Effect of Diabetic Retinopathy on Retinal Nerve Fiber Layer Thickness

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ABSTRACT
Background: Diabetic retinopathy is one of the most common causes of vision loss in developed countries.
Objective: The objective of this study was to assess the effect of diabetic retinopathy (DR) on the retinal nerve fiber layer (RNFL) thickness. **Patients and methods:** This study was carried out on 55 eyes of 35 patients designed as a prospective, interventional case series at Sohag Hospital from January, 2016 to December, 2016. A complete ophthalmologic examination was performed including best-corrected visual acuity (BCVA) using the ETDRS charts, intraocular pressure (IOP) measurement, slit-lamp biomicroscopic examination, fundus examination and fluorescein angiography. **Results:** The RNFL (inferior and total) thickness at each follow-up was increased significantly from baseline to 1 month and 6 months post-PRP then decreased significantly from 1 month to 6 months follow up (p < 0.001). The superior RNFL was increased significantly from baseline to 1 month post-PRP and then decreased at 6 month follow up (p < 0.001). While no significant change from 1 month to 6 months follow up (p > 0.05).
Conclusion: Increase in the macular Ganglion cell (GC) thickness and RNFL at 1 month of follow-up that may be related to laser induced intraretinal inflammation which triggers increased capillary permeability and ensuing axonal edema due to the cytokine release.
Keywords: Diabetic retinopathy, Retinal nerve fiber layer thickness.

INTRODUCTION

Diabetic retinopathy (DR) is one of the most important facet of diabetes and a major cause of visual loss and blindness in individuals between 20 and 65 years of age [1].

According to Diabetic Retinopathy Study Group (DRS), severe visual loss (acuity poorer than 5/200) may occur in 37% of untreated eyes having high-risk characteristics of proliferative diabetic retinopathy (PDR) within six years [2]. Ganglion cell analysis (GCA) algorithm of Cirrus Optical coherence tomography (OCT) can successfully detect and measure the thickness of the macular ganglion cell–inner plexiform layer (GCIPL) with excellent intervisit reproducibility [3].

Diabetes can also damage nonvascular cells of the retina. In autopsy samples, retinal ganglion cells are lost, at least in part, through apoptosis [4]. Histological studies of neural components of the retina have revealed that diabetes-induced biochemical mechanisms can potentially cause neural cell degeneration [5]. In addition, numerous studies have evidenced that alteration of different metabolic pathways in diabetes induces functional deficits and loss of different types of retinal cells including ganglion cells, bipolar cells, and eventually photoreceptors [6].

OCT has been proposed as a powerful tool for retinal measurement and it provides detailed information with a high resolution [7]. It also allows direct measurement of retinal nerve fiber layer (RNFL) thickness by in-vivo visualization of the retina and RNFL [8].

AIM OF THE WORK

The objective of this study was to assess the effect of diabetic retinopathy (DR) on the retinal nerve fiber layer (RNFL) thickness.

PATIENTS AND METHODS

This study was carried out on 55 eyes of 35 patients designed as a prospective, interventional case series at Sohag Hospital in the period from January, 2016 to December, 2016. A complete ophthalmologic examination was performed, including best-corrected visual acuity (BCVA) using the ETDRS charts, intraocular pressure (IOP) measurement, slit-lamp biomicroscopic examination, fundus examination, fluorescein angiography.

Ethical approval and written informed consent :
An approval of the study was obtained from Aswan **University academic and ethical committee. Every patient signed an informed written consent for acceptance of the study.**

Inclusion criteria:
Patients with severe non-PDR and PDR were defined by early treatment diabetic retinopathy study (ETDRS) by the presence of one of the following criteria between 40 and 60 years of age:
(1) Severe intra-retinal hemorrhages in four quadrants.
(2) Venous beading in at least two quadrants.
(3) Moderate to severe intra-retinal microangiopathy in at least one quadrant.
(4) Capillary dropouts in more than one quadrant.

Exclusion criteria:
The following patients were excluded from the study:
(1) Advanced and high-risk PDR.
(2) Patients with densely opaque media (as cataract or vitreous hemorrhage).
(3) Glaucomatous patients.
(4) Hypertensive patients.
(5) Patients with any other associated retinopathies.

