normal, SG1 and SG2 respectively.

As per the Barbados Eye Study most of the diabetic patients were in the age group of 50-60 years,which is similar to our study.Similarly, in the previous study by Rania et al 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 50-60 years as well.

Among the 50 diabetic patients ,31 were females and 19 were males.

As per the previous studies such as Barbados Eye Study,Barbados a female preponderence for diabetes was found ,similar to our study. Similarly, in the previous study by Irini Chatzivalli et al females were more , but in contradiction male preponderence in the study conducted by Rania et al.

We compared the BCVA in log MAR among the DM with the normal subjects and found a significant reduction of BCVA in both DM groups(SG2>SG1).Our study results were similar to the study by Jin li et al.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,significant in superior and inferior quadrants in the left eye. In the SG2, the peripapillary RNFL in the inferior and temporal quadrant was thicker than that in the SG1 group,which is similar to the results of the study by Sindi Dwijayanthi et al where they also found significant thickening in the nasal quadrant in advanced DR corresponding to uncontrolled DM. Our results are similar to the studies by Irini Chatzivalli et al,Hyung Bin Lim et al, 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 and Irini Chatzivalli et al 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 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 andMohammad AM et al 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 SG1 (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 SG2 (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.

In the study by Rania et al and Irini Chatzivalli et al 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.

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,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.

In SG1, there was thinning of peripapillary RNFL with increasing HbA1C levels (global as well as quadrant-wise values) in both the eyes.However,this correlation did not reach statistical significance.

In SG2 (HbA1c >/=7%) we found increased thickness of peripapillary RNFL with increasing HbA1C levels (global as well as quadrant-wise values) in both the eyes.This correlation reached statistical significance in all except superior and inferior quadrants in right eye and only in the temporal quadrant of left eye.

In the study by Rania et al, there was a significant thinning in the peripapillary RNFL in patients with HbA1c <7% (controlled DM) as a result of retinal neurodegeneration and this reduction was increased in patients with HbA1c >/=7%(uncontrolled DM).They found a negative correlation of peripapillary RNFL thickness with HbA1c in all the quadrants except in the temporal quadrant where it was positively correlated which is consistent with the findings of our study. Increase in the peripapillary RNFL thickness in SG 2 (uncontrolled DM) may be due to the increased cell damage caused by hyperglycaemia and low –grade inflammation,resulting in the damage of the BRB causing intraretinal edema.

In a study by Irini Chatzivalli et al,there was a significant decrease in the global peripapillary RNFL thickness with increment of HbA1c (</>7%) , a negative correlation which is in contradiction to our study results.

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 right 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 ,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.

CONCLUSION

- Thinning of peripapillary RNFL occurs in patients with type 2 DM, possibly due to retinal neurodegeneration.
- Peripapillary RNFL thickness as higher in patients with uncontrolled DM compared to patients with well controlled DM.
- Thinning of peripapillary RNFL occurs with increasing duration of DM in well-controlled DM.
- OCT can thus be used to detect retinal neurodegeneration in patients with DM.

Table 1: Correlation of peripapillary RNFL thickness to HbA1c levels in SG1

Sg1	RE		LE	
Parameters	r (Pearson's corr. coefficient)	P value	r (Pearson's corr. coefficient)	P value
Global. RE RNFL	-0.07	0.76	-0.049	0.35
SUP	-0.058	0.8	-0.0002	0.203
NAS	-0.033	0.89	-0.033	0.218
INF	-0.049	0.83	-0.105	0.747
TEMP	-0.15	0.52	0.061	0.270

p<0.05 significant

Table 2: Correlation of peripapillary RNFL thickness to HbA1c levels in SG2

Sg2	RE		LE	
Parameters	r (Pearson's corr. coefficient)	P value	r (Pearson's corr. coefficient)	P value
Global LE RNFL	0.46	0.005*, S	0.355	0.15
SUP	0.41	0.06	0.42	0.06
NAS	0.48	0.032*	0.18	0.42
INF	0.34	0.14	-0.35	0.12
TEMP	0.62	0.003*	0.47	0.033

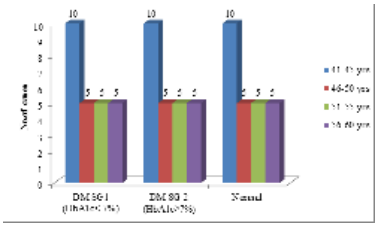
p <0.05

Table 3: Association of peripapillary RNFL thickness with DM treatment

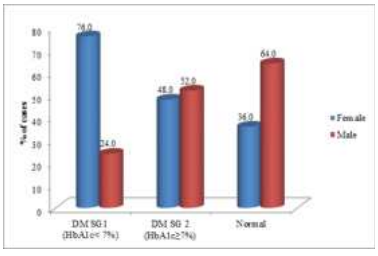
MEDS	Sg1 (HbA1c< 7%)					SG 2(HbA1c≥7%)				
	No.	RE Global RNFL		LE Global RNFL		No.	RE Global RNFL		LE Global RNFL	
		Mean	SD	Mean	SD		Mean	SD	Mean	SD
Oral	25	90.08	7.31	87.64	4.60	17	86.76	15.19	90.00	16.34
Insulin	0	-	-	-	-	8	112.00	21.99	83.25	13.02
Oral v/s Insulin	-	-					t = 2.93, P = 0.015*, S		t = 1.11, P=0.28, NS	

t test

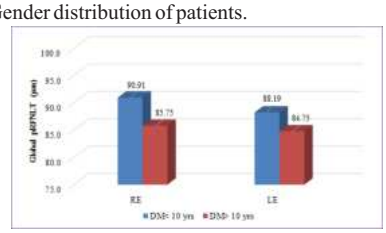
p <0.05 significant



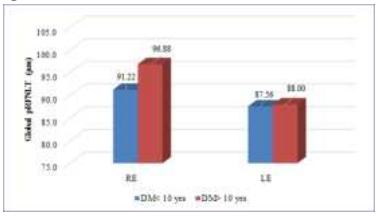
Graph 1: Age-wise distribution of patients.



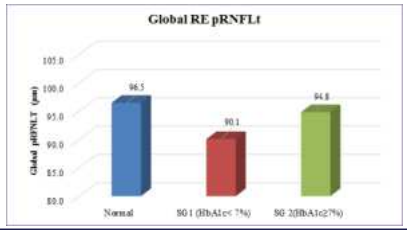
Graph 2: Gender distribution of patients.



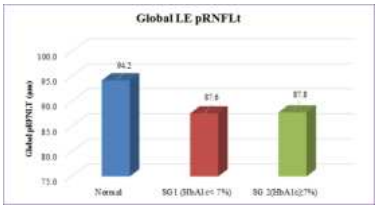
Graph 3: Association of DM duration to global peripapillary RNFL thickness in Sg1



Graph 4: Association of DM duration to global peripapillary RNFL thickness in SG2



Graph 5: Correlation of quadrant wise peripapillary RNFL thickness in SG1,2 and normal subjects in RE



Graph 6: Correlation of quadrant wise peripapillary RNFL thickness in SG1,2 and normal subjects in LE

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