Changes in Choroidal Thickness After Panretinal Photocoagulation for Diabetic Retinopathy: A 12-Week Longitudinal Study

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PURPOSE. To investigate the longitudinal changes in choroidal thickness of the eyes of diabetic retinopathy patients during 12 weeks after panretinal photocoagulation (PRP).

METHODS. This prospective, comparative study included 46 eyes undergoing four-session PRP. At baseline and 1, 4, 8, and 12 weeks after completion of the PRP treatments, subfoveal choroidal thickness (SFCT) was measured by using enhanced depth imaging optical coherence tomography. Also measured were central macular thickness (CMT) and best-corrected visual acuity (BCVA).

RESULTS. The mean SFCT at baseline was 309 ± 77 μm, changing to 323 ± 78 μm, 315 ± 75 μm, 299 ± 68 μm, and 289 ± 71 μm at 1, 4, 8, and 12 weeks, respectively. This constituted a statistically significant increase at 1 week and a significant decrease at 12 weeks. The mean baseline CMT was 294 ± 92 μm, which increased significantly 1 week after PRP to 344 ± 123 μm, remaining higher at 4 weeks (340 ± 117 μm) and 8 weeks (318 ± 100 μm), but subsiding to baseline at 12 weeks (311 ± 96 μm). The mean BCVA at baseline and the last visit were 0.63 ± 0.28 logMAR and 0.53 ± 0.42 logMAR, respectively. There was no significant difference in BCVA between eyes with and without central-involved diabetic macular edema at all time points. Compared with the baseline, the mean BCVA dropped at 1 week and 4 weeks but recovered by 12 weeks.

CONCLUSIONS. Choroidal thickness decreased 12 weeks after PRP, suggesting that PRP may reduce choroidal vascular permeability or cause atrophy of choroidal vessels over a 12-week period.

Keywords: choroidal thickness, central macular thickness, enhanced depth imaging, optical coherence tomography, panretinal photocoagulation, diabetic retinopathy

Diabetic retinopathy (DR) is a leading cause of blindness in working-age populations worldwide. The main causes of vision loss in DR are diabetic macular edema (DME) and proliferative DR. Panretinal photocoagulation (PRP) using an argon laser is a well-established and effective treatment for proliferative DR. Panretinal photocoagulation (PRP) using an argon laser is a well-established and effective treatment for proliferative DR. However, DME sometimes develops or exacerbates after PRP, and transient reduction of visual acuity may occur.

It is generally recognized that retinal vascular damage is prominent in the pathogenesis and clinical features of DR. Previous studies suggest that choroidal angiopathy is also associated with DR, for example, delayed choroidal vascular filling, and reduction in choroidal blood flow and volume. Furthermore, the choroid of eyes with DR exhibits neovascularization, vascular degeneration, and aneurysms, and blood vessels that are more tortuous and narrow than normal blood vessels. Recently, it has become evident from choroidal thickness measurements that the choroid is probably involved in the pathogenesis of DR. However, reports have been contradictory regarding choroidal thickness in proliferative DR and DME; most studies report a decrease, some report an increase, and some report no significant change. The discrepancies may be attributed to different patient profiles. For example, some studies include DR patients who have undergone previous PRP treatment.

Historically, clinical evaluation of the choroid has been mainly performed invasively with indocyanine green angiography, which does not allow for precise quantification of the cross-sectional thickness. The recent advent of enhanced depth imaging–optical coherence tomography (EDI-OCT) has enabled noninvasive in vivo visualization of the choroidal cross-sectional structure. This technique has been used in a number of studies to measure choroidal thickness in various ocular diseases, including DR.

The long-term influence of PRP on choroidal thickness is still unknown. There are no reports of the effect of PRP treatment on choroidal thickness in DR patients undergoing monitoring for more than 1 month, although two studies have followed these effects for 1 week and 1 month, respectively, with only a single follow-up visit. Herein, we report the effect of PRP on the choroid during a follow-up of 12 weeks.

SUBJECTS AND METHODS

This was a prospective comparative study. The Institutional Review Board of Nanjing Medical University Affiliated Wuxi...
Second Hospital approved the protocol. All participants gave their informed consent to participate in the clinical examination program, and our study was performed in accordance with the tenets of the Declaration of Helsinki.

