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Mohammed S. Ahmed
Shoag Teaching Hospital, dr.m.shikhoun@gmail.com

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Prospective changes in the retinal nerve fiber layer and the ganglion cell layer prepan and postpan retinal photocoagulation with argon laser in the management of diabetic retinopathy patients

Mohammed S. Ahmed
Department of Ophthalmology, Shoag Teaching Hospital, Sohag, Egypt

Abstract

Introduction
Diabetic retinopathy (DR) is the primary retinal vascular complication of diabetes mellitus and is a leading cause of vision impairment and blindness. Argon laser is a common laser that is used for DR treatment. This study was carried out aiming to assess the effect of DR on the retinal nerve fiber layer (RNFL) thickness prepan and postpan retinal photocoagulation (PRP).

Patients and methods
This study was carried out on 100 eligible eyes in 62 consecutive patients. The authors performed a complete ophthalmologic examination, including best-corrected visual acuity using the early treatment diabetes retinopathy analysis charts, intraocular pressure measurement, slit-lamp biomicroscopic examination, fundus examination, and fluorescein angiography. The RNFL (inferior and total) thickness at every follow-up visit was increased significantly from baseline to 1 month, and 6 months post-PRP and then decreased significantly at follow-up from 1 month to 6 months ($P < 0.001$). There was a significant increase in superior RNFL from baseline to 1-month post-PRP and then decreased at the 6-month follow-up ($P < 0.001$).

In contrast, there was no significant change from the 1-month to the 6-month follow-up ($P > 0.05$). In conclusion, an increase in the macular ganglion cell thickness and RNFL at follow-up after 1 month may be correlated to laser-induced intraretinal inflammation, resulting in increased capillary permeability and axonal edema due to cytokine release.

Conclusion
In conclusion, an improvement in macular ganglion cell thickness and RNFL at 1 month of follow-up can be associated with laser-induced intraretinal inflammation, resulting in increased capillary permeability and axonal edema due to the release of cytokine.

Keywords: Diabetic retinopathy, ganglion cell complex, panretinal photocoagulation, retinal nerve fiber layer thickness

Introduction

Diabetic retinopathy (DR) is the primary retinal vascular complication of diabetes mellitus and is a leading cause of vision impairment and blindness in the working-age population globally [1].

According to the Diabetic Retinopathy Study Group (DRS), severe visual loss (acuity poorer than 5/200) may occur in 37% of untreated eyes with high-risk characteristics of proliferative diabetic retinopathy (PDR) within 6 years [2]. The ganglion cell analysis (GCA) algorithm of cirrus optical coherence tomography (OCT) can successfully detect and measure

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Correspondence to: Mohammed S. Ahmed, MD,
Department of Ophthalmology, Shoag Teaching Hospital, Sohag, Egypt
Tel: +20 100 717 0600;
E-mail: dr.m.shikhoun@gmail.com

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the thickness of the macular ganglion cell-inner plexiform layer (GCIPL) with excellent intervisit reproducibility [3].

Diabetes can also damage the nonvascular cells of the retina. In autopsy samples, retinal ganglion cells are lost, at least in part, through apoptosis [4]. Histological studies of the retina's neural components have revealed that diabetes-induced biochemical mechanisms can potentially cause neural cell degeneration [5]. have also shown that modifying different diabetes metabolic pathways triggers functional defects and failure of multiple retinal cell types, including ganglion cells, bipolar cells, and ultimately photoreceptors [6].

OCT is used to visualize and understand retinal and choroidal pathologies and current generation OCT instruments provide better resolution and faster measurements [7]. It also facilitates direct measurement by in-vivo simulation of the retina and retinal nerve fiber layer (RNFL) of the RNFL thickness [8].

Argon laser is a common laser used to treat DR whose 488 nm (blue) and 514 nm (green) are prominent spectral peaks, that is, comparatively shorter wavelengths [9].