GCC and RNFL Scanning Procedures:

All OCT examinations were performed by a single, well-trained technician (under my observations). Optical coherence tomography macular scan and optic nerve head (ONH) scan were performed using the Topcon SD-OCT model 2000 version 7.11 in fine analysis mode (Figure 1). The Topcon 3D OCT 2000 measures the RNFL thickness, the RGC with the IPL (GCIP) and the GCC. It uses raster scanning of a 7 mm² area that is centered on the fovea with a scan density of 128 (horizontal) × 512 (vertical) scans. The boundaries of the anatomical layers are determined by the program software using a validated automated segmentation algorithm. The macular inner retinal layers (MIRL) analysis software detects the center of the fovea at the macular cube automatically and selects a 6 mm × 6 mm region centered at the foveal center. The software divides the macular square into a 6 × 6 grid containing 100 cells of 0.6 mm × 0.6 mm to assess regional abnormalities in MIRL thickness. Average regional thickness of GCC, GCIP and RNFL in each cell is calculated and compared to the normative database of the device.

Fig. (1): Topcon model 2000 version 7.1 (actual model installed)

Follow-up protocol:

Follow-up examinations were scheduled at 1 and 6 months after PRP. A complete ophthalmologic examination was performed at each follow-up.

Statistical analysis

- The results are expressed as mean and standard deviation for numerical values. The normality of the distribution of the study sample was assessed by means of the Shapiro-Wilk (SW) test.
- P values were calculated using the following tests: -
- T test for paired comparison was used for the comparison between the numerical and normally distributed data of the two paired groups. Wilcoxon Signed-Rank test was used for the comparison between the numerical and not normally distributed data of the two paired groups. T test for unpaired comparison test was used for the comparison between the numerical, and not normally distributed data of the two non- paired groups.
- Rank sum (mann whitny) u test was used for the comparison between the numerical and not normally distributed data of the two non-paired groups. Significance difference was set at $P \leq 0.05$.

RESULTS

Fifty-five eyes of 35 patients were enrolled in this study but because of occurrence of uncorrectable error in OCT machine we completed follow up only of 29 eyes of 18 patients. Table 1 showed the demographic and clinical characteristics of the patients.

Table (1): Patient demographic and clinical characteristics

Characteristics	Value
No. of patients	18
No. of eyes	29
Age (yrs.)	52.17 ± 14.15*
Male / female	8 / 10
D M type 1 / D M type 2	5 / 13

* Values are presented as the mean ± standard deviation.

Changes in macular GCL thickness:

Macular GCL (superior and total) thickness at each follow-up increased significantly from the baseline to 1 month then decreased significantly at 6 months post PRP (P<0.05). The inferior ganglion cell layer decreased significantly from 1 month to 6 months follow up (P<0.05) while no significant changes from baseline were recorded at 1 and 6 months (p>0.05) (table 2)

Table (2): Changes in GCL scores within the follow-up period

GCL	Baseline	1 month	6 months	P value	Significance
Superior	72.82 ± 18.68	77.65 ± 19.52	75.34 ± 19.21	0.001#	Significant
				0.01*	Significant
				0.001 ‡	Significant
Inferior	68.34 ± 11.59	71.65 ± 15.16	70.10 ± 15,12	0.01#	Not significant
				0.37*	Not significant
				0.001 ‡	Significant
Total	71.65 ± 14.58	77.24 ± 14.32	74.24 ± 13.87	0.001#	Significant
				0.02*	Significant
				0.001 ‡	Significant

Values are presented as the mean ± standard deviation. #: Comparison between scores measured at the baseline and the first month of follow-up. *: Comparison between scores measured at the baseline and the sixth month of follow-up. ‡: Comparison between scores measured at the first and sixth months of follow-up.