Subjects
The participants were selected from patients with type 2 diabetes who chose to receive PRP treatment in the Department of Ophthalmology, Nanjing Medical University Affiliated Wuxi Second Hospital. In accordance with the recommendations of the Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group,21,22 PRP should be performed in eyes with severe nonproliferative DR and non–high-risk proliferative DR. All patients included in the present study needed PRP treatment, as based on the fundus findings and fluorescein fundus angiography (FFA) results.

Patients were excluded by the presence of refractive errors of more than ±3.0 diopters, intraocular pressure (IOP) of more than 21 mm Hg (noncontact tonometer), and retinal diseases other than DR, such as age-related macular degeneration and retinal vein occlusion. In addition, patients were excluded if they had a history of uveitis, glaucoma, central serous chorioretinopathy, polypoidal choroidal vasculopathy, ocular trauma, and any type of intraocular surgery (including cataract surgery), because these diseases18,23 and intraocular surgeries24–26 may significantly affect choroidal thickness. Moreover, patients were excluded by eyes that had previously received any treatment (including intravitreal or sub-Tenon injections of triamcinolone or anti–vascular endothelial growth factor [anti-VEGF], or focal or grid laser photocoagulation), or with apparent epiretinal membrane or vitreomacular traction. Outside of the exclusion factors, DR patients with type 2 diabetes were initially included, with or without center-involved DME.

The “zero” time point (baseline) defined the day when the first session of PRP began. All included patients had a complete ophthalmic examination, including best-corrected visual acuity (BCVA), slit lamp biomicroscopy, noncontact tonometry, detailed fundus examination with indirect ophthalmoscope, FFA, and a spectral domain–OCT (SD-OCT) scan with an EDI mode. Patients with an SD-OCT scan signal strength < 7 or an unidentifiable sclerochoroidal border were dismissed from the study. Fluorescein fundus angiography was also performed at the last visit (12 weeks) to determine the necessity for additional focal treatment. If needed, additional focal photocoagulation was performed.

Panretinal Photocoagulation
Panretinal photocoagulation was performed as an outpatient procedure in our department. The pupil was dilated with tropicamide phenylephrine eye drops (Santen Pharmaceutical, Osaka, Japan), after which a topical anesthetic (0.04% Benoxil) was administered. A wide-field laser contact lens (Mainster, Ocular, Bellevue, WA, USA) was coupled onto the cornea with an ophthalmic gel, to view the retina and focus the laser onto the area of interest. An ophthalmic gel, to view the retina and focus the laser onto the area of interest. An ocular gel, to view the retina and focus the laser onto the area of interest. An ophthalmic gel, to view the retina and focus the laser onto the area of interest. A topical anesthetic (0.04% Benoxil) was administered. A wide-field laser contact lens (Mainster, Ocular, Bellevue, WA, USA) was coupled onto the cornea with an ophthalmic gel, to view the retina and focus the laser onto the area of interest. A topical anesthetic (0.04% Benoxil) was administered. A wide-field laser contact lens (Mainster, Ocular, Bellevue, WA, USA) was coupled onto the cornea with an ophthalmic gel, to view the retina and focus the laser onto the area of interest. A topical anesthetic (0.04% Benoxil) was administered. A wide-field laser contact lens (Mainster, Ocular, Bellevue, WA, USA) was coupled onto the cornea with an ophthalmic gel, to view the retina and focus the laser onto the area of interest. A topical anesthetic (0.04% Benoxil) was administered. A wide-field laser contact lens (Mainster, Ocular, Bellevue, WA, USA) was coupled onto the cornea with an ophthalmic gel, to view the retina and focus the laser onto the area of interest. A topical anesthetic (0.04% Benoxil) was administered. A wide-field laser contact lens (Mainster, Ocular, Bellevue, WA, USA) was coupled onto the cornea with an ophthalmic gel, to view the retina and focus the laser onto the area of interest. A topical anesthetic (0.04% Benoxil) was administered. A wide-field laser contact lens (Mainster, Ocular, Bellevue, WA, USA) was coupled onto the cornea with an ophthalmic gel, to view the retina and focus the laser onto the area of interest. A topical anesthetic (0.04% Benoxil) was administered. A wide-field laser contact lens (Mainster, Ocular, Bellevue, WA, USA) was coupled onto the cornea with an ophthalmic gel, to view the retina and focus the laser onto the area of interest. A topical anesthetic (0.04% Benoxil) was administered. A wide-field laser contact lens (Mainster, Ocular, Bellevue, WA, USA) was coupled onto the cornea with an ophthalmic gel, to view the retina and focus the laser onto the area of interest. A topical anesthetic (0.04% Benoxil) was administered.

