Original Article

The Effect of Panretinal Photocoagulation (PRP) versus Intravitreal Bevacizumab (IVB) Plus PRP on Peripapillary Retinal Nerve Fiber Layer (RNFL) Thickness Analyzed by Optical Coherence Tomography in Patients with Proliferative Diabetic Retinopathy

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Abstract

Purpose: The current study aimed to evaluate changes in peripapillary retinal nerve fiber layer (RNFL) thickness in diabetic patients with bilateral proliferative diabetic retinopathy (PDR) after receiving panretinal photocoagulation (PRP) or intravitreal bevacizumab (IVB) with PRP.
Methods: Ocular examination and peripapillary optical coherent tomography (OCT) were performed for each patient at baseline, 1, 3, 6, and 10 months after treatment. Both eyes of each patient were randomized into either PRP or PRP + IVB group.
Results: Sixty-four eyes (32 patients) were enrolled in this randomized clinical trial. In the PRP group, global RNFL thickness initially increased and reached statistical significance in the third month (from 105.9 ± 21.4μm at baseline to 119 ± 41.6μm at 3 months, $P = 0.03$). Subsequent decline was observed with no significant difference from baseline at 10 months (106 ± 19.3μm, $P = 0.914$). There were no statistically significant changes in the PRP + IVB group (from 101.7 ± 22.2μm at baseline to 109.3 ± 26.9μm at 3 months, $P = 0.996$ and 101.9 ± 16.5μm at 10 months, $P = 0.999$). In the latter group, slight increase in RNFL thickness was observed in the first month (107.7 ± 21.1μm). RNFL thickness was similar to baseline in the two

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groups at month 10, with the exception of significant increase in superior-temporal sector in the PRP group (145.3 ± 13.4μm vs. 127.2 ± 17.3μm, $P = 0.045$).
Conclusion: Compared to eyes treated with PRP, eyes treated with adjunctive IVB showed less significant post-treatment changes in RNFL thickness.

Keywords: Bevacizumab; Diabetes; Panretinal Photocoagulation; Retinal Nerve Fiber Layer; Retinopathy

INTRODUCTION

Panretinal photocoagulation (PRP) is the standard of care for proliferative diabetic retinopathy (PDR) which decreased severe visual loss by 50% in the Diabetic Retinopathy Study (DRS)[1,2] However, laser is a destructive process and can lead to functional impairment and visual compromise.[2,3] Retinal nerve fiber layer (RNFL) thickness has been shown to be affected by PRP and appropriate titration of intensity should aim to achieve photocoagulation of the outer retina while limiting damage to the ganglion cells.[4,5] The effect of PRP on RNFL thickness is not fully understood, with studies demonstrating mixed results showing an increase, decrease, and no change in RNFL thickness after treatment.[4,6,7] Several factors that influence RNFL thickness have been suggested, including diabetes, degree of diabetic retinopathy, number of laser spots, hemoglobin A1c (HbA1c), and history of glaucoma.[4,6,8-12]

Intravitreal bevacizumab (IVB) has gained popularity in the management of proliferative diabetic retinopathy, often used as an adjunct to PRP. It was proposed that anti-VEGF medications may change the function of the retina.[13] However, a study done by Horsley et al did not find a change in RNFL thickness in patients who received chronic anti-VEGF therapy for age- related macular degeneration.[14] There are limited prospective studies that have examined the changes in RNFL after PRP.[15] Moreover, the combined effects of PRP and IVB on RNFL have not been previously described.

METHODS

The study protocol was approved by the Institutional Review Board of Tehran University of Medical Sciences and complied with the tenets of the Declaration of Helsinki. The study was conducted at Farabi Eye Hospital from October 2013 to March 2014. Informed consent was obtained from all participants. This randomized clinical trial was registered at www.irct.ir with the registration number IRCT2014030116782N1.