GCL Sup.
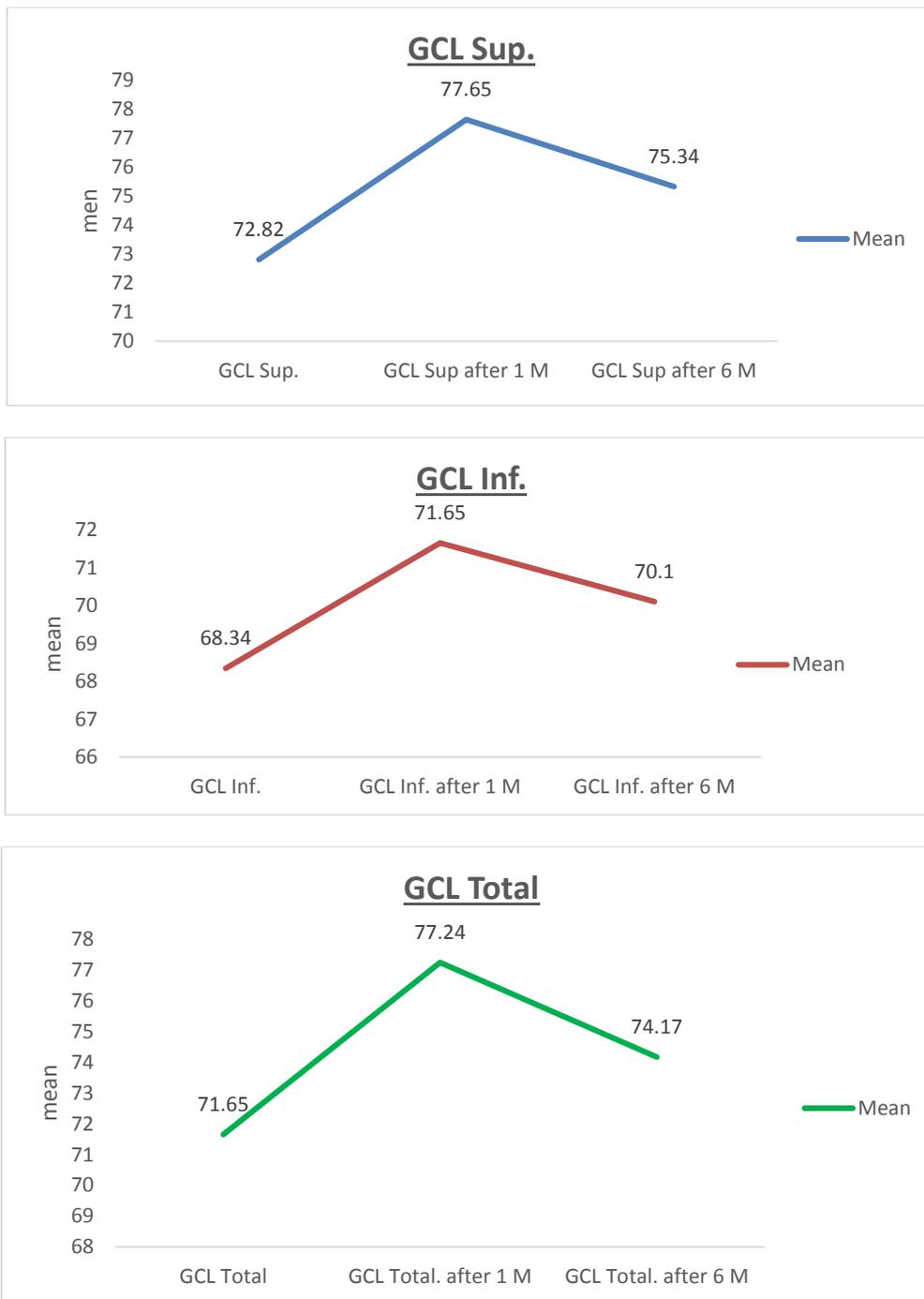

GCL Inf.

GCL Total

Figure (2): differences between the descriptive analysis of GCL at the baseline, after 1 month and after 6 months.

Changes in peripapillary RNFL thickness:

The RNFL (inferior and total) thickness at each follow-up increased significantly from baseline to 1 month and 6 months post-PRP then decrease significantly from 1 month to 6 months follow up ($p < 0.001$). The superior RNFL increased significantly from baseline to 1 month post-PRP and then decrease at 6 month follow up ($p < 0.001$), while there was no significant change from 1 month to 6 months follow up ($p > 0.05$) as shown in table (3).

**Table (3):** Changes in peripapillary RNFL scores within the follow-up period.

RNFL	Baseline	1 month	6 months	P value	Significance
Superior	114.34 ± 22.19	126.31 ± 20.64	125.17 ± 22.75	0.001 #	Significant
				0.001 *	Significant
				0.41 ‡	Not significant
Inferior	105.75 ± 27.71	116.82 ± 27.66	114 ± 27.65	0.001 #	Significant
				0.001 *	Significant
				0.001 ‡	Significant
Total	92.17 ± 17.45	101.20 ± 18.32	98.27 ±17.78	0.001 #	Significant
				0.001 *	Significant
				0.001 ‡	Significant