Choroidal Thickness Measurement
All patients underwent EDI-OCT before (baseline) and 1, 4, 8, and 12 weeks after PRP treatment in our department. The choroidal images were obtained by analyzing the EDI-OCT with a Cirrus HD-OCT machine with eye-tracking ability (software version 6.5.0.772, model 4000; Carl Zeiss Meditec, Dublin, CA, USA). The operating principle of the Cirrus HD-OCT has been described elsewhere in detail.28 Two high-definition five-line raster scans with EDI through the fovea (one horizontal and one vertical) were obtained for each eye. Each subfoveal choroidal thickness (SFCT) from the horizontal and vertical line scans was manually measured by using the built-in Cirrus linear measurement tool. The choroidal thickness was determined as the perpendicular distance between the outermost edge of the hyperreflective line of the retinal pigment epithelium (RPE) and the sclerochoroidal border.

Averaged values of the SFCT from the horizontal and vertical sections were recorded as the final measurement results for each eye. Two independent observers performed all measurements (ZWZ and QZ). Their measurements were then averaged for statistical analysis. If the difference in thickness measurements of the two observers exceeded 20% of the mean of the two values, another senior observer checked the measurements and gave a final adjudication.

Patients’ eyes were dilated at each visit to reduce errors. It has been reported that mydriatics have no influence on choroidal thickness.29,30 Patients were examined at the same time of day at each visit, to avoid a significant diurnal variation in choroidal thickness.31,32

Macular Thickness Measurement
The average central macular thickness (CMT) of the central field of the ETDRS grid (1-mm-diameter circle centered at the fovea) was obtained automatically from SD-OCT with a fast macular scan protocol. Center-involved DME was diagnosed by using SD-OCT and defined as a central retinal thickness > 300 μm.33,34

Statistical Analyses
All values of choroidal thickness are expressed as the mean ± standard deviation. Statistical analyses were performed by using SPSS software (version 18.0; SPSS, Chicago, IL, USA). A one-sample Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables before a test of significance. As a result, most continuous variables were normally distributed with the exception of the values of CMT at baseline (P = 0.033) and BCVA at 12 weeks after PRP (P = 0.031). In addition, the data of change in BCVA at all time points after PRP did not conform to the law of normal distribution (P < 0.01).

Choroidal thicknesses after PRP treatment were compared relative to the baseline with repeated-measures analysis of variance (ANOVA) and the Bonferroni post hoc test. Variables from two groups were compared by using Student’s t-test for independent samples. Best-corrected visual acuity was determined by using a logarithmic visual acuity chart and was then converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Correlations were assessed by using Pearson correlation or Spearman rank correlation test according to whether the data were normally distributed. Multiple linear regression using the stepwise method was used to seek factors that could predict the change in BCVA after PRP. The two-tailed Student’s t-test results were considered significant at P < 0.05.
RESULTS

Five participants were dismissed with an unidentifiable sclerorchoroidal border in the OCT image at 1 week post PRP. Finally, the study consisted of 32 participants (19 women, 13 men) with a mean age of 59 ± 11 years (range, 38–72 years; Table 1). A total of 46 eyes were included, comprising 13 eyes (from 11 patients) with center-involved DME (including two eyes with subretinal fluid, four eyes with cystoid macular edema, and seven eyes with just thickened retinas) and 33 eyes (from 26 patients) without center-involved DME. Patients received a mean ± standard deviation of 1340 ± 85 laser spots for PRP. There was no significant difference between eyes with or without center-involved DME in the number of laser spots, with a mean of 1346 ± 75 or 1336 ± 90 in eyes with or without center-involved DME, respectively (P = 0.729). The individual data points for the measures of SFCT (Fig. 1A), CMT (Fig. 1B), and BCVA (Fig. 1C) at all time points are shown in Figure 1.

The mean SFCT of the 46 eyes at baseline was 309 ± 77 μm, increasing to 323 ± 78 μm at 1 week, 315 ± 75 μm at 4 weeks, 299 ± 68 μm at 8 weeks, and 289 ± 71 μm at 12 weeks after PRP (Fig. 2A). ANOVA with the Bonferroni post hoc test showed that SFCT significantly increased from the baseline at 1 week (P = 0.025), subsided to the baseline at 4 and 8 weeks (P = 0.99 and P = 0.149, respectively), and significantly decreased at 12 weeks (P = 0.006).

