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# Panretinal laser photocoagulation decreases large foveal avascular zone area in non-proliferative diabetic retinopathy: A prospective OCTA study☆,☆☆

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ABSTRACT

*Purpose:* To analyze the macular microvascular changes after panretinal photocoagulation (PRP) in patients with non-proliferative diabetic retinopathy (NPDR) and a large foveal avascular zone area, using optical coherence tomography angiography.

*Methods:* Twenty-four eyes of 24 patients with peripheral ischemia, superficial foveal avascular zone (FAZ) area of larger than 0.350 $mm^2$, naive severe NPDR, and no clinically significant diabetic macular edema were included in this prospective study. The PRP was applied in 360-degree in a single session. The main outcome measures of the study were the difference in best-corrected visual acuity, central macular thickness, superficial and deep vascular plexus vessel densities, FAZ features, choroidal and outer retinal flow areas at the baseline versus at one and six months after PRP treatment.

*Results:* The study group consisted of 13 men and 11 women with a mean age of 68.11 ± 6.47 years. The baseline FAZ area was higher than at one and six months after PRP (0.416 ± 0.70, 0.399 ± 0.065 and 0.407 ± 0.066 $mm^2$; p = 0.001 and p = 0.002, respectively). At one month after PRP, deep capillary plexus vascular density in perifoveal region was statistically significantly lower than at six months after PRP and the baseline. (45.43 ± 4.27, 47.91 ± 4.26 and 49.04 ± 5.64 %; p = 0.001 and p = 0.001, respectively).

*Conclusion:* The PRP effects retinal microvascular morphology in patients with NPDR and a large FAZ area.

## 1. Introduction

Diabetes mellitus (DM) is a worldwide chronic disease that causes microvasculopathy complications and diabetic retinopathy (DRP) related blindness, due to poor glycemic control [1,2]. Early diagnosis and treatment of DRP are the turning point for healthcare system as well as the patient [3]. Laser photocoagulation (LPC) is a game-changer treatment tool for the prevention of retinal ischemia in DRP and other retinal occlusive vascular events [4,5]. The mechanism of action of panretinal photocoagulation (PRP) is suppression of vascular endothelial growth factor (VEGF) production via destruction of ischemic and active photoreceptor cells. In untreated ischemic retinopathies, the disease progresses into a proliferative stage, and neovascular glaucoma is also triggered in the future [6]. For this reason, routine examination of retina with fundus fluorescein angiography (FFA) for ischemia, and when ischemia is detected, LPC of the peripheral and ischemic regions are the milestone of the treatment [7]. Although the PRP reduces the VEGF level of the posterior pole and is performed for therapeutic

*Abbreviations:* PRP, Panretinal photocoagulation; OCTA, Optical coherence tomography angiography; CSDME, Clinically-significant diabetic macular edema; BCVA, Best-corrected visual acuity; CMT, Central macular thickness; FAZ, Foveal avascular zone; PERIM, Foveal avascular zone perimeter; FD-300, vessel density in a 300μm wide region around foveal avascular zone; OCT, Optical coherence tomography; DM, Diabetes mellitus; DRP, Diabetic retinopathy; LPC, Laser photocoagulation; VEGF, Vascular endothelial growth factor; FFA, Fundus fluorescein angiography; NPDR, Non-proliferative diabetic retinopathy; PDR, Proliferative diabetic retinopathy.

☆ The study was conducted at the Department of Ophthalmology, Afyonkarahisar Health Sciences University, Merkez, Afyon, Turkey.☆☆ This research was presented as oral presentation (free paper) in EURETINA 2020 virtual congress.

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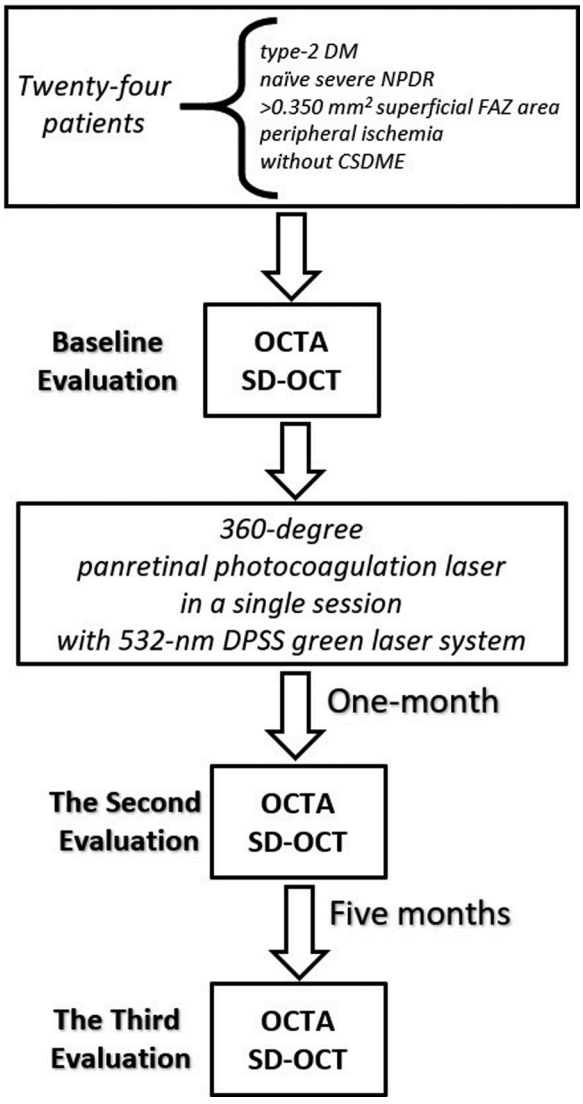