Thirty-two patients (64 eyes) were enrolled in this study, with each eye randomized to a separate treatment arm. Inclusion criteria were the presence of bilateral PDR requiring treatment (based on early treatment diabetic retinopathy study (ETDRS) criteria, normal intraocular pressure (IOP), and refractive error of +/- 3 diopters (D). Any other ocular morbidities (glaucoma, ocular hypertension, and/or significant corneal opacity, cataract, or vitreous opacity/hemorrhage that precluded imaging), history of prior treatment for diabetic retinopathy, center involved diabetic macular edema with macular thickness ≥350 μm, pregnancy, uncontrolled systemic hypertension (blood pressure ≥180/110), and inability to undergo randomization were the exclusion criteria. None of the included patients suffered from vitreous hemorrhage during the treatment period and follow- up that interfered with spectral domain optical coherence tomography (SD-OCT) or required additional treatment.

Patients underwent complete ocular evaluation including best corrected visual acuity (BCVA) measurement by Snellen chart (which was converted into LogMAR), slit lamp examination of the anterior and posterior chambers, Goldmann applanation tonometry, and fundus examination by indirect ophthalmoscopy, and 90-D lens biomicroscopy at each visit. None of the studied eyes showed any traction retinal detachment at baseline or during follow- up visits. SD-OCT (Spectralis SD-OCT, Heidelberg Engineering, Germany: Spectralis software version 5.3.2) and A scan measuring axial length (Quantel Medical, Aviso) were performed for each patient at baseline as well as at 1, 3, 6 and 10 months after treatment. RNFL thickness was measured in a peripapillary circle scan 3.4 mm in diameter at 6 sectors containing temporal, nasal, superior-temporal, superior-nasal, inferior-temporal, and inferior-nasal sections.

Systemic blood pressure and hemoglobin A1c (HbA1c) were checked at baseline. For each subject, one eye was randomized (based on random block method) to receive PRP alone and the fellow eye was assigned to the PRP with intravitreal bevacizumab (PRP + IVB) group. Three sessions of PRP were performed using green laser (wavelength: 514, spot size: 500 μm, duration: 0.2 s with pulse power titrated to achieve moderate intensity) at an interval of one week between the sessions to achieve a total of 1,800 spots. IVB (1.25 mg/0.05 ml) was injected into the randomized eye after the first session of PRP using standard ophthalmic technique with the medication being injected 3-4 mm posterior to the limbus. Focal macular laser for clinically significant non-foveal macular edema was performed at the same time as the first session of PRP.

Statistical Analyses

The data are reported as mean ± SD and analyzed using the Statistical Package for Social Sciences (SPSS) software (Version 18.0. Chicago: SPSS Inc.). The normal distribution of data was confirmed by Shapiro-Wilk test and paired *t*-test was used for comparison of RNFL thickness between the two groups. Alteration in RNFL thickness at baseline versus follow-up visits in each group was assessed based on Linear Mixed Model variables. The relationship between RNFL thickness versus duration of diabetes and HbA1c at each visit was evaluated by Spearman correlation. Statistical significance was defined as *P* value less than 0.05.

RESULTS

Sixty-four eyes of 32 patients were included in the study. Twenty-nine patients completed six months follow-up while 19 patients completed the whole follow-up period (10 months). The mean age was 53.6 ± 6.6 years (range, 40-65 years) and there were 26 female subjects. Mean HbA1c and duration of diabetes were 8.4 ± 1.7% (range, 6.2-12.9%) and 12.5 ± 5.2 years (range, 5-22 years), respectively. There was no significant difference in axial length between the two groups (22.99 ± 0.63 mm in PRP group and 22.94 ± 0.65mm in PRP plus IVB group, $P = 0.77$) [Table 1]. Nine eyes in the PRP group and seven eyes in the PRP with IVB group received focal macular laser photocoagulation (MPC). Bilateral MPC was done in both eyes of two patients. Twenty-six eyes received one injection and six eyes received two injections of IVB in PRP plus IVB group.

Changes in BCVA did not reach statistical significance in the PRP group (from 0.22 ± 0.32 logMAR to 0.28 ± 0.34 logMAR, $P = 0.169$) and PRP with IVB group (from 0.22 ± 0.24 logMAR to 0.27 ± 0.26 LogMAR, $P = 0.267$) from baseline to the final follow-up visit. The relationship between RNFL thickness and duration of diabetes was not significant at any study interval (r = -0.052 and $P = 0.318$, r = -0.084 and $P = 0.103$, r = 0.-110 and $P = 0.047$, r = -0.004 and $P = 0.948$, r = -0.076 and $P = 0.215$) at baseline, 1, 3, 6, and 10 months, respectively). A weak positive association was observed between global RNFL thickness with HbA1c only at 3 and 10 months (r = 0.041 and $P = 0.424$, r = 0.061 and $P = 0.240$, r = 0.120 and $P = 0.046$, r = 0.081 and $P = 0.118$, r = 0.143 and $P = 0.023$ at baseline, 1, 3, 6, and 10 months, respectively, by Spearman correlation).