**TABLE 1.** Demographics and Clinical Data of the Patients

<table>
<thead>
<tr>
<th>Eyes, n</th>
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<tbody>
<tr>
<td>Total</td>
<td>46</td>
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<tr>
<td>With central-involved DME</td>
<td>13</td>
</tr>
<tr>
<td>Without central-involved DME</td>
<td>33</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Sex, female/male</td>
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<tr>
<td>Duration of diabetes mellitus, y</td>
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<tr>
<td>Hemoglobin A1c, %</td>
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<tr>
<td>BCVA, logMAR</td>
<td>0.55 ± 0.38</td>
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</table>

**FIGURE 1.** Scatterplots showing individual data points of subfoveal choroidal thickness (A), central macular thickness (B), and best-corrected visual acuity (C) at all time points.
The mean CMT of 46 eyes at baseline was 294 ± 682 µm and at 1, 4, 8, and 12 weeks post PRP was 344 ± 123 µm, 340 ± 117 µm, 318 ± 100 µm, and 311 ± 96 µm, respectively (Fig. 2B). Repeated-measures ANOVA indicated a statistical difference between the mean CMT at baseline and the mean at all post-PRP times (P < 0.001). The Bonferroni post hoc test revealed that CMT significantly increased from the baseline at 1 week (P < 0.001) and 4 weeks (P < 0.001), and remained higher at 8 weeks (P = 0.041), but subsided to the baseline at 12 weeks (P = 0.254).

The mean preoperative vision at baseline was 0.55 ± 0.38 logMAR, which worsened significantly to 0.62 ± 0.45 logMAR (P = 0.018) at 1 week, to 0.63 ± 0.41 logMAR at 4 weeks (P < 0.0001), and improved back to baseline at 8 weeks (0.58 ± 0.39 logMAR) and 12 weeks (0.52 ± 0.33 logMAR; P = 0.25 and P = 0.99, respectively; Fig. 2C).

Eyes were divided into groups by the presence or absence of central-involved DME, and variables between the two groups were compared (Table 2). For the eyes with central-involved DME, results of the Bonferroni post hoc test indicated that there was a significant increase in CMT only at 1 week (P = 0.041), which subsided to baseline at 4 weeks. For the eyes without central-involved DME, the increase in CMT was significant at each time point (P < 0.001, P = 0.001, and P = 0.003).

Concerning BCVA, the Bonferroni post hoc test revealed that in eyes with DME involving the center of the macula, BCVA worsened significantly from baseline at 4 weeks (P < 0.001) and at 8 weeks (P = 0.032), but returned to the baseline at 12 weeks (P = 0.99). In eyes without central-involved DME, the BCVA worsened significantly from baseline at 4 weeks (P =
Discussion
In this study, we included only patients with severe nonproliferative DR or non-high-risk proliferative DR who needed PRP. Before PRP treatment, the mean baseline SFCT was 308.58 ± 76.72 μm, which was thicker than the SFCT (261.93 ± 88.42 μm) of healthy Chinese subjects with a mean age of 49.73 ± 17.89 years previously reported. We found that a four-session PRP treatment for DR could increase foveal choroidal thickness as early as 1 week. This is in agreement with the study of Cho et al., who have evaluated 21 patients and found that PRP is associated with increases in both SFCT and macular thickness 1 week after completion of three sessions of PRP. In the present study, the SFCT subsided to baseline by 4 and 8 weeks, and decreased significantly at the last visit (12 weeks after PRP). Lee et al. have even reported that the choroidal thickness significantly decreases after two sessions of PRP as early as 1 month after treatments.

The exact mechanisms underlying the early increases in SFCT after PRP are still unknown but we can gain insights from previous studies. First, the increase of SFCT may be due to vasodilation, induced by possible choroidal vascular obstruction from laser photocoagulation. Panretinal photocoagulation induces an increase in both choroidal blood flow and choroidal blood volume, as measured by a laser Doppler flowmetry technique, under the foveal area of patients with severe nonproliferative DR, 1 month after PRP. Laser photocoagulation of rat eyes induces inflammation in the untreated retina, which could increase nitric oxide synthase expression, resulting in the vasodilatation of choroidal vessels.