**Fig. 1.** The flow chart of the study design. (DM: Diabetes mellitus, NPDR: Non-proliferative diabetic retinopathy, CSDME: Clinically significant diabetic macular edema, FFA: Fundus fluorescein angiography, OCTA: Optical coherence tomography angiography and SD−OCT: Spectral domain-optical coherence tomography, DPSS: Diode-pumped solid-state).

purposes, it causes various reversible and irreversible retinal changes [8–10]

Non-invasive three-dimensional optical coherence tomography angiography (OCTA) technology enables qualitative and high-speed morphological imaging of the vascular system at the retinal and choroid levels without the use of any dye [11,12]. With this technology, superficial and deep vascular plexus microvascular density, foveal avascular zone (FAZ) features, choriocapillaris flow areas can be measured quantitatively. Thus, the possible microvascular morphological effects of PRP on the macular region could be evaluated [13].

In this study, we aimed to investigate the macular microvascular morphological effects of PRP in patients with non-proliferative diabetic retinopathy (NPDR) and a large foveal avascular zone area using optical coherence tomography angiography (OCTA).

## 2. Materials and methods

Twenty-four eyes of 24 patients were included in this prospective study. The whole procedure was performed following the tenets of the Declaration of Helsinki. An institutional review board approval was obtained from the local ethics committee (2011-KAEK-2) (Approval code: 20.09.2019/10–283). Informed signed consent was obtained from whole patients.

### 2.1. Study design

The flow chart of the study design is shown in Fig. 1. All of twenty-four consecutive patients included in the study had bilateral naive severe NPDR, superficial FAZ area of $> 0.350$ mm$^2$, peripheral ischemia and no clinically-significant diabetic macular edema (CSDME). After pharmacological dilation of the pupil, a 532-nm diode-pumped solid-state (DPSS) green laser (Ellex® Laserex Integre 532, Adelaide, Australia) (Supplementary Material 1) was applied with the appropriate settings to obtain a mild grey-white burn. Focusing on the whole area of ischemia detected using FFA (Spectralis, Heidelberg Engineering, Inc., Heidelberg, Germany), a 360-degree laser treatment was applied to retina from the equator to the middle periphery in a single session. Severe NPDR was regarded as with the 4−2-1 rule in fundus examination: 20 or more dot-blot hemorrhages in each of all *four* quadrants, definite venous beading in *two* or more quadrants and prominent intraretinal microvascular abnormality (IRMA) in *one* or more quadrants.[1] The following inclusion criteria were applied: 1) Diagnosed with severe NPDR, 2) Observing peripheral ischemia on FFA, 3) Superficial FAZ area of $> 0.350$ mm$^2$, 4) No history of previous treatment (any type of injection or laser) due to DRP, 5) Using only oral metformin for the treatment of type-2 DM and 6) $19 <$ Axial length (mm) $< 23$. The exclusion criteria included: 1) Opacity on the cornea or lens in the anterior segment that prevents OCTA imaging, 2) Having a retinal disease other than severe NPDR, 3) Having a history of undergoing posterior segment surgery, 4) Having a diagnosis of systemic disease other than type-2 DM, 5) Using insulin or a history of insulin use and 6) Spherical error more than 2.00 D.

The main outcome measures of the study were the difference in best-corrected visual acuity (BCVA), central macular thickness (CMT) using spectral-domain optical coherence tomography (SD−OCT, Spectralis, Heidelberg Engineering, Inc., Heidelberg, Germany), whole, foveal, parafoveal and perifoveal regions of superficial and deep vascular plexus vessel density, the FAZ area, the FAZ perimeter (PERIM), vessel density in a 300 μm wide region around the FAZ (FD-300), choroidal and outer retinal flow area using OCTA at the baseline versus at one and six months after PRP treatment.

