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RETINAL DISORDERS

Changes in choroidal vascular parameters following pan-retinal photocoagulation using swept-source optical coherence tomography

Jee Taek Kim[1] · Nari Park[1]

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Abstract

Background To assess the effect of pan-retinal photocoagulation (PRP) on choroidal vascular parameters in eyes with advanced diabetic retinopathy (DR).

Methods Forty patients (65 eyes) with severe nonproliferative DR or proliferative DR who underwent PRP were included. Changes in choroidal vascular parameters were assessed at 3, 6, and 12 months after PRP by using swept-source optical coherence tomography (OCT) and OCT angiography and were compared with baseline values.

Results Choroidal vascularity index (CVI) significantly decreased from 66.27% ± 1.55% at baseline to 65.85% ± 1.61%, 65.77% ± 1.29%, and 65.74% ± 1.60% at 3, 6, and 12 months after PRP, respectively. The ratio of luminal area to stromal area (L/S ratio) also significantly decreased from 1.98 ± 0.15 at baseline to 1.94 ± 0.14, 1.95 ± 0.13, and 1.93 ± 0.14 at 3, 6, and 12 months after PRP, respectively. The subfoveal choroidal thickness (SFCT) similarly showed a significant decrease from 319.50 ± 56.64 μm at baseline to 299. 07 ± 51.14 μm, 294.70 ± 58.96 μm, and 280.93 ± 53.57 μm at 3, 6, and 12 months after PRP, respectively. However, the choriocapillaris vessel density in both the fovea and parafovea showed no significant differences following PRP.

Conclusion Eyes with advanced DR showed a significant reduction in CVI, L/S ratio, and SFCT over 12 months after PRP treatment.

Keywords Choroidal vascular index · Diabetic retinopathy · Pan-retinal photocoagulation

Introduction

Diabetic retinopathy (DR) is one of the leading causes of preventable blindness in the working aged population worldwide [1]. The changes in the choroid in eyes with DR were previously investigated by histophathological assessments, indocyanine green angiography, and optical coherence tomography (OCT) [2–5]. The choroid consists of the choriocapillaris, the inner Sattler's layer of medium sized-blood vessels, and the outer Haller's layer of large sized-vessels; these vascular layers are surrounded by stromal tissues, such as the connective tissue and extracellular fluid [6]. Since the visualization of the choroid by using enhanced-depth imaging OCT has become widespread, the choroidal layer in patients with DR has been intensively investigated. Several studies have shown that the choroid is affected by pan-retinal photocoagulation (PRP) treatment, primarily in terms of changes in its thickness [7–9]. Changes in the ratio of the choroidal luminal area to the total choroidal area, which is termed the choroidal vascularity index (CVI), have been recently observed in several chorioretinal diseases [10–12]. Moreover, with the advent of swept-source OCT and OCT angiography (OCTA), deeper and better visualization of the choroid and quantification of choriocapillaris have become possible [13, 14]. However, changes in CVI or choriocapillaris following PRP have not been longitudinally investigated to date. Thus, the purpose of this study was to analyze the changes in choroidal vascular parameters following PRP.

✉ Jee Taek Kim
jeetaek@cau.ac.kr

[1] Department of Ophthalmology, College of Medicine, Chung-Ang University Hospital, 102 Heukseok-ro, Dongjak-gu, Seoul #06974, South Korea

Subjects and methods

Subjects

This retrospective observational study was approved by the institutional review board committee of Chung-Ang University Hospital, Seoul, South Korea, and it adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients before PRP treatment. Patients who underwent PRP for advanced DR (severe nonproliferative DR or proliferative DR) between September 1, 2015 and August 31, 2016 and were followed up for at least 12 months were included. The medical records of these patients were retrospectively reviewed.

The exclusion criteria were as follows: prior PRP treatment or retinal surgery; a history of ocular trauma; any history of other retinal or choroidal disease, such as choroidal neovascularization or pigment epithelial detachment; refractive error more than ±3.0 diopters; and any systemic disease other than diabetes. Eyes with media opacities such as dense cataract or vitreous hemorrhage and eyes with low image quality index (< 90) were also excluded.