The first laser used to treat early DR was ruby laser photocoagulation by Beetham and colleagues. More conventional argon laser photocoagulation of DR was then described by Zweng and colleagues. Panretinal photocoagulation (PRP) in DRS has been shown to reduce the risk of serious visual failure by 60% over 2 years, particularly in patients with PDR and the following high-risk characteristics: any disk neovascularization (NVD) associated with vitreous hemorrhage, mild to severe NVD (1/4–1/3 of the disk, normal photograph 10 A), and retinal NVD elsewhere (New vascularization elsewhere (NVE), 1/). Later, the early treatment diabetes retinopathy analysis (ETDRS) indicated that patients with extreme non-PDR could also benefit from scattering photocoagulation. While PRP is frequently used to minimize the likelihood of extreme PDR vision loss effectively, substantial visual side effects, such as impaired vision, decreased field of vision, and diminished color and contrast sensitivity, are correlated with therapy [10].

The mechanism of lasers' action for retinal applications has been retinal photocoagulation, where light energy is transformed into heat at the retinal level, leading to protein denaturation. Several pathways have been suggested for how laser photocoagulation functions in the retina: first, from direct contact on vessels, leading to closing and decreased leakage, and, second, from reduced oxygen requirement and improved oxygenation of the inner retina after scarring and retinal pigment epithelium and photoreceptor burns. The third hypothesis is that retinal pigment epithelium activation following photocoagulation damage contributes to the release of cytokines and eventually decreases the load of the vascular endothelial growth factor and hence edema. This hypothesis is of utmost importance today, as it indicates the prospect of nondamaging laser therapy that facilitates retinal rejuvenation [11]. These modifications are associated with increased leukocyte rolling and the corresponding increase in vascular permeability, resulting in damage to the entire retinal membrane, including the retinal ganglion cells. There is also a significant decrease in RNFL thickness due to apoptosis of neuronal cells and disruption due to glycosylation of the end products of diabetes also plays a part [12].

This study was carried out aiming to assess the effect of DR on the RNFL thickness pre-PRP and post-PRP.

Patients and methods

Time frame: this study was carried out during the period from January 2018 to November 2020.

Study population: this study was carried out on 100 eligible eyes in 59 consecutive patients who attended the Ophthalmology Outpatient Clinic at Sohag Teaching Hospital during the study period.

Inclusion criteria: we identified patients with severe non-PDR and PDR using ETDRS on the basis of the presence of one of the following criteria between 42 and 68 years of age:

(1) Severe intraretinal hemorrhages in four quadrants.
(2) At least two quadrants of venous beading.
(3) In at least one quadrant, the intraretinal microangiopathy was moderate to severe.
(4) In more than one quadrant, there were capillary dropouts.

Exclusion criteria: we excluded those patients from the study who had

(1) Advanced and high-risk PDR.
(2) Densely opaque media (as cataract or vitreous hemorrhage).
(3) Glaucoma.
(4) Hypertensive retinopathy or other retinopathies.

Methods

(1) Cases were assessed preoperatively. History taking included detailed medical history and detailed ocular history. A complete ophthalmologic examination was performed, including best-corrected visual acuity using the ETDRS charts, intraocular pressure measurement, slit-lamp biomicroscopic examination, fundus examination, and fluorescein angiography.
(2) Ganglion cell complex (GCC) and retinal nerve fiber layer (RNFL) scanning procedures: both OCT examinations calculated the same consistency index. OCT Macular Scanning and Optical Nerve Head Scanning were performed using the glaucoma module by calculating RNFL thickness, RGC with IPL (GCIP) GCC. It uses a seven mm2 raster scan based on fovea with a 128 (horizontal) scan density ×512 (vertical) scan. The limits of the anatomical layers are calculated by the program software using a validated automatic segmentation algorithm. The macular inner retinal layers analysis program automatically senses the middle of the fovea at the macular cube and selects an area of 6 × 6 mm at the foveal center. The program partitions the macular square into 6 × 6 grids containing 100 cells

of 0.6 × 0.6 mm to measure regional anomalies in the macular inner retinal layer thickness. The average regional thickness of GCC, GCIP, and RNFL in each cell is calculated and compared to the normative database and color-coded maps of the device.

