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PARADIGM SHIFT IN SCREENING TECHNIQUES FOR EARLY DIAGNOSIS OF PRE-RETINOPATHY CHANGES IN DIABETIC POPULATION

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ABSTRACT **Aims and Objective:** To evaluate role of OCT based Retinal nerve fibre layer (RNFL) thickness and GCC (Ganglion cell complex) thickness measurement for detection of pre retinopathy changes in diabetic patients. **Methods** : This a comparative cross-sectional study of two groups of 110 eyes were examined by SD-OCT with peripapillary RNFL, and macular GCC assessment. The study group includes 55 eyes of diabetic patients with no diabetic retinopathy changes with their age matched controls (55 eyes). Their RNFL thickness in superior, temporal, inferior and nasal quadrants and GCC thickness in supero-nasal, superior, supero-temporal, infero-temporal, inferior and infero-nasal were compared in both groups. **Results:** The two groups were matched concerning the age, gender and the intra-ocular pressure (IOP) level. A significant difference between the two groups was found for the average, as well as the 4 sectors thickness (p<0.001). The GCC thickness, was significantly less in the diabetic eyes in all 6 sectors and average (p<0.001). **Conclusion:** RNFL and GCC loss seems to be the earliest retinal changes in diabetic patients. These results can explain the neurodegeneration theory for diabetic retinopathy. OCT based screening of RNFL and GCC thickness can serve as an early biomarker of diabetic retinopathy.

KEYWORDS : Diabetic retinopathy, GCC RNFL thickness, ganglion cell, SD-OCT

INTRODUCTION:

Diabetes retinopathy (DR) is a microangiopathy commonly seen in cases of diabetes mellitus (DM) patients. It is estimated that approximately 191 million people may be suffering from diabetes by year 2030[1]. DR is one of the leading causes of blindness in developed countries. Several studies have shown neural apoptosis, loss of ganglion cell bodies in the earlier stages of Dr[2]

Retinal Nerve Fibre Layer (RNFL) and ganglion cell complex (GCC) are affected in several diseases like glaucoma, optic neuritis. In our study, GCC and RNFL thickness of diabetic patients with no clinical DR was compared with non-diabetic group. We wanted to evaluate the role of OCT as a diagnostic test which can serve as a biomarker to identify patients at risk of developing DR.

MATERIALS AND METHODS

A comparative, cross sectional, observational study was conducted at a major tertiary care hospital in the department of Ophthalmology from July 2021 to January 2022. Patients were recruited as per the inclusion and exclusion criteria. Peripapillary RNFL and macular cube thickness was measured with Zeiss Cirrus HD 500 OCT model with software version 10.0.0.14618 of both eyes of patients of two groups that is diabetic patients without DR changes and their age matched normal patients. The GCC thickness and RNFL thickness was compared between the two groups. The study was compliant with the declaration of Helsinki statement and informed written consent was obtained from all patients to participate in the study. Patients with moderate and severe NPDR, other macular pathology, other causes of retinopathy, high myopia, and those with suspected glaucoma were excluded from the study.

After detailed systemic and ocular history detailed ophthalmic evaluation including best corrected visual acuity (BCVA), Intra ocular pressure (IOP), slit lamp examination, dilated fundus evaluation and OCT was done. RNFL is measured in four quadrants and GCC is measured in 6 sectors. All automated readings were also checked by manual segmentation of RNFL & GCC and corrections applied.

Statistical Analysis:

All data were analysed using the IBM SPSS Statistical program version 20, taking into consideration mean, median, standard deviation, range, coefficient of variation, independent t-test, bivariate analysis, and multivariate analysis. "P" values <.05 were accepted as statistically significant, and all data is expressed as "mean ± standard deviation". An independent samples t test was used to compare the studied ocular measurements between the study and control groups. When the Levene test P values were >.05 for the studied variables, the independent samples t test was used. In cases in which assumptions for parametric t tests were violated, Mann-Whitney U test was used instead.

RESULTS:

RNFL thickness in superior, temporal, inferior and nasal quadrants as shown in figure 1 and GCC thickness in supero-

nasal, superior, supero-temporal, infero-temporal, inferior and infero-nasal as shown in figure 2 were measured.

The table 1 shows that our two groups were well age and gender matched population. They were divided into two groups based on their 2 hour post prandial blood sugar. The parapapillary RNFL and macular GCC was significantly reduced in diabetic patients when compared to non-diabetic population also the independent t test among two group showed a p value of <0.001 as shown in table 2.