Values are presented as the mean ± standard deviation.
#: Comparison between scores measured at the baseline and the first month of follow-up.
*: Comparison between scores measured at the baseline and the sixth month of follow-up.
‡: Comparison between scores measured at the first and sixth months of follow-up.
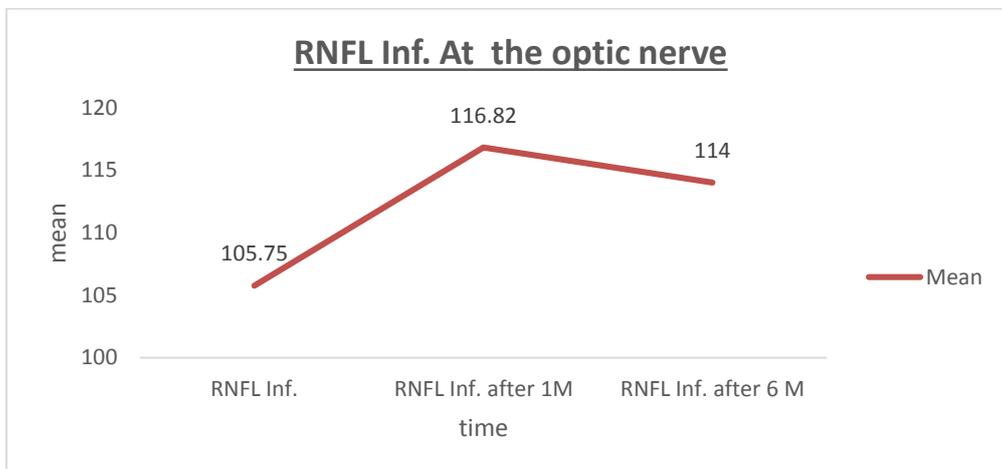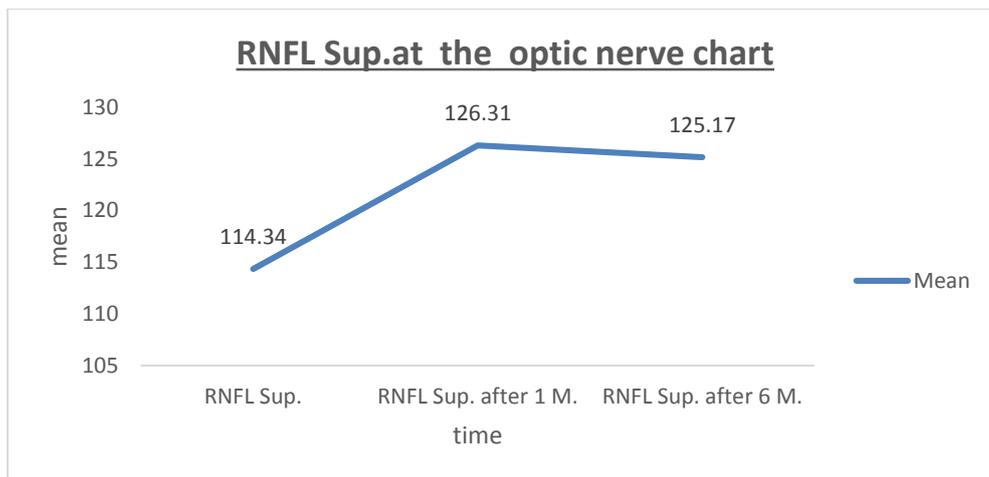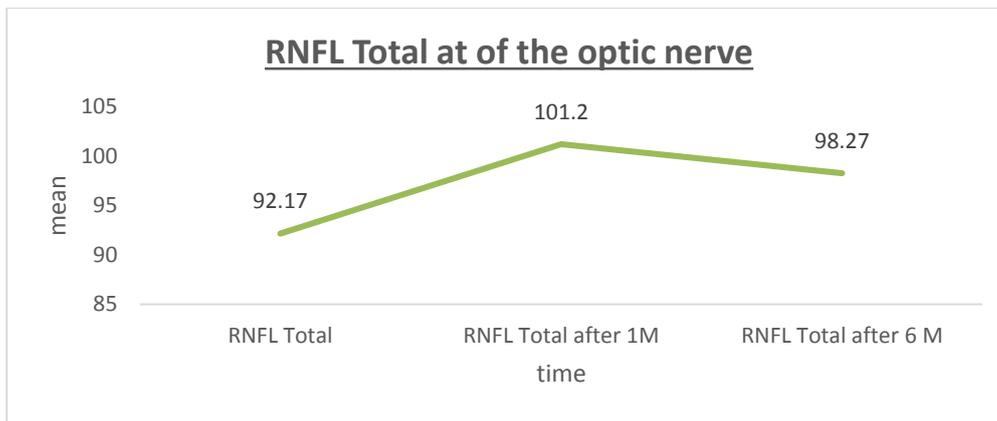
Figure (3): differences between peripapillary RNFL at the baseline, after 1 month and after 6 months

DISCUSSION

Retinopathy should not be viewed as a vascular pathology in isolation and that a similar argument can be applied to neuropathy; it should not be considered as an isolated neural disease. Anatomical and physiological changes to the retina in diabetes highlight the importance of considering neural and vascular complications as potentially linked processes [9].