(3) Panretinal photocoagulation (PRP, macular grid): PRP was performed by applying laser burns over the entire retina, sparing the central macular area. It was performed over two sessions, 1 week apart in PRP, and one session in the macular grid, by applying laser around macular arcades. In the first session, we treated the retina's inferior half, followed by the second session's superior half. PRP was carried out using the slit-lamp delivery system and the Mainster wide-field lens. Laser burns were applied to start at a circumference of 500 μ from the disc and 2 DD from the fovea to the central retina wall. Laser settings were as follows: Spot size = 200 μ, duration = 0.1–0.2 s, and power = 200–320 mW (sufficient to produce moderate intensity/gray–white burns). The burns were placed one spot size apart, except in NVD areas where the entire frond was treated. The procedure was continued peripherally to achieve ~ 800–1000 burns in each session, with a total of about 2000–3000 burns over two settings, 1 week apart. Focal macular photocoagulation (for microaneurysms) was performed in the first session of PRP.

Mainster wide-field lens: this is a contact lens that provides excellent ophthalmoscopic resolution and image binocularity across the entire field of view. It allows an extensive range of slit-lamp magnifications to be used. Image magnification is ×0.68, laser spot magnification is ×1.5, contact diameter is 16 mm, the lens height is 27.8 mm, and the field of vision is 118° static up to 127° dynamic [13].

(4) Protocol of follow-up: follow-up tests were set for 1 and 6 months after PRP. At each follow-up, a complete ophthalmological examination was performed.

Statistical analysis

Data were collected, revised, coded, tabulated, and analyzed using the Statistical Package for the Social Science (IBM SPSS) version 22. IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. The data were expressed in this study as mean and SD for numerical values. The normality of the research sample distribution was assessed using the Shapiro–Wilk (SW) measure. The *t*-test for paired comparison was used to compare the numerical and normally distributed data of the two paired groups. The Wilcoxon Signed-rank test was used to compare the numerical and non-normally distributed data of the two paired groups. The *t*-test for the unpaired comparison test was used to compare the numerical and non-normally distributed data of the two nonpaired groups. The rank-sum (Mann–Whitney) *U*-test was used to compare the numerical and non-normally distributed data of the two nonpaired groups. The confidence interval was set at 95%, and the accepted error margin was set at 5%., The *P* value was thus found to be significant at a level of less than 0.05.

Results

One hundred eligible eyes in 62 consecutive patients were enrolled in the current study. Their demographic and clinical data are shown in Table 1.

Changes in macular GCL thickness

Macular GCL (superior and total) thickness at each follow-up increased significantly from the baseline to 1 month and then decreased significantly at 6 months post-PRP ($P < 0.05$). The inferior ganglion cell layer increased significantly from baseline to 1 month and decreased significantly from the 1-month to the 6-month follow-up ($P < 0.05$), while no significant changes from baseline were recorded at 6 months ($P > 0.05$) (Table 2, Figures 1–3).

Changes in the thickness of peripapillary RNFL

The RNFL thickness (inferior and total) at each follow-up increased significantly from baseline to 1 month and 6 months post-PRP and then it significantly decreased in follow-up from 1 month to 6 months ($P < 0.001$). The superior RNFL significantly increased from baseline to 1-month post-PRP and then decreased at the 6-month follow-up ($P < 0.001$); meanwhile, there was no significant change from the 1-month to 6-month follow-up ($P > 0.05$) (Table 3, Figures 4–6).

Discussion

Retinopathy cannot be treated as a vascular pathology in itself, and a related point may be made to neuropathy; it cannot be seen as an isolated neuronal disorder. Physiological and anatomical changes to the retina in diabetes underline the importance of considering neural and vascular complications as potentially linked processes [14].

Based on the previously mentioned facts, this prospective interventional case series was conducted aiming to assess the effect of DR on the RNFL thickness pre-PRP and post-PRP.

The present study revealed that macular GCL thickness (superior and total) increased significantly at each follow-up from the baseline to the follow-up at 1 month and then decreased significantly at 6 months post-PRP ($P < 0.05$). The inferior ganglion cell layer increased significantly from baseline to 1 month and decreased significantly from the one-month to the 6-month follow-up ($P < 0.05$). The GCL

Table 1: Patient demographic and clinical characteristics

Characteristics	Value
No. of patients	62
No. of eyes	100
Age (years)	55.32±15.12
Male/female	30/32
DM type 1/DM type 2	27/35

Values are presented as the mean±SD. DM, diabetes mellitus.