Baseline examination

All subjects underwent a comprehensive ophthalmologic evaluation, including measurement of best-corrected visual acuity, intraocular pressure, and refractive error, as well as slit-lamp examination, fundus examination, and swept-source OCT (DRI Triton OCT, Topcon, Tokyo, Japan) and OCTA. Fluorescein angiography was performed to determine the severity of DR using an ultra-wide-field confocal scanning laser ophthalmoscope (Panoramic 200MA™; Optos PLC, Dunfermline, UK). The severity of DR was graded, and the PRP treatment was performed according to the Early Treatment Diabetic Retinopathy Study protocol [15–17].

Pan-retinal photocoagulation

PRP was performed under topical anesthesia with a 532-nm solid-state green diode laser (OcuLight GLx laser; Iridex Corp. Mountain View, CA, USA) and a TransEquator contact lens (VolkOptical Inc., Mentor, OH, USA) by a single retinal specialist (JTK). PRP was peformed from the vascular arcades to the peripheral retina in all eyes in two sessions, one or two weeks apart. The laser power was titrated from 200 mW until a gray-white opacity was achieved. The pulse duration was 200 ms, and the spot size was 300 μm; a 1.5-width spot spacing was used.

Optical coherence tomography

Swept-source OCT was performed using the DRI Triton OCT device (Topcon, Tokyo, Japan), with a wavelength of 1050 nm and a scan speed of 100,000 A-scans per second, which yielded an axial resolution of 7 μm and horizontal resolution of 20 μm. OCT B-scan imaging was performed with a 6 × 6-mm cube-scan and a 9-mm five-line cross-scan. "Follow-up five-Line cross-scan" and "SMARTrack 3D cube-scan" were used to ensure that OCT B-scan imaging was performed at the same location throughout the follow-up period. The central retinal thickness (CRT) was obtained from an automatic thickness map that was created on the basis of the conventional Early Treatment Diabetic Retinopathy Study grid in the 6 × 6-mm cube-scan mode after confirmation of the grid position. The subfoveal choroidal thickness (SFCT) was defined as the distance between the Bruch's membrane and the choroid-sclera interface at the fovea and measured from the 9-mm five-line cross-scan using a built-in caliper tool.

Optical coherence tomography angiography

OCTA imaging was performed at the 3 × 3-mm center of the fovea with a resolution of 320 × 320 pixels from four repeated B-scans using the DRI Triton OCT device.

OCTA images of the choriocapillaris were obtained from the Bruch's membrane to 10.4 μm outside the Bruch's membrane using the automated segmentation algorithm in the DRI Triton OCT software (IMAGEnet 6, software version 1.21; Topcon Corp., Tokyo, Japan). The software provided a color-coded perfusion density map of the OCTA image. The macular area of the choriocapillaris image was divided into five zones by the built-in 2.5-mm ETDRS grid software, and the perfused vessel density of each subfield was measured automatically using the built-in grid software. Foveal vessel density was defined as central subfield perfused vessel density, and parafoveal vessel density was defined as the averaged vessel densities of four parafoveal subfields.

Choroidal vascularity index

Horizontal and vertical OCT images at the fovea center from the five-line cross-scans were selected. Binarization and segmentation of OCT images were performed using the protocol described by Agrawal et al. [11] Binarization of the OCT image was performed using ImageJ software (http://imagej.nih.gov/ij, version 1.80) A representative image for binarization processing to obtain CVI is shown in Fig. 1. The total choroidal area with a width of 1500 μm centered on the fovea was selected using the polygon tool and added to the ROI manager. The image was converted to an 8-bit image