There was no significant difference between the number of laser spots between the two groups (1772.50 ± 336.30 in PRP plus IVB group and 1849.09 ± 361.80 in PRP group, $P = 0.3$). Mean RNFL thickness at baseline and subsequent follow-up visits are summarized in Table 2 for both treatment arms. The global RNFL thickness was not significantly different between the treatment arms at any time points; however, significant difference was observed between the groups (higher thickness in PRP group) at 3 and 10 months in the superior-temporal sector ($P = 0.042$ and $P = 0.003$, respectively).

Baseline RNFL thickness was similar between the treatment groups. In the PRP plus IVB group, RNFL thickness increased one month after treatment, although the change was not significant. Moreover, by 10 months, RNFL values were lower than baseline globally and in every sector, with the exception of temporal and nasal sectors. None of the changes in the PRP + IVB group globally or in any sector was significant when compared to baseline RNFL values. Global RNFL thickness was significantly higher than baseline in the PRP group at 3 months; however, gradual decline was observed to values that were not significantly different from baseline. Statistically significant differences were observed at various points in the nasal, inferior-temporal, and superior-temporal sectors in the PRP group, while other sectors on the RNFL map did not have any significant changes. RNFL thickness tended to increase at 1 month and continued to rise till 3 months, followed by progressive decline from the 6th to 10th months. This trend was observed in global RNFL thickness and values of every sector, with the exception of temporal and superior-temporal sectors. In the temporal and superior-temporal quadrants, an increase in RNFL thickness was observed between 6 months and 10 months; and although the final RNFL thickness was lower than baseline in the temporal quadrant, statistically significant higher value was observed in the superior-temporal quadrant. This increase in RNFL thickness at 10 months in the PRP group was the only significant change compared to baseline at final follow-up in either treatment arm. Table 2 and Figure 1 provide information of the trends in RNFL thickness in both groups.

The difference in RNFL thickness between treatment groups did not reach statistical significance except

Table 1. Demographic and medical characteristics of patients

	Age (years)	Duration DM (years)	HbA1c	BCVA (LogMAR)	Final BCVA (LogMAR)
PRP group	53.5±6.7	12.2±5.0	8.5±1.8	0.22±0.32	0.28±0.34
PRP + IVB group	53.2±6.6	12.8±5.4	8.2±1.6	0.22±0.24	0.27±0.26
P	0.859	0.712	0.509	0.994	0.953
Total	53.6±6.6	12.5±5.2	8.4±1.7	0.22±0.28	0.27±0.30

PRP, panretinal photocoagulation; IVB, intravitreal bevacizumab; BCVA, best corrected visual acuity, DM, diabetes mellitus

Table 2. Alterations in retinal nerve fiber layer (RNFL) thickness in patients with proliferative diabetic retinopathy after treatment with panretinal photocoagulation (PRP group) versus panretinal photocoagulation and intravitreal bevacizumab (PRP plus IVB group) at 1, 3, 6, and 10 months after treatment in comparison to the baseline