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

GCL	At baseline	After 1 month	After 6 months	*P*	Significance
Superior	71.57±9.68	79.25±10.82	75.24±9.21	0.001#	Significant
				0.032*	Significant
				0.028‡	Significant
Inferior	65.21±11.59	72.75±12.16	68.20±11.25	0.01#	Significant
				0.147*	Not significant
				0.032‡	Significant
Total	70.32±12.78	79.17±12.25	75.25±9.25	0.001#	Significant
				0.015*	Significant
				0.042‡	Significant

Values are presented as the mean±SD. GCL, ganglion cell layer. #Comparison between scores measured at the baseline and the first month of follow-up. ‡Comparison between scores measured at the first and sixth month of follow-up. *Comparison between scores measured at the baseline and the sixth month of follow-up.

Table 3: Changes in peripapillary RNFL scores within the follow-up period

RNFL	Baseline	1 month	6 months	*P*	Significance
Superior	112.44±19.15	127.21±18.24	126.23±21.52	0.001#	Significant
				0.001*	Significant
				0.784‡	Not significant
Inferior	104.18±22.51	118.12±11.26	114.15±9.54	0.001#	Significant
				0.001*	Significant
				0.036‡	Significant
Total	87.27±12.15	103.12±16.12	97.27±12.18	0.001#	Significant
				0.001*	Significant
				0.024‡	Significant

Values are presented as the mean±SD. RNFL, retinal nerve fiber layer. #Scores comparison between measured at the baseline and follow-up at the first month. *Comparison between scores measured at the baseline and follow-up at the sixth month. ‡Comparison between scores measured at the first and sixth month of follow-up.

thickening during the early post-PRP period could be explained by PRP-induced retinal inflammation and edema in the early post-PRP phase.

A prospective case series study that examined 35 patients (35 eyes) undergoing PRP revealed that macular GCL thickness at each follow-up increased significantly from the baseline and decreased significantly at 12 months compared with the 1 month post-PRP [15].

The present study revealed that the RNFL (inferior and total) thickness at each follow-up increased significantly from baseline to post-PRP at 1 month and 6 months and then decreased significantly at follow-up from the first month to 6 months ($P < 0.001$). Significantly, the superior RNFL increased from baseline to 1 month post-PRP and then decreased in follow-up at 6 months ($P < 0.001$). Simultaneously, the change in follow-up from 1 month to 6 months was no significant ($P > 0.05$). This early retinal thickening was most likely due to postlaser inflammatory effects.

A prospective longitudinal study carried out on 39 patients (39 eyes) who had DR requiring PRP revealed that the average median RNFL thickness significantly increased at 2 months after the procedure. Although other quadrants showed a similar trend of increasing thickness at 2 months, it was not significant. At 4 months postlaser treatment, RNFL thickness in all quadrants reduced to baseline levels with insignificant thickness changes compared with before laser treatment, and the authors concluded that PRP causes transient thickening of the RNFL, which recovers within 4 months postlaser treatment [16].

The findings of the present study are also in line with those of a longitudinal prospective cohort study that examined 42 eyes of 42 patients with PDR undergoing PRP. Peripapillary RNFL thickness was measured using spectral-domain OCT at baseline, 1 year, and 3 years following PRP. A statistically significant difference in the average RNFL thickness was found at baseline and 1 year and 3 years after PRP. At the 1-year follow-up, superior, inferior, and nasal RNFL measurements were reduced significantly from baseline. The reduction in RNFL remained statistically significant for superior and inferior quadrants 3 years after PRP [17].