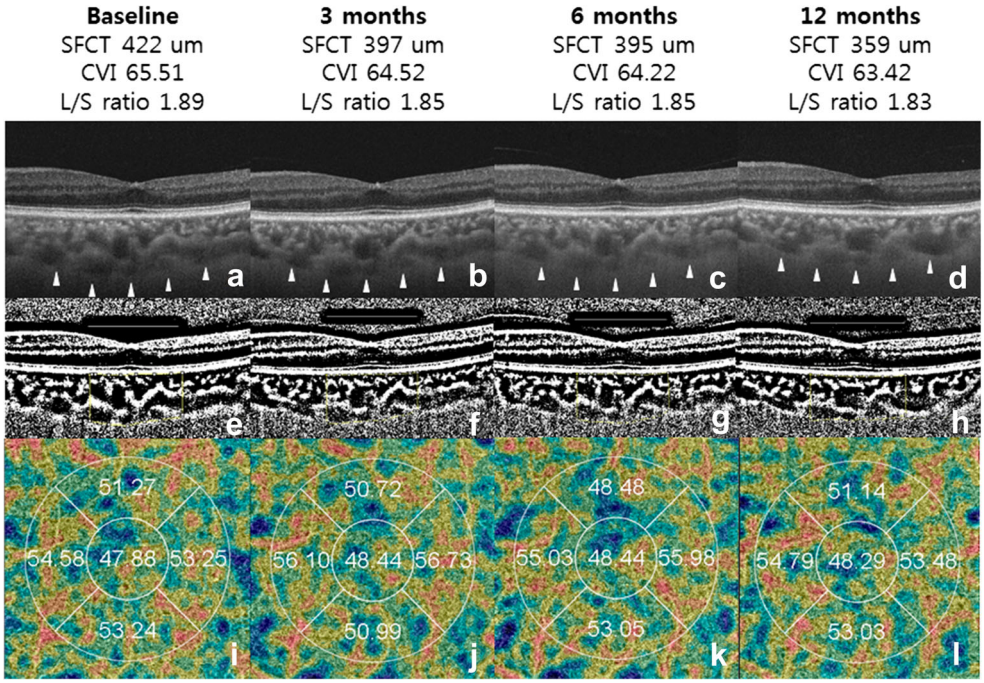

Fig. 1 Representative case with severe nonproliferative diabetic retinopathy that showed a decrease in choroidal vascular parameters following pan-retinal photocoagulation. The upper, middle, and lower rows show a swept-source optical coherence tomography (OCT) B-scan image, a binary image using ImageJ software, and OCT angiography images of the choriocapillaris slab. The subfoveal choroidal thickness decreased from 422 μm at baseline to 359 μm at 12 months after PRP. The choroidal vascularity index decreased from 65.51% at baseline to 63.42% at 12 months. The luminal/stromal ratio was 1.89 at baseline and decreased to 1.83 at 12 months

and adjusted by the Niblack autolocal threshold method. The dark pixels were selected using the color threshold tool, and this area was also added to the ROI manager as a luminal area. The area of the white pixels was defined as the stromal area (SA). CVI was defined as the luminal area/total choroidal area. The ratio of luminal area to stromal area was defined as the luminal/stromal (L/S) ratio.

Laboratory examination

For systemic workup over the follow-up period, the following laboratory assessments were performed before and 12 months after PRP: measurement of hemoglobin A1c and fasting blood sugar levels, postprandial 2-h (PP2) blood glucose and creatinine levels, estimated glomerular filtration rate (eGFR), urine microalbumin level, and microalbumin/creatinine (M/C) ratio in urine. Only laboratory workups performed within 4 weeks from the visit to the retina clinic were investigated.

Statistical analysis

Two independent masked observers (NP, JTK) measured the SFCT, CVI, and L/S ratio, and the averaged values were used for the statistical analysis. The mean values of CRT, SFCT, CVI, and vessel density of the choriocapillaris were analyzed during the 12-month follow-up period. The data are presented as the mean ± standard deviation. Statistical analyses were performed using SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). The changes in CRT, SFCT, CVI, L/S ratio, and vessel density of the choriocapillaris in the fovea and parafovea throughout the follow-up period were analyzed using linear mixed-effects model. The correlations between the changes in vascular parameters 12 months after PRP and the baseline values were analyzed using univariate linear regression. The changes of laboratory profiles were analyzed using paired-t test. A P value <0.05 was considered statistically significant.