Table 1: Mean and standard deviation with p value by independent t test analysis matching the biological parameters of diabetic patients and the control group.

Table 1: Biological parameters matching		
Parameter	Group	Mean +/- Std. Deviation
Age	Diabetics	51.92 +/- 11.712 μm
	Non-Diabetics	54.27 +/- 9.405 μm
Gender	Diabetics	1.47 +/- 0.502 μm
	Non-Diabetics	1.53 +/- 0.502 μm
PPBS	Diabetics	214.2364 +/- 91.39881 μm
	Non-Diabetics	111.9153 +/- 23.98502 μm

Table 2: Mean and standard deviation with p value by independent t test analysis matching the OCT parameters of diabetic patients and the control group.

Table 2: Cumulative Data			
RNFL Temporal	Diabetics	55.9273 +/- 11.59382 μm	<0.001
	Non-Diabetics	66.2727 +/- 12.32876 μm	
RNFL Superior	Diabetics	104.8818+/- 24.87058 μm	<0.001
	Non-Diabetics	123.1727 +/- 16.64476 μm	
RNFL Nasal	Diabetics	63.7364 +/- 13.46124 μm	<0.001
	Non-Diabetics	77.4727 +/- 12.75004 μm	
RNFL Inferior	Diabetics	107.8636+/- 26.87295 μm	<0.001
	Non-Diabetics	131.9273 +/- 18.47697 μm	
Average RNFL	Diabetics	83.1023 +/- 14.38607 μm	<0.001
	Non-Diabetics	99.7114 +/- 11.53427 μm	
GCC Superotemporal	Diabetics	72.68 +/- 14.18 μm	<0.001
	Non-Diabetics	83.27 +/- 9.061 μm	
GCC Superior	Diabetics	72.11 +/- 17.661 μm	<0.001
	Non-Diabetics	87.26 +/- 9.462 μm	
GCC Superonasal	Diabetics	74.93 +/- 17.198 μm	<0.001
	Non-Diabetics	87.45 +/- 9.377 μm	
GCC Inferonasal	Diabetics	73.13 +/- 17.12 μm	<0.001
	Non-Diabetics	87.45 +/- 9.377 μm	
GCC inferior	Diabetics	69.58 +/- 17.665 μm	<0.001
	Non-Diabetics	87.03 +/- 10.08 μm	
GCC Inferotemporal	Diabetics	72.85 +/- 16.24 μm	<0.001
	Non-Diabetics	83.27 +/- 9.061 μm	
Average GCC	Diabetics	72.61 +/- 15.484 μm	<0.001
	Non-Diabetics	85.96 +/- 8.508 μm	

Mean Average GCC in diabetic patient was 72.61 +/- 15.48 μm, whereas it was 85.96 +/- 8.50 μm in non-diabetic population. This difference was statistically significant (independent t test p value of <0.001) as shown in figure 3. Average RNFL thickness among the 2 groups. Mean Average RNFL thickness was 83.10 +/- 14.38 μm and 99.74 +/- 11.53 μm in diabetic patients and control group respectively as shown in figure 4.

DISCUSSION:

The exact cause of RNFL and GCC thinning is still unknown. It may be attributed to sub optimal perfusion of the inner retinal layers. Another possible mechanism is the decreased insulin level which leads to hyper-glycemia and accumulation of advanced glycation end products[3]. These in turn, may accelerate the apoptosis of neuroglial cells in the inner retinal layers.

In our study, the difference in RNFL and GCC in all sectors in age and gender matched diabetics and non-diabetics was statistically significant. Rodrigues EB et al and van Dijk HW showed comparable results[4,2]. Afef M. et al in their study concluded that the average, superior and inferior RNFL thickness was significantly reduced in diabetics[5]. Pekel E. et al found significant difference between the RNFL between diabetics and non-diabetics, only in the supero nasal quadrant[6]. Table 3 compares the RNFL thickness in diabetics and non-diabetics of their study with ours.