Paul *et al.*[18] used the HRA-OCT Spectralis machine to evaluate RNFL in type 2 diabetes mellitus patients and reported that most of their patients with RNFL thinning had temporal quadrant lesions. In addition, Lopes de Faria *et al.* [19], using the nerve fiber analyzer (GDx), reported significant nerve fiber layer loss in the retina's superior segment in patients with type 1 diabetes mellitus without DR. Sugimoto *et al.*[20] used Stratus OCT to assess RNFL during glycemic control

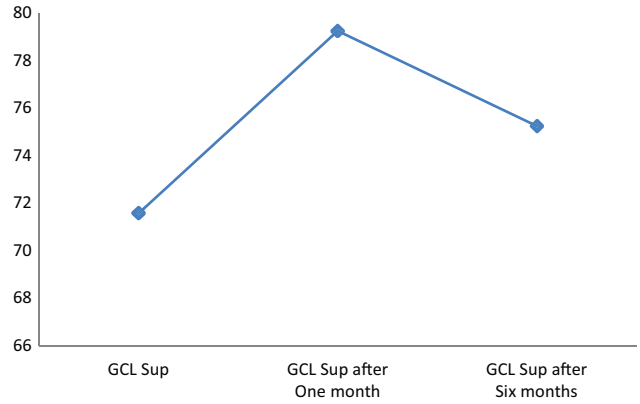

Figure 1: Changes in superior ganglion cell layer scores within the follow-up period.

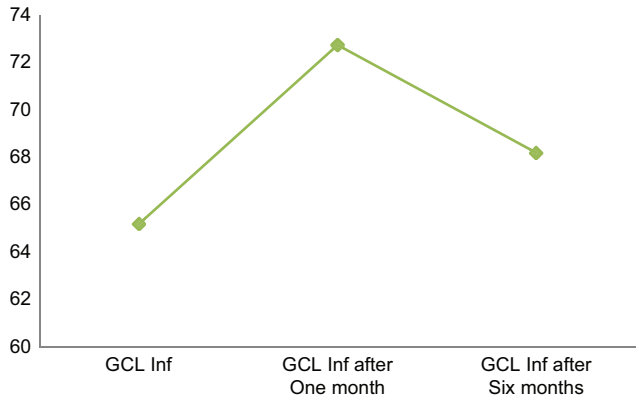

Figure 2: Changes in inferior ganglion cell layer scores within the follow-up period.

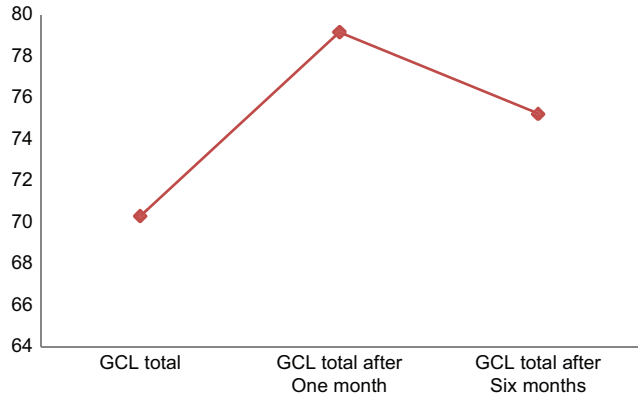

Figure 3: Changes in total ganglion cell layer scores within the follow-up period.

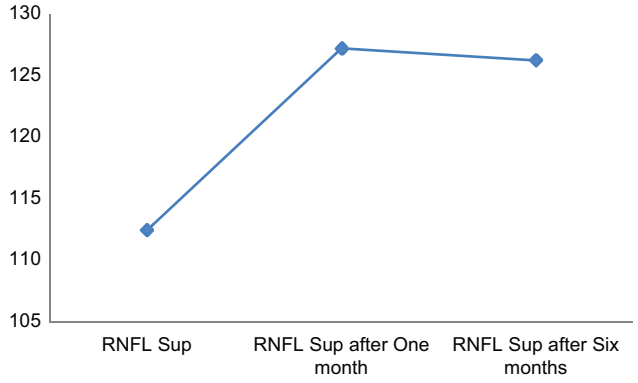

Figure 4: Changes in superior peripapillary retinal nerve fiber layer scores within the follow-up period.