Results

Baseline characteristics

Sixty-five eyes (severe nonproliferative DR, $n = 24$; nonproliferative DR, $n = 41$) of 40 patients were included in this study. The mean age of the patients was 57.12 ± 11.33 years (range, 40–88 years), the mean duration of diabetes was 12.5 ± 6.2 years (range, 7–22 years), and the mean value of glycated hemoglobin level was 7.94% ± 2.43% (range, 5.9%–12.5%). The mean best-corrected visual acuity was 0.26 ± 0.29 logMAR (range, 0–1.0 logMAR), the mean intraocular pressure was 14.46 ± 3.43 mmHg (range, 7–20 mmHg), and the mean spherical equivalent was −0.52 ± 1.76 diopters (range, −4.75 to4.25). Demographic data of the patients are presented in Table 1.

The mean power in PRP was 322.3 ± 155.6 mW (range, 200–500 mw), and the total number of photocoagulation burns was 1611.6 ± 167.8. The inter-observer reproducibilities of the SFCT, CVI, L/S ratio ranged from 0.986 to 0.990, 0.988 to 0.992, and 0.984 to 0.990, respectively.

Table 1 Demographic and clinical profiles

	Total	Range
Number of eyes/patients	65/40	
Severe nonproliferative DR/proliferative DR (eyes, n)	24/41	
Age (years)	57.12 ± 11.33	40 to 88
intraocular pressure (mmHg)	14.46 ± 3.43	7 to 20
HbA1c (%)	7.94 ± 2.43	5.9 to 12.5
Hypertension (patients, n)	17	
Visual acuity (logMAR)	0.26 ± 0.29	0 to 1.0
Refractive error (diopter)	−0.52 ± 1.76	−4.75 to 4.25

DR, diabetic retinopathy

Changes in central retinal thickness and subfoveal choroidal thickness following PRP

The CRT was 283.53 ± 106.77 μm at baseline, 307.42 ± 97.07 μm at 3 months, 286.12 ± 84.91 μm at 6 months, and 268.08 ± 54.86 μm at 12 months after PRP (Table 2, Fig. 2 A). The changes were not significant in comparision with the baseline values. The SFCT was 319.50 ± 56.64 μm at baseline and decreased to 299. 07 ± 51.14 μm at 3 months, 294.70 ± 58.96 μm at 6 months, and 280.93 ± 53.57 μm at 12 months after PRP ($P < 0.001$) (Table 2, Fig. 2 B).

Changes in choroidal vascularity index and the ratio of luminal area to stromal area following PRP

The CVI was 66.27% ± 1.55% at baseline and decreased to 65.85% ± 1.61% at 3 months, 65.77% ± 1.29% at 6 months, and 65.74% ± 1.60% at 12 months ($P < 0.001$) after PRP (Table 2, Fig. 2 C). The L/S ratio was 1.98 ± 0.15 at baseline and decreased to 1.94 ± 0.14 at 3 months, 1.95 ± 0.13 at 6 months, and 1.93 ± 0.14 at 12 months ($P < 0.001$) after PRP (Table 2, Fig. 2 D).

Changes in the choriocapillaris vessel density in the fovea and parafovea following PRP

Vessel densities of the choriocapillaris in the fovea and parafovea were 48.58% ± 4.93% and 52.29% ± 1.88% at baseline, respectively. The vessel densities in both the fovea and parafovea did not show statistically significant changes after PRP (Table 2, Fig. 2E, F).

Laboratory examinations

Fasting blood sugar levels before and 12 months after PRP were significantly different. HbA1c level, PP2 blood glucose level, and eGFR decreased 12 months after PRP in comparison with the respective baseline values. Creatinine level, urine microalbumin level, and the microalbumin/creatinine (M/C) ratio in urine also increased 12 months after PRP. However,

Table 2 Changes in the central retinal thickness and choroidal vascular parameters after panretinal photocoagulation