Site	Time	Group		Difference	95% CI		*P*†	*P* of trend difference¥
		PRP + IVB	PRP		Lower	Upper		
Superior nasal	Baseline	101.7±22.2	105.9±21.4	−1.5	−9.0	6.0	0.689	0.593
	Month 1	107.7±21.1	110±21.9	−1.7	−10.2	6.7	0.678	
	P change§	0.065	0.273					
	Month 3	109.3±26.9	119±41.6	−8.1	−24.6	8.4	0.322	
	P change§	0.238	0.057					
	Month 6	104.5±22.9	117.1±40.2	−11.0	−27.2	5.1	0.172	
	P change§	0.479	0.099					
	Month 10	101.9±16.5	106±19.3	−3.2	−12.0	5.6	0.451	
	P change§	0.407	0.701					
Inferior nasal	Baseline	112.3±38.3	122.8±23	−7.7	−22.3	6.9	0.290	0.560
	Month 1	115.3±24.9	122.9±23.2	−5.7	−14.2	2.8	0.181	
	P change§	0.971	0.988					
	Month 3	112.4±24.4	128.9±35.7	−14.6	−31.2	2.0	0.082	
	P change§	0.990	0.534					
	Month 6	116.2±27.3	120.6±25.7	−2.4	−13.3	8.5	0.658	
	P change§	1.000	0.623					
	Month 10	102.7±34	111.9±26.1	−8.5	−26.8	9.8	0.340	
	P change§	0.583	0.149					
Nasal	Baseline	76.1±19.5	73.6±19.3	3.9	−6.3	14.1	0.444	0.072
	Month 1	79.8±14.4	85.3±22.3	−4.5	−13.9	4.9	0.334	
	P change§	0.800	0.006*					
	Month 3	79.4±14.8	93.2±33.9	−12.8	−26.0	0.4	0.057	
	P change§	0.971	0.002*					
	Month 6	77.8±18.4	88±37.6	−9.5	−25.6	6.7	0.239	
	P change§	0.998	0.025*					
	Month 10	81.3±44.4	77.5±12.9	5.4	−16.5	27.2	0.610	
	P change§	0.675	0.613					
Superior temporal	Baseline	135±32.8	139.4±26.8	−1.8	−9.4	5.7	0.621	0.018*
	Month 1	140.8±23.2	142.8±27.7	−1.6	−11.0	7.8	0.729	
	P change§	0.490	0.136					
	Month 3	137.9±30.6	151.3±23.3	−11.9	−23.3	−0.4	0.042*	
	P change§	0.998	0.006*					
	Month 6	135.7±20	141.6±23.1	−5.0	−12.3	2.3	0.170	
	P change§	0.986	0.242					
	Month 10	127.2±17.3	145.3±13.4	−18.0	−28.9	−7.1	0.003*	
	P change§	0.963	0.045*					
Inferior temporal	Baseline	146.6±38.5	147.4±31.6	1.1	−7.1	9.4	0.781	0.608
	Month 1	150.7±26.7	157.3±35.4	−4.4	−14.0	5.2	0.356	
	P change§	0.821	0.009*					
	Month 3	149.7±26.4	160.2±34.5	−9.3	−24.0	5.5	0.209	
	P change§	0.954	0.050					
	Month 6	148.1±27.1	151.2±27.7	−0.7	−12.8	11.3	0.900	
	P change§	1.000	0.341					
	Month 10	141.8±29	139.6±20.7	4.2	−11.1	19.5	0.569	
	P change§	0.971	0.590					
Temporal	Baseline	85.9±39.2	86.2±36.8	0.7	−12.0	13.5	0.910	0.267
	Month 1	87.8±23.9	89.9±32	−1.4	−14.4	11.6	0.827	
	P change§	0.997	0.523					

Contd...

Table 2. Contd....

Site	Time	Group		Difference	95% CI		*P*†	*P* of trend difference¥
		PRP + IVB	PRP		Lower	Upper		
	Month 3	81.4±18.8	94.1±45.3	−12.1	−32.0	7.7	0.220	
	P change§	0.984	0.348					
	Month 6	87.3±19.9	79.1±23.1	8.5	−4.4	21.4	0.186	
	P change§	1.000	0.490					
	Month 10	86.3±21	82.7±15.2	4.9	−4.4	14.2	0.283	
	P change§	0.989	0.815					
Global	Baseline	102.8±28	104.9±17.1	−0.4	−7.8	7.1	0.923	0.443
	Month 1	105.9±14.7	111.3±18.9	−4.3	−11.3	2.8	0.225	
	P change§	0.797	0.054					
	Month 3	104.1±14.8	116.4±30	−11.1	−23.2	0.9	0.068	
	P change§	0.996	0.030*					
	Month 6	104.3±12.8	108.7±21.2	−3.2	−11.9	5.5	0.453	
	P change§	0.997	0.378					
	Month 10	101.3±20.2	102.7±9.9	−0.2	−8.3	7.8	0.954	
	P change§	0.999	0.914					