### 2.2. OCTA measurements

OCTA images were obtained using the RTVue XR Avanti AngioVue OCTA (version 2018.0.0.18, Optovue, Fremont, CA). Central macular scanning images (6 × 6 mm) were acquired using the AngioVue Imaging System Optovue RTVue XR 100 Avanti with software. OCTA measurements were performed according to the Early Treatment Diabetic Retinopathy Study grid, containing three concentric rings with diameters of 1, 3 and 6 mm to divide the macula into foveal, parafoveal and perifoveal regions. The outer retinal and choroidal flow area of the 2.97 mm central macular circle diameter was determined using flow circle mode in OCTA. The FAZ area, PERIM, and FD-300 were also obtained using the FAZ mode in OCTA. To ensure accurate segmentation and sufficient image quality, all scan images were made with a quality index of $\geq 7/10$. Poor-quality scans were excluded from the study. OCTA and OCT analyses were performed in follow-up mode to minimize the errors between consecutive analyzes. The axial length measurement was performed with the optical biometer (AL-Scan, Nidek CO., Gamagori, Japan). The measurements were performed before the laser application (baseline), one and six months after than, and then compared statistically with each other. All scans were performed by the same researcher at the same time of the day (between 9:00 A.M. and 11:00 A.M.) after at least 8 -hs starvation period to avoid diurnal fluctuations.

**Table 1**
Demographics of the study group.

| | *Study group (n:24)* |
|---|---|
| *Age (year)* | 68.11 ± 6.47 |
| *Male:female ratio* | 13:11 |
| *Disease duration (years) (mean ± SD)* | 12.45 ± 4.10 |
| *BMI (kg/m$^2$) (mean ± SD)* | 29.53 ± 3.17 |
| *Axial length (mm) (mean ± SD)* | 22.09 ± 1.31 |
| *HbA1c (%) (mean ± SD)* | 7.13 ± 0.94 |

BMI: Body mass index.

### 2.3. Statistical analysis

Statistical analysis was performed using SPSS software, version 22.0 (IBM SPSS, Chicago, IL, USA). Descriptive statistical methods (mean, standard deviation) were used in the evaluation of the data. The categorical variables were analyzed using the chi-square test. Normality distribution of all parameters was analyzed by the Shapiro-Wilk test. The difference in abnormal distribution parameters was evaluated for significance using the Friedman test for three consecutive measurements. If a significant difference was detected, the binary consecutive differences between values were analyzed by the Wilcoxon signed-ranks test. Also, the Spearman correlation tests were used to determine the correlation among parameters. The evaluations were made at the 95 % confidence interval, and the p-values of less than 0.05 were regarded as a statistically significant difference.

## 3. Results

The study group consisted of 13 men and 11 women with an average age of 68.11 ± 6.47 years. All patients had type-2 diabetes mellitus and were taking 1.000 mg/day oral metformin for diabetic regulation. The HbA1c (%) was 7.13 ± 0.94 at the baseline, 7.08 ± 0.78 in one month after the PRP and 7.12 ± 0.54 in six months after the PRP (p = 0.831). The demographic data of the study group are shown in Table 1. Severe NPDR findings were found in both eyes of the patients. Five patients had phakic left eyes. Only the right eyes were included to ensure randomization and follow-up. All included eyes were pseudophakic. The patient, who had a history of the recent cataract surgery, had been operated approximately six months ago. The BCVA was 0.105 ± 0.073 at the baseline, 0.095 ± 0.086 in one month after the PRP and 0.097 ± 0.081 LogMAR in six months after the PRP (p = 0.368). The laser treatment was performed with 404.22 ± 85.16 mW, 433.85 ± 150.62 pulses count, 200 μm spot size and 150 ms pulse duration. The laser was not applied to the macular region. No complication was observed in the laser treatment.

The results obtained from the study group are summarized in Table 2. The mean OCTA image quality index of the patients was 8.37 ± 0.49 at the baseline, 8.29 ± 0.46 in one month after the PRP and 8.41 ± 0.50 in six months after the PRP (p = 0.459). The sample image obtained by OCTA as en-face and B-scan is shown in Fig. 2. The baseline FAZ area was statistically significantly higher than at one and six months after PRP (0.416 ± 0.70, 0.399 ± 0.065 and 0.407 ± 0.066 mm$^2$; p = 0.001 and p = 0.002, respectively) (Fig. 3). At one month after PRP, deep capillary plexus vascular density in perifoveal region was statistically