	Baseline	3 months	6 months	12 months	*P* value*	F
Central retinal thickness (μm)	283.53 ± 106.77	307.42 ± 97.07	286.12 ± 84.91	268.08 ± 54.86	0.321	1.262
Δ Central retinal thickness (μm)		19.13 ± 86.16	−5.92 ± 44.70	−15.83 ± 96.10		
Subfoveal choroidal thickness (μm)	319.50 ± 56.64	299.07 ± 51.14	294.70 ± 58.96	280.93 ± 53.57	<0.001*	38.490
Δ Subfoveal choroidal thickness		20.43 ± 19.30	24.80 ± 21.76	38.57 ± 19.92		
Choroidal vascularity index (%)	66.27 ± 1.55	65.85 ± 1.61	65.77 ± 1.29	65.74 ± 1.60	<0.001*	8.088
Δ Choroidal vascularity index (%)		−0.42 ± 0.95	−0.50 ± 0.99	- 0.53 ± 1.05		
Luminal/stromal ratio	1.98 ± 0.15	1.94 ± 0.14	1.95 ± 0.13	1.93 ± 0.14	<0.001*	7.442
Δ Luminal/stromal ratio		0.033 ± 0.101	0.025 ± 0.107	0.021 ± 0.101		
Foveal vessel density	48.58 ± 4.93	48.73 ± 4.45	48.39 ± 3.79	49.33 ± 3.53	0.149	1.880
Δ Foveal vessel density		−0.16 ± 4.96	6.86 ± 16.3	6.04 ± 18.4		
Parafoveal vessel density	52.29 ± 1.88	52.24 ± 1.31	52.29 ± 1.37	52.10 ± 1.53	0.695	0.483
Δ Parafoveal vessel density		0.05 ± 1.71	7.21 ± 18.79	7.37 ± 18.59		