Table 3: Comparison of RNFL thickness data of various studies[5,6] with our study

Study	Afef M. et al study		Pekel E et al study		Our study	
Sector RNFL	Diabetics	Non-diabetics	Diabetics	Non-diabetics	Diabetics	Non-diabetics
Average RNFL in μm	89.7 ± 10.5	99.7 ± 20.6	95.1 ± 8.0	96.5 ± 6.6	83.10 ± 14.38	99.71 ± 11.53
Temporal RNFL in μm	64.5 ± 10.3	64.8 ± 11.8	66.1 ± 8.9	64.4 ± 9.3	55.92 ± 11.59	66.27 ± 12.32
Superior RNFL in μm	112.3 ± 11.3	115.6 ± 11.7	115.8 ±13.5	119.7 ± 14.7	104.88 ± 24.87	123.17 ± 16.64
Nasal RNFLin μm	72.6 ± 10.1	72.9 ± 13.1	73.0± 10.1	73.5 ± 9.1	63.73 ± 13.46	77.47 ± 12.75
Inferior RNFL in μm	114.2 ± 10.7	119.2 ± 12.3	125.6 ±15.4	127.8 ± 11.5	107.86 ± 26.87	131.92 ± 18.47

We conclude that the GCC thickness in diabetics is significantly thinner than in age & gender matched controls. As per Afef M. et al, the sector wise as well as average GCC thickness was significantly reduced in diabetic patients[5]. As per Pekel E. et al the sectoral thickness values of GCC in the diabetic eyes were thinner than that of the controls, but this difference was statistically significant only in the superior-nasal area[6]. Table 4 compares GCC data of above studies with our study. In contrast to our findings, Pollreisz A et al. [using PlexElite system (Carl Zeiss Meditec, Jena, Germany)] showed no significant difference between the ganglion cell layer complex between diabetics and non-diabetic population[7]. This may be attributed to combined measurement of RNFL, GCL and IPL taken by them.

Table 4: Comparison of GCC thickness data of various studies[5,6] with our study

Study	Afef M. et al study		Pekel E et al study		Our study	
Sector GCC	Diabetics	Non-diabetics	Diabetics	Non-diabetics	Diabetics	Non-diabetics
Average GCC in μm	80.6 ± 10.2	86.2 ±8.5	82.2 ± 6.1	83.9 ± 4.7	72.61 ± 15.48	85.96± 8.50
Superior GCC in μm	79.5 ± 7.4	85.6 ± 8.6	82.8 ± 6.8	84.8 ± 5.2	72.11 ± 17.66	87.26± 9.46
Supero Temporal GCC in μm	Superior GCC	Superior GCC	81.0 ± 6.3	81.7 ± 4.9	72.68 ± 14.18	83.27 ± 9.06
Supero Nasal GCC in μm	79.5 ± 7.4	85.6 ± 8.6	82.7 ± 7.4	85.3 ± 5.7	74.93 ± 17.19	87.45± 9.37
Inferior GCC in μm	73.8 ± 9.6	81.4 ± 7.8	81.4 ± 6.6	83.0 ± 4.8	69.58 ± 17.66	87.03± 10.08

Infero Nasal GCC in μm	Inferior GCC	Inferior GCC	82.3 ± 7.0	84.3 ± 6.0	73.13 ± 17.12	87.45± 9.37
Infero Temporal GCC in μm	73.8 ± 9.6	81.4 ± 7.8	82.9 ± 6.4	84.1 ± 4.6	72.85 ± 16.24	83.27± 9.06

Pre retinopathy may also be evaluated by assessment of retinal function tests. Reis A, et al used psychophysical tests of ganglion cell and electro-physiological recordings (mfERG) for same. They noted reduced retinal neuronal function in type 1 diabetic patients with no clinically diagnosed Dr[8].

The limitation of our observational study could be the sample size. A prospective randomized control trial with larger sample size is required to establish the role of OCT based screening of RNFL and GCC thickness as an early risk factor for development diabetic retinopathy.

Gold standard methods for diagnosis and screening of DR have been clinical slit lamp biomicroscopy and fundus photography. However, there have been significant technological advances which can aid in diagnosis of pre-retinopathy, even before setting in of clinically apparent diabetic retinopathy. Fundus photography with incorporated Artificial Intelligence[9], OCT Angiography (OCTA)[10] and GCC and RNFL thickness analysis are capable of this and should be incorporated in DR screening protocols.

CONCLUSION:

OCT of peripapillary RNFL and macular cube for GCC thickness are quite reliable for diagnosis of pre-retinopathy in diabetic individuals. It can serve as a biomarker to identify patients at risk of developing diabetic retinopathy. However larger sample size may throw further light of above. A follow up scan of these patients after 2 years and 5 years. Is to be planned for further analysis of how these patients develop diabetic retinopathy and its effect on the GCC and RNFL needs to be done.

Data Availability: On request, data can be made available. Corresponding author has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Key Messages: Screening for diabetic retinopathy can be further enhanced by OCT analysis for RNFL and Ganglion cell layer thickness. As it seems to be the early diagnostic factor for developing diabetic retinopathy.

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