Secondly, the restriction of choroidal blood flow after PRP could be another important reason why SFCT increased after PRP. Cats with damage to the outer retina, induced by an argon laser, have decreased choroidal blood flow of the choriocapillaris accompanying laser lesions, and this reduction in choroidal blood flow in the peripheral photoacoagulated lesion may redistribute the blood supply and bring about an increase in choroidal circulation in the foveal area.

A third reason why SFCT increased after PRP involves the permeability of the choroidal vessels. Panretinal photocoagulation induces the accumulation of leucocytes in the retina, which increase retinal vascular permeability. This could also happen in the choroid. Photocoagulation causes an increase in VEGF and one of the roles of VEGF is to enhance vascular permeability.

A fourth reason why SFCT increased after PRP may be that choroidal effusion caused by a disruption of the choriocapillaris, induced by laser photocoagulation, could lead to thickening of the subfoveal choroid. Some studies have reported that transudation is induced in 59% to 90% of eyes.
Changes in Choroidal Thickness After PRP for DR

leukocytes in the retina, which may increase retinal vascular permeability. PRP, such as PRP-induced retinal inflammation and edema, to the same mechanisms that underlie the increase in SFCT after laser treatment. Therefore, in eyes with DR treated with intravitreal ranibizumab or bevacizumab injection in conjunction with PRP, the effect of the laser on the macula could be reduced, with a decrease in CMT, whether DME is present or not.52,53 The BCVA of eyes without central-involved DME was already relatively poor at baseline in the present study (0.55 and 0.38 logMAR). However, the opacity of the lens cannot account for this, because patients with severe opacity of the lens were excluded in our study. The poor baseline BCVA may be related to the poor health care given for diabetes mellitus and poor self-management of diabetic patients in China. In 2013, a quarter of the people with diabetes worldwide were in China, where 11.6% of adults had diabetes and 50.1% were prediabetic, many of whom were undiagnosed, untreated, or uncontrolled.50 Consequently, the complications of diabetes mellitus, such as DR, are epidemic in Chinese diabetic patients. Although 33 eyes in the present study did not have central-involved DME, the macular functions of these patients may have been already damaged, as reported by De Benedetto et al.,57 and there was no significant difference in baseline BCVA between eyes with or without central-involved DME (Table 2). The effect of PRP on the BCVA in our study was consistent with previous reports, in which initial transient impaired vision returns to baseline after 3 months or more of follow-up in most patients.47,48 In our study, the BCVA of five eyes (10.87%) was lower than baseline owing to persistent macular edema, and another two of 12 eyes (16.67%) were treated with a combination of anti-VEGF injections and photocoagulation and the SFCT changed significantly between the eyes without central-involved DME and the BCVA at a short and relatively long period after PRP. Moreover, we also found that a higher baseline CMT was significantly associated with greater BCVA worsening in multiple linear regression analysis at 1, 4, and 8 weeks after PRP. Therefore, the baseline CMT might be used to predict the prognosis of visual acuity after PRP within 2 months, but the long-term (3 months or more) visual prognosis of DR patients treated only with PRP might not be predicted from the baseline CMT in the present study. By contrast, the baseline SFCT, or the change in SFCT, was not a good predictor for the prognosis of visual acuity after PRP at all time points. Of note, because of the small sample size in our study, it was not easy to detect reliable, statistically significant results with correlation analysis. In a future study, a relatively large sample size will be needed to explore correlation between variables.

The potential shortcomings of our study were the sample size, which was relatively small, and the follow-up time of 12 weeks, which prevents conclusions regarding longer follow-up. Another limitation was that automated measurement via software is currently not available commercially. Therefore, the choroidal thickness was manually calculated by using the built-in measuring tool. In addition, we only measured the choroidal thickness under the fovea, without evaluating changes in choroidal thickness by location.

In conclusion, our study addressed the influence of PRP on SFCT over a relatively long follow-up period. Subfoveal choroidal thickness was increased significantly from the baseline at 1 week, subsided to the baseline at 4 and 8 weeks, and significantly decreased at 12 weeks. We suggest that PRP may be able to reduce choroidal vascular permeability or cause atrophy of the choroidal vessels within 12 weeks. Our results warrant further evaluation with a longer-term follow-up.
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References


Changes in Choroidal Thickness After PRP for DR