In this study, macular ganglion cell layer (GCL) (superior and total) thickness at each follow-up increased significantly from the baseline to 1 month then decreased significantly at 6 months post PRP (P < 0.05). The inferior ganglion cell layer decreases significantly from 1 month to 6 months follow up (P < 0.05), while no significant changes from baseline were recorded at 1 and 6 months (p > 0.05).

In a time-domain OCT based retrospective chart review conducted by **Kim et al.** [10] reported statistically significant decrease in the average RNFL thickness at 2 years after PRP treatment, whereas the mean RNFL thickness score slightly increased during the initial 3 months after photocoagulation. Authors reported statistically significant reduction in RNFL thickness within the superior and inferior quadrants at 2 years post-PRP. Besides, they found a borderline significance in the decrease of nasal quadrant RNFL thickness at 2 years after photocoagulation. However, any reduction in RNFL thickness within the temporal quadrant was not observed up to 36 months post-PRP.

In this study, the GCL thickened during the early post-PRP period then decreased thereafter. These thickenings of the macular GCL could be explained by PRP-induced retinal inflammation and edema in the early post-PRP phase. A statistically significant increase of total GCL thickness (+5.59 μm; p < 0.05) at 1 month after photocoagulation, however significant reduction in total GCL thickness (-3 μm; p < 0.05) was measured after the 6 month of post treatment follow up. A statistically significant increase of superior GCL thickness (+4.83 μm; p < 0.05) at 1 month after photocoagulation, followed by

significant reduction in superior GCL thickness (-2.31 μm; p < 0.05) at the sixth month was recorded.

In the present study, it was found that the global, the superior and the temporal quadrant RNFL thicknesses in the diabetic patients without DR were significantly less than those of the patients with proliferative diabetic retinopathy. However, there was no statistically significant difference between patients with proliferative diabetic retinopathy (PDR). In addition, there was no statistically significant difference in RNFL thickness of the inferior and nasal quadrants.

Paul et al. [11] used HRA-OCT Spectralis machine to assess RNFL in patients with type 2 diabetes mellitus and reported that most of their patients with RNFL thinning had temporal quadrant lesions. Additionally, **Lopes de Faria et al.** [12], using the nerve fiber analyzer (GDx), reported significant nerve fiber layer loss in the superior segment of the retina in patients with type 1 diabetes mellitus without DR. Also, **Sugimoto and colleagues** [13] used Stratus OCT to assess RNFL during glycemic control in patients with type 2 diabetes mellitus. All patients were examined at initial visit, 1 month, 2 months and 4 months after the initial examination. On each occasion, glycosylated hemoglobin (HbA1c) levels and OCT scanning for RNFL thickness were evaluated. No significant RNFL change was seen between the initial and 1-month or 2-month examinations. A significant decrease was seen in the superior quadrant between the initial and 4-month examinations. No significant change was found in the other quadrants.

The findings of the present study corroborate with an experimental study conducted by **Kern and Engerman** [14] in two animal models of DR. They showed that the early events of diabetic retinal disease (microaneurysms and acellular capillaries) were not uniformly distributed across the retina and both lesions were significantly more prevalent in the superior temporal retina rather than in inferior nasal areas. Among other studies, an experimental study was conducted by **Chung et al.** [15] to evaluate the

blood flow response to hyperoxia and hypercapnia in peripapillary retinal tissue superior and inferior to the optic nerve head using confocal scanning laser Doppler flowmetry. Their results revealed that the superior temporal regions were more responsive to vasoconstriction and less responsive to vasodilatation and thus more prone to develop oxidative damage and nerve cell loss.

In the present study, The RNFL (inferior and total) thickness at each follow-up increased significantly from baseline to 1 month and 6 months post-PRP then decreased significantly from 1 month to 6 months follow up ($p < 0.001$). The superior RNFL increased significantly from baseline to 1 month post-PRP and then decreased at 6 month follow up ($p < 0.001$). While there was no significant change from 1 month to 6 months follow up ($p > 0.05$).

CONCLUSION

In conclusion, increase in the macular GC thickness and RNFL at 1 month of follow-up may be related to laser-induced intra-retinal inflammation which triggers increased capillary permeability and ensuing axonal edema due to the cytokine release.

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