*Linear mixed-effect model

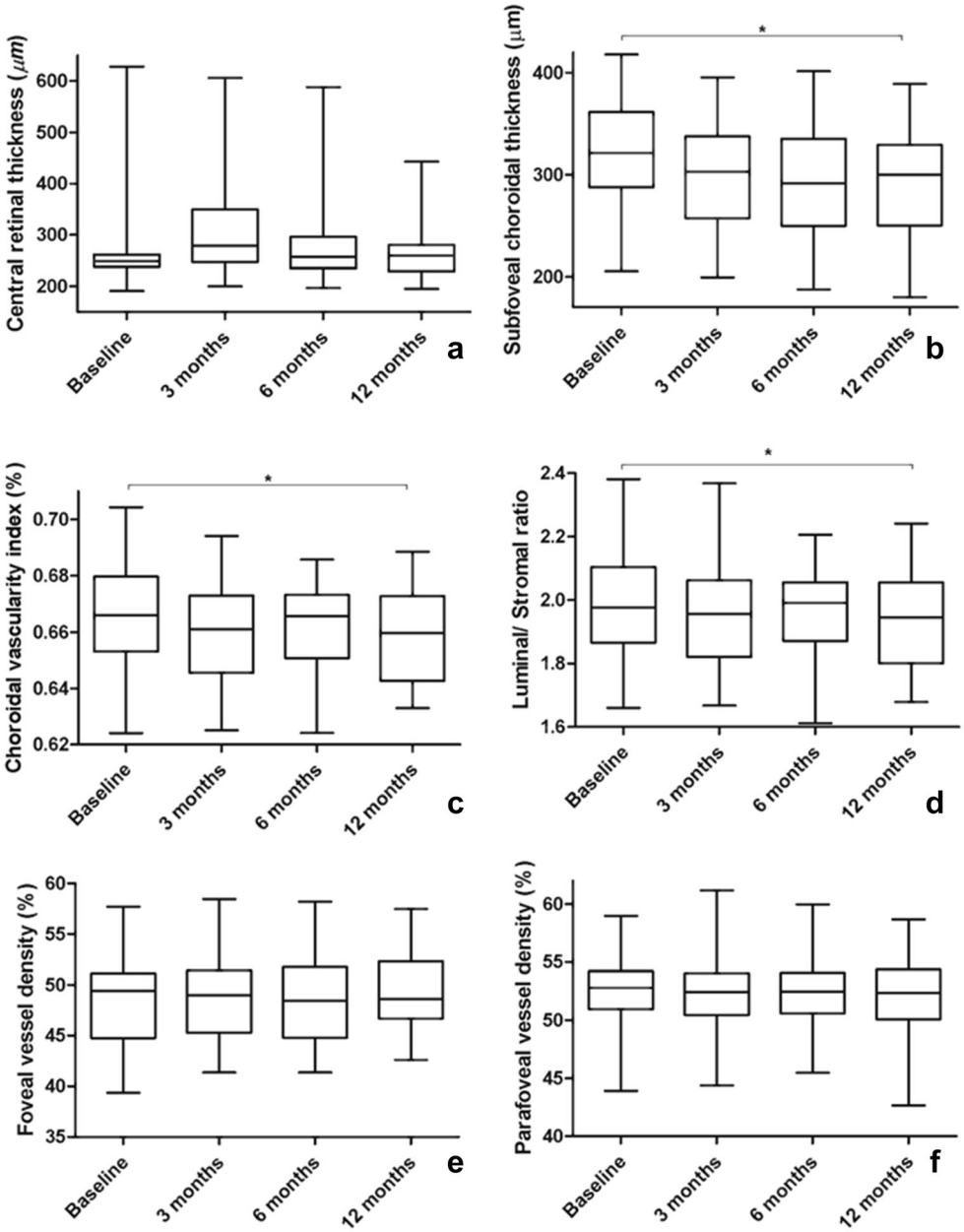

Fig. 2 Comparisons of changes in the central retinal thickness (CRT; A), subfoveal choroidal thickness (SFCT; B), choroidal vascularity index (CVI; C), ratio of luminal area/stromal area (L/S ratio; D), foveal vessel density (E), and parafoveal vessel density (F) over 12 months following panretinal photocoagulation (PRP). *$P < 0.001$. A. CRT showed a minimal increase at 3 months after PRP; however, the increase in the central retinal thickness normalized 6 months after PRP. The changes were not significant. B, C, D. SFCT, CVI, and L/S ratio showed a significant decreasing pattern over 12 months after PRP. E, F. The changes in the foveal and subfoveal vessel density were not significant after PRP

the differences between the values before and 12 months after PRP were not significantly different (Table 3).

Correlation between the changes in vascular parameters 12 months after PRP and baseline values

The changes in central retinal thickness, subfoveal choroidal thickness, and luminal/stromal ratio 12 months after PRP were significantly correlated with baseline parameters ($P < 0.001$; $P < 0.001$; $P = 0.02$, respectively). However, the differences in CVI and choriocapillaris vessel densities in comparison with the baseline values were not significant. Scatter plots of the changes in vascular parameters against baseline values are shown in Fig. 3.

Discussion

Our longitudinal study showed a significant decrease in the SFCT, CVI, and L/S ratio over a 12-month follow-up period after PRP. However, the choriocapillaris in the fovea and parafovea did not show significant changes.

With enhanced-depth imaging OCT, a few studies have shown a significant decrease in the SFCT after PRP [7–9, 18–20]. We observed a significantly thinner choroid in PRP-treated eyes in comparision with treatment-naïve eyes in patients with advanced DR in an earlier study [7]. Our results were consistent with previous studies showing decreased SFCT after PRP [8, 9, 19, 20].

Table 3 Changes in systemic parameters after panretinal photocoagulation

	Number of patients	Baseline	12 months	*P* value
HbA1c	31	7.64 ± 1.84	7.11 ± 1.07	0.091*
FBS	33	161.86 ± 58.72	116.39 ± 34.36	0.003*
PP2	25	197.0 ± 77.64	179.7 ± 51.19	0.37*
Cr	32	1.04 ± 0.52	1.39 ± 1.44	0.151*
eGFR	28	82.53 ± 33.70	78.07 ± 40.71	0.227*
MA	24	198.26 ± 240.94	532.57 ± 808.63	0.198†
MC ratio	25	1366.75 ± 2230.50	1416.54 ± 1983.28	0.363†

Cr = creatinine; eGFR = estimated glomerular filtration rate; FBS = fasting blood glucose; HbA1c = hemoglobin A1c; MA = microalbumin; MC ratio = microalbumin/creatinine ratio of urine;

PP2 = postprandial 2-h blood glucose

*Paired t test; †Wilcoxon rank test for nonparameteric variables

To analyze the effect of PRP on the choroid in detail, we additionally investigated the changes in CVI, L/S ratio, and vessel density of the choriocapillaris. Sonoda et al. described a method for quantification of the luminal area in the choroid (defined as CVI) by using the binary conversion image in OCT B-scans [21]. A few recent studies have reported changes in the CVI of eyes with DR. Tan et al. reported a significantly lower CVI in a patient with diabetes mellitus than in controls [10]. Kim et al. and Gupta et al. also described a significant decrease in CVI with worsening DR [22, 23].