P: *P* value of comparison between baseline and follow up times in each group, †Based on paired t-test (comparison between 2 groups), §Based on Linear Mixed Model (LMM), adjustment for multiple comparisons performed by Sidak test, ¥Based on interaction analysis in Linear Mixed Model, demonstrating probable differences between the two groups pertaining to the changes during the study, *statistically significant. The measurement scale is in micrometers, difference: difference of the means between the two groups

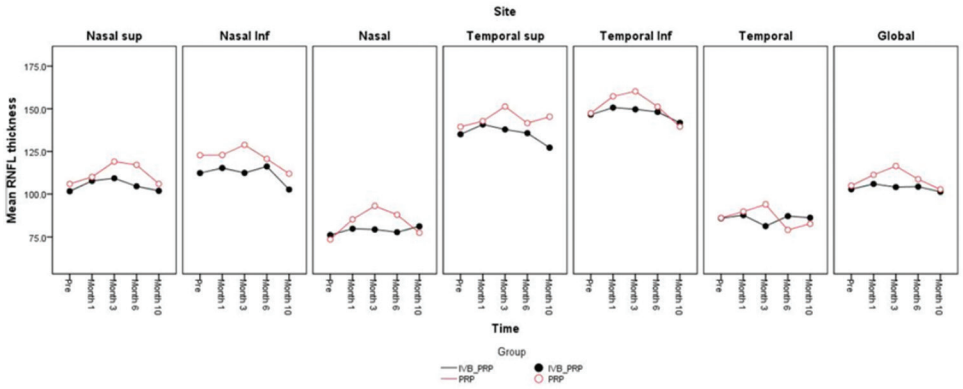

Figure 1. Graph of changes in retinal nerve fiber (RNFL) layer thickness of patients with diabetic retinopathy after treatment with panretinal photocoagulation (PRP) versus PRP plus intravitreal bevacizumab (IVB).

at 3 months and 6 months in the superior-temporal quadrant [*P* = 0.018, Table 2].

DISCUSSION

A number of factors may influence RNFL thickness. The effect of ophthalmic interventions, in particular PRP, on RNFL thickness has been an area of active study with conflicting results.[4,6,7] Lee et al reported an initial increase in RNFL thickness until 6 months, which eventually decreased compared to baseline at 24 months.[15] Other studies have reported increase in RNFL thickness at 6 weeks and 6 months, while a study by Kim et al found no change at 6 months.[4,7,16] Diabetes, diabetic retinopathy, and ganglion cell loss may contribute to RNFL loss and must be considered when examining the effects of PRP.[10-12] Ghassemi et al found that RNFL thickness increased at 6 months in patients who underwent red or green laser, and the change did not depend on the laser color.[16] Park and Jee observed that PRP with conventional laser was associated with decreased RNFL thickness at six months and one year; however, no changes were observed in RNFL thickness after PASCAL laser—, suggesting protection of the RNFL by PASCAL due to the use of less energy than conventional PRP.[17] The current study examined the role of IVB, an increasingly commonly utilized adjunct to PRP in the treatment of PDR, on changes in RNFL thickness. Additionally, the influence of HbA1c and duration of diabetes was explored.

A study conducted by Kim et al did not demonstrate a significant change in the peripapillary RNFL thickness

in patients undergoing PRP compared to controls at 6 months. However, the study observed that higher HbA1c (but not duration of diabetes) was significantly correlated with greater reduction in post-PRP RNFL thickness.[4] In the current study HbA1c showed positive correlation with RNFL thickness at every time point. Interestingly, change in RNFL thickness correlated significantly with HbA1c at the 3rd and 10th month time points; however, this correlation was weak. Kim et al suggested greater tissue vulnerability to photocoagulation with elevated blood glucose; however, HbA1c is a global index of average blood sugar over 3 months and as such, the effect of blood sugar on RNFL change at the time of PRP is not known.[4]