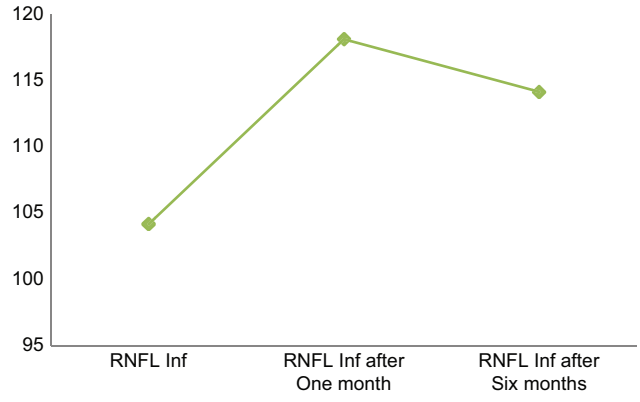

Figure 5: Changes in inferior peripapillary retinal nerve fiber layer scores within the follow-up period.

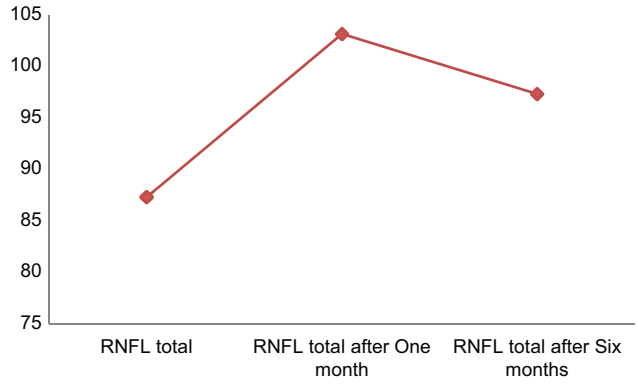

Figure 6: Changes in total peripapillary retinal nerve fiber layer scores within the follow-up period.

in patients with type 2 diabetes mellitus. All patients were examined at the initial visit, and 1 month, 2 months, and 4 months after the first examination. On each occasion, they evaluated glycosylated hemoglobin levels and OCT scanning for RNFL thickness. No significant RNFL change was reported between the initial and 1-month or 2-month examinations. They reported a significant decrease in the superior quadrant between the initial and 4-month examinations, but they did not find a significant change in the other quadrants.

The findings of the present study are in line with those of a retrospective study that included 566 eyes diagnosed with DR of 324 Chinese patients. The authors reported a nonuniform distribution of microaneurysms, intraretinal hemorrhages/exudates, capillary nonperfusion areas, and NVD across the retina in their patients. In mild nonproliferative DR, the highest

frequency of microaneurysms was found in the posterior pole, followed by the inferior nasal and the nasal (55.4%) fields. In moderate nonproliferative DR, microaneurysms were frequently distributed in the posterior pole, nasal, superior, inferior nasal, and inferior (92.9%) fields, whereas hemorrhage/exudates were most prevalent in the posterior pole. In severe nonproliferative DR and proliferative DR, intraretinal microvascular abnormality, capillary nonperfusion areas, and NVD in the nasal field were more frequent than in the inferior field. In comparison, both lesions were found more in the combined posterior pole, and nasal and inferior nasal fields than in the posterior pole or combined in the early and extreme stages of DR [21].

An experimental study, among other studies, was carried out by Chung *et al.*[22] to assess the response to hyperoxia and hypercapnia of blood flow using confocal scanning laser Doppler flowmetry in peripapillary superior and inferior retinal tissue to the optic nerve head. Their data revealed that the superior temporal regions were more vasoconstriction responsive and less vasodilatation responsive, and so they were more liable to develop oxidative damage and nerve cell loss.

There were several limitations related to the study design and conduct that are essential to consider when interpreting these results. These limitations include the fact that the sample size was small, which does not lend much statistical power to the results. Furthermore, the short follow-up period of 6 months cannot provide a complete evaluation of changes. This is why more extensive studies with more extended follow-up periods are needed to confirm the results of the present study.

Conclusion

In conclusion, an improvement in macular GC thickness and RNFL at 1 month of follow-up can be associated with laser-induced intraretinal inflammation, resulting in increased capillary permeability and axonal edema due to cytokine release.

Ethical approval

The study protocol received approval from our Institute's Review Board. Administrative approval and official permissions were obtained before data collection. Informed written consent was obtained from patients included in the study following the guarantee of data confidentiality to them.

Conflicts of interest

There are no conflicts of interest.

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