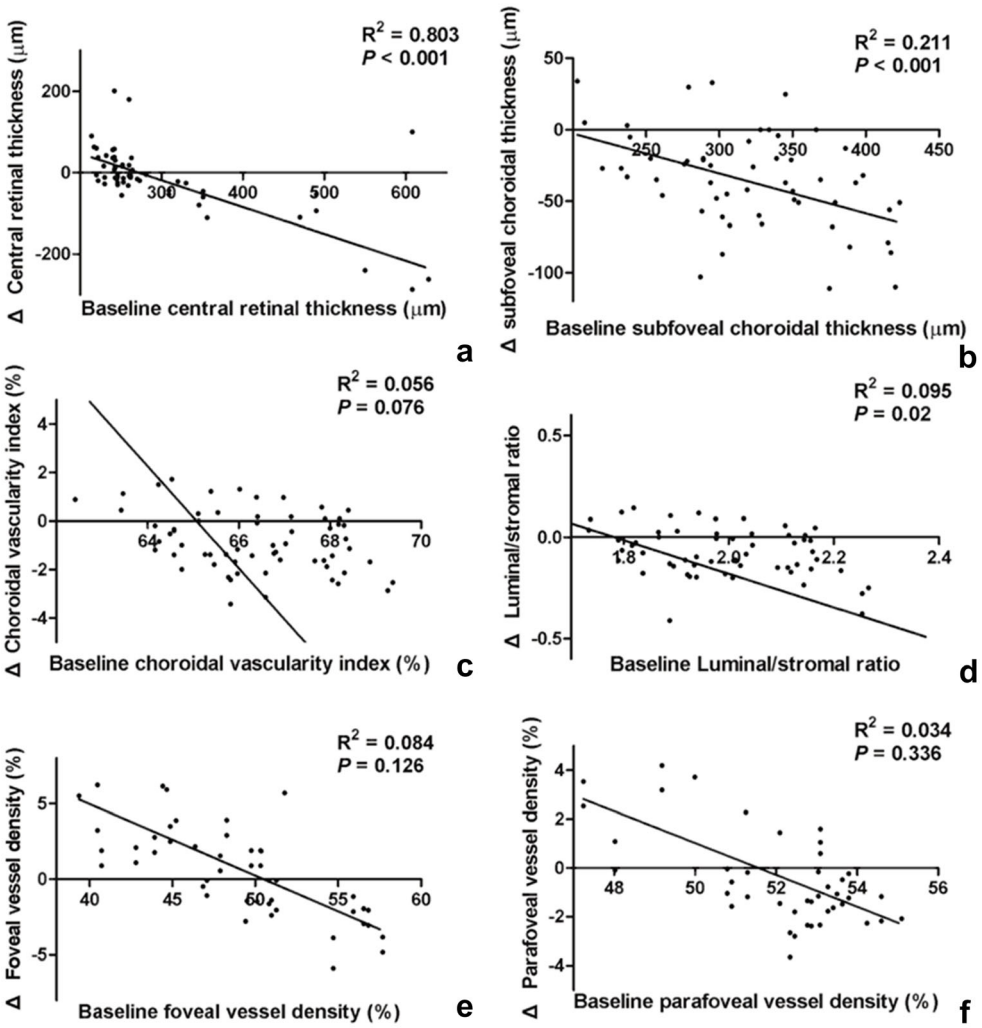

Fig. 3 Univariate association between baseline value and the changes in the central retinal thickness (CRT; A), subfoveal choroidal thickness (SFCT; B), choroidal vascularity index (CVI; C), ratio of luminal area/stromal area (L/S ratio; D), foveal vessel density (E), and parafoveal vessel density (F) 12 months following panretinal photocoagulation (PRP). A, B, D. The changes in CRT, SFCT, and L/S ratio over 12 months after PRP were negatively correlated with the baseline values. C, E, F. The changes in CVI, foveal vessel density, and parafoveal vessel density were not significantly correlated with the baseline value