A statistically significant increase in global RNFL thickness was observed at month 3 in PRP group; however, RNFL thickness returned to near baseline values by the 6th and 10th months, which is similar to previously described trends.[6,15] A similar trend was observed in most of the RNFL sectors after PRP; however, the changes were not statistically significant. The increase in RNFL in the first month after laser may be due to impaired axonal flow and intra-retinal inflammation.[16,18] Subsequent decrease in RNFL thickness may occur with reduction in inflammation and atrophy ganglion cells emerges with resultant peripapillary RNFL loss.[15,19,20] In the PRP with IVB group, increase in RNFL thickness, although not significant, was observed in the first month, which returned to baseline values by final follow up. Duration of effect of IVB is approximately one month and the return to baseline values and the difference between the treatment arms after one month are unlikely to be due to direct pharmacologic effects of IVB. Instead, it seems plausible that the administration of IVB at the time of PRP may inhibit release of the same proinflammatory cytokines that have been proposed to be the cause of aggravation of macular edema after PRP.[21,22] It is interesting to note that both groups demonstrated an initial increase in RNFL thickness, which returned to baseline values by 10 months, but the changes in the PRP with IVB group did not reach significance at any point and showed faster return to baseline values.

Some regional differences in RNFL thickness were observed at various study intervals during the current trial. Lim et al observed that nasal and inferior RNFL were significantly thinner in the PRP group and although an increase in temporal thickness was noted, the change was not significant.[6] Lee et al showed increased temporal RNFL thickness in the setting of decreased average RNFL thickness and decreased thickness in the other quadrants following PRP at 24 months.[15] The increase in temporal RNFL thickness following PRP has also been demonstrated in an animal study.[23] Similarly, in the current study, significant increase in RNFL thickness was observed in the superior-temporal sector compared to baseline values at 10 months in the PRP group, which was not seen at 10 months in the PRP with IVB group. The superior-temporal sector was the only location at the 10th month where the difference in treatment response and the trend in response between the two groups were statistically significant. The cause of this pattern of regional change is not known; however, the increase in temporal RNFL thickness has been postulated to be related to variations in the macular structure.[15] Macular thickness has been shown to increase and subsequently decline following PRP.[6,15] In the current study, both groups received similar amount of focal macular laser for clinically significant non-foveal macular edema (PRP group: 9, PRP with IVB: 7). The use of IVB was likely responsible for the reduction in the post-PRP increase in macular thickness and as a result could be the reason for the difference between treatment arms in the superior-temporal sector at 10 months.

There are several limitations in the current study including the small sample size, concurrent use of macular laser, and a follow- up time of ten months, which precludes tracking possible long-term changes in RNFL thickness. Considering the observed standard deviation, the power of the study to detect a difference of 10 microns between the two groups in various comparisons (at various times) would be from 26% to 92% as per *post hoc* power analysis. This would indicate that at some time points during follow- up, the current study had insufficient power to detect a clinically significant difference between the two groups, which can be considered as a limitation of the study.

The PRP with IVB group did not demonstrate statistically significant changes globally or in any sector at all study points, unlike the PRP group that showed several statistically significant changes. This could indicate that the use of IVB may mitigate the effects of PRP and provide protection in maintaining RNFL thickness. Additional macular protective effects of IVB may be present at the time of PRP, given the lack of increase in RNFL thickness in the superior-temporal sector as seen in the PRP group. Further investigations are necessary to determine the functional effects of these interventions, the long-term effects of PRP + IVB, and the effect of multiple injections of IVB given along with repeated PRP treatments.

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Conflicts of Interest

All authors certify that have no financial interests.

REFERENCES

1. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 1991;98:766-785.