The changes in both CVI and L/S ratio in our study indicated a significant decreasing tendency throughout the follow-up period after PRP. These findings suggest that the vascular luminal area of the choroid was reduced after PRP. Using laser Doppler velocimetry, Grunwald et al. and Patel et al. had reported reduced blood flow to the retina in DR patients following PRP [24–26]. Similarly, using Doppler OCT, Song et al. described decreased vessel diameter, velocity, and blood flow in the retina after laser treatment [27], while Savage et al. used a pneumotonometer to show decreased choroidal blood flow after PRP [28]. In a recent study, Iwase et al. used laser speckle flowgraphy and enhanced-depth imaging OCT to report that ocular blood flow and choroidal vascular luminal area showed greater reduction in laser-treated eyes than in untreated eyes [29]. Our results showed reduced vascular parameters after PRP, and these findings suggest decreased blood flow to the choroid. In this aspect, the findings of our study are consistent with those of earlier studies.

To investigate the changes in systemic parameters over the follow-up periods, several key profiles associated with diabetes control and diabetic kidney disease were analyzed. The patients tended to show good diabetes control and aggravated chronic kidney disease. The changes, however, were not significant.

With the advent of OCTA, several studies have shown changes in the choriocapillaris in retinal diseases [30–32]. PRP has been performed as a standard treatment for advanced DR [15]. The localized laser treatment directly coagulates both the retinal pigment epithelium and underlying choriocapillaris around the laser burn lesion [33, 34]. However, there have been no studies regarding the indirect effects of PRP on the choriocapillaris of the central fovea. Our study results showed no change of vessel density in both the fovea and parafovea after PRP. Choriocapillaris circulation in the fovea is crucial for supplying nutrients and oxygen to the fovea [6].

This study has several limitations. The first limitation is its retrospective design with a small sample size. Second, diurnal variation was not considered. Diurnal variation has been reported to affect the choroidal vascular parameters, including SFCT, luminal area, and choriocapillaris [35–37]. Third, the changes in systemic factors were not fully considered because of the retrospective design. The effect of systemic health on the choroid has been investigated in several studies [38]. The changes of systemic parameters associated with diabetes, however, were not significant over the follow-up periods in this study. Morever, this study analyzed intrapersonal change; hence, the confounding effects were probably minimal. Fourth the choroidal vascular parameters were analyzed in the 1500-μm posterior pole only. A previous study has shown the influence of the scanning area on CVI [39]. Nevertheless, because the peripheral choroid is affected by PRP ablation, we aimed to analyze the changes in the posterior pole. Fifth, the changes in retinal morphology (e.g., intraretinal edema or hard exudate) could affect the choroidal reflectivity and the analysis results. Thus, this aspect should be considered. Finally, the changes of vascular parameters had high variability of measurement, as shown in Fig. 3. Previously described limitations, including diurnal variation, blood pressure, and systemic status, might be responsible for this inconsistencies in the measurement of vascular parameters. Moreover, the measurement of total choroidal area using the polygon tool is subjective. Lining, along with the choroid-sclera interface, are subject to modification according to the quality of OCT B-scan images. We believe that this subjectivity might cause measurement variability of the vascular parameters. Especially, the vessel density changes of the fovea and parafovea showed higher variability compared with other vascular parameters. Although the eyes with low-quality OCTA images were excluded, the presence of several image artifacts might potentially affect variability. The limitations of this study will be addressed in future studies. Despite these limitations, this is the first longitudinal study to compare the effect of PRP on choroidal vascular parameters.

In conclusion, SFCT, CVI, and L/S ratio reduced significantly after PRP during the 12-month follow-up period, whereas the choriocapillaris in both the fovea and parafovea show no change during the same follow-up period.

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Compliance with ethical standards

Conflict of interest Author JT Kim declares that he has no conflict of interest. Author N Park declares that she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Chung-Ang University Hospital, Seoul, South Korea and with the 1964 Helsinki declaration.

Informed consent Informed consent was obtained from all individual participants included in the study.

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