2. The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. *Ophthalmology* 1981;88:583-600.
3. Dastgheib K, Bressler SB, Green WR. Clinicopathologic correlation of laser lesion expansion after treatment of choroidal neovascularization. *Retina* 1993;13:345-352.
4. Kim HY, Cho HK. Peripapillary retinal nerve fiber layer thickness change after panretinal photocoagulation in patients with diabetic retinopathy. *Korean J Ophthalmol* 2009;23:23-26.
5. Brinkmann R, Hüttmann G, Rögener J, Roider J, Birngruber R, Lin CP. Origin of retinal pigment epithelium cell damage by pulsed laser irradiance in the nanosecond to microsecond time regimen. *Lasers Surg Med* 2000;27:451-464.
6. Lim MC, Tanimoto SA, Furlani BA, Lum B, Pinto LM, Eliason D, et al. Effect of diabetic retinopathy and panretinal photocoagulation on retinal nerve fiber layer and optic nerve appearance. *Arch Ophthalmol* 2009;127:857-862.
7. Ritenour RJ, Kozousek V, Chauhan BC. The effect of panretinal photocoagulation for diabetic retinopathy on retinal nerve fiber layer thickness and optic disc topography. *Br J Ophthalmol* 2009;93:838-839.
8. Lopes de Faria JM, Russ H, Costa VP. Retinal nerve fibre layer loss in patients with type 1 diabetes mellitus without retinopathy. *Br J Ophthalmol* 2002;86:725-728.
9. Yamazaki Y, Koide C, Miyazawa T, Kuwagaki N, Yamada H. Comparison of retinal nerve-fiber layer in high- and normal-tension glaucoma. *Graefes Arch Clin Exp Ophthalmol* 1991;229:517-520.
10. Chihara E, Matsuoka T, Ogura Y, Matsumura M. Retinal nerve fiber layer defect as an early manifestation of diabetic retinop athy. *Ophthalmology* 1993;100:1147-1151.
11. Takahashi H, Goto T, Shoji T, Tanito M, Park M, Chihara E. Diabetes-associated retinal nerve fiber damage evaluated with scanning laser polarimetry. *Am J Ophthalmol* 2006;142:88-94.
12. Cheung CYL, Leung CKS, Lin D, Pang CP, Lam DS. Relationship between retinal nerve fiber layer measurement and signal strength in optical coherence tomography. *Ophthalmology* 2008;115:1347-1351.
13. Nishijima K, Ng YS, Zhong L, Bradley J, Schubert W, Jo N, et al. Vascular endothelial growth factor-A is a survival factor for retinal neurons and a critical neuroprotectant during the adaptive response to ischemic injury. *Am J Pathol* 2007;171:53-67.
14. Horsley MB, Mandava N, Maycotte MA, Kahook MY. Retinal nerve fiber layer thickness in patients receiving chronic anti-vascular endothelial growth factor therapy. *Am J Ophthalmol* 2010;150:558-561.
15. Lee S, Kwag JY, Lee HJ, Jo YJ, Kim JY. The longitudinal changes of retinal nerve fiber layer thickness after panretinal photocoagulation in diabetic retinopathy patients. *Retina* 2013;33:188-193.
16. Ghassemi F, Ebrahimiadib N, Roohipoor R, Moghimi S, Alipour F. Nerve fiber layer thickness in eyes treated with red versus green laser in proliferative diabetic retinopathy: Short-term results. *Ophthalmologica* 2013;230:195-200.
17. Park YR, Jee D. Changes in peripapillary retinal nerve fiber layer thickness after pattern scanning laser photocoagulation in patients with diabetic retinopathy. *Korean J Ophthalmol* 2014;28:220-225.
18. Nonaka A, Kiryu J, Tsujikawa A, Yamashiro K, Nishijima K, Kamizuru H, et al. Inflammatory response after scatter laser photocoagulation in nonphotocoagulated retina. *Invest Ophthalmol Vis Sci* 2002;43:1204-1209.
19. Tso MO, Wallow IH, Elgin S. Experimental photocoagulation of the human retina. I. Correlation of physical, clinical, and pathologic data. *Arch Ophthalmol* 1977;95:1035-1040.
20. Brooks DE, Komàromy AM, Källberg ME. Comparative retinal ganglion cell and optic nerve morphology. *Vet Ophthalmol* 1999;2:3-11.
21. Shimura M, Yasuda K, Nakazawa T, Abe T, Shiono T, Iida T, et al. Panretinal photocoagulation induces pro-inflammatory cytokines and macular thickening in high-risk proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol* 2009;247:1617-24.
22. Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, Antoszyk AN, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med* 2015;372:1193-1203.
23. Blankenship GW. Red krypton and bluegreen argon panretinal laser photocoagulation for proliferative diabetic retinopathy: A laboratory and clinical comparison. *Trans Am Ophthalmol Soc* 1986;84:967-1003.