**Table 2**
Results and comparison of the baseline and post-PRP measurements (PRP: Panretinal photocoagulation).

| Parameters | Baseline | One month after PRP | Six months after PRP | p* | |
|---|---|---|---|---|---|
| BCVA (LogMAR) | 0.105 ± 0.073<br>(0.100, 0.025–0.200) | 0.095 ± 0.086<br>(0.100, 0.000–0.175) | 0.097 ± 0.081<br>(0.100, 0.000–0.175) | 0.368 | |
| Superficial whole vascular density (%) | 47.15 ± 4.52<br>(47.05, 42.90–52.18) | 45.95 ± 4.24<br>(46.70, 43.35–49.95) | 46.82 ± 4.49<br>(46.60, 42.90–51.02) | 0.227 | |
| Superficial foveal vascular density (%) | 15.59 ± 5.04<br>(14.25, 11.33–20.80) | 16.95 ± 4.91<br>(15.25, 13.15–22.13) | 15.97 ± 4.72<br>(14.90, 12.60–20.80) | 0.254 | |
| Superficial parafoveal vascular density (%) | 47.80 ± 4.37<br>(47.50, 43.35–52.45) | 45.92 ± 5.46<br>(48.70, 40.63–50.23) | 46.59 ± 4.53<br>(48.70, 42.13–50.23) | 0.137 | |
| Superficial perifoveal vascular density (%) | 47.38 ± 4.95<br>(47.70, 42.45–52.60) | 45.71 ± 4.49<br>(47.35, 41.45–49.23) | 46.17 ± 4.15<br>(47.35, 42.50–49.48) | 0.204 | |
| Deep whole vascular density (%) | 49.10 ± 4.81<br>(50.30, 43.55–52.60) | 47.69 ± 5.12<br>(49.35, 42.93–52.00) | 48.06 ± 4.84<br>(49.35, 44.35–52.20) | 0.165 | |
| Deep foveal vascular density (%) | 29.01 ± 6.41<br>(29.15, 23.00–35.50) | 28.65 ± 4.00<br>(28.35, 24.33–32.40) | 28.90 ± 4.05<br>(29.35, 24.33–32.60) | 0.196 | |
| Deep parafoveal vascular density (%) | 53.78 ± 2.65<br>(54.05, 51.93–56.40) | 52.36 ± 2.53<br>(52.50, 50.23–54.18) | 52.53 ± 2.56<br>(52.50, 50.23–54.18) | 0.564 | |
| Deep perifoveal vascular density (%) | 49.04 ± 5.64<br>(50.25, 43.13–53.38) | 45.43 ± 4.27<br>(44.70, 42.83–49.98) | 47.91 ± 4.26<br>(48.60, 44.60–50.50) | 0.001 | p1: **0.001**<br>p2: 0.109<br>p3: **0.001** |
| FAZ (mm$^2$) | 0.416 ± 0.70<br>(0.396, 0.366–0.481) | 0.399 ± 0.065<br>(0.374, 0.358–0.459) | 0.407 ± 0.066<br>(0.374, 0.359–0.459) | 0.002 | p1: **0.001**<br>p2: **0.002**<br>p3: **0.004** |
| PERIM (mm) | 2.44 ± 0.37<br>(2.34, 2.10–2.80) | 2.41 ± 0.30<br>(2.29, 2.23–2.58) | 2.42 ± 0.31<br>(2.30, 2.25–2.58) | 0.815 | |
| FD-300 (%) | 51.68 ± 2.56<br>(50.78, 50.53–52.13) | 51.60 ± 4.05<br>(50.68, 48.19–55.96) | 51.74 ± 3.78<br>(50.68, 48.62–54.57) | 0.417 | |
| Outer retinal flow (%) | 8.19 ± 3.51<br>(7.08, 6.21–9.73) | 8.34 ± 3.19<br>(7.05, 5.45–11.21) | 8.25 ± 3.06<br>(7.06, 6.19–10.76) | 0.502 | |
| Choriocapillaris flow (%) | 18.77 ± 1.11<br>(18.87, 17.84–19.44) | 18.58 ± 1.50<br>(19.02, 16.83–19.60) | 18.62 ± 1.38<br>(19.02, 17.57–19.42) | 0.168 | |
| CMT (μm) | 265.25 ± 9.47<br>(260.50, 258.25–275.25) | 265.13 ± 9.53<br>(262.00, 256.00–273.25) | 265.50 ± 9.46<br>(261.50, 259.00–273.75) | 0.637 | |
| HbA1c (%) | 7.13 ± 0.94<br>(7.1, 7–7.4) | 7.08 ± 0.78<br>(7, 7–7.75) | 7.12 ± 0.54<br>(7, 7–7.5) | 0.831 | |

Mean ± standard deviation with median, 25th and 75th percentiles in 95 % confidence interval in parenthesis. p < 0.05 was considered statistically different and stated bold. *:Friedman test results. p1,p2 and p3: Wilcoxon signed-ranks test results. p1:Baseline-One month after PRP, p2: Baseline-Six months after PRP, p3: One month after PRP-Six months after PRP.
PRP: Panretinal photocoagulation, BCVA: Best-corrected visual acuity, FAZ: superficial foveal avascular zone area, PERIM: foveal avascular zone perimeter in mm, FD-300: vessel density 300 μm from the fovea and CMT: Central macular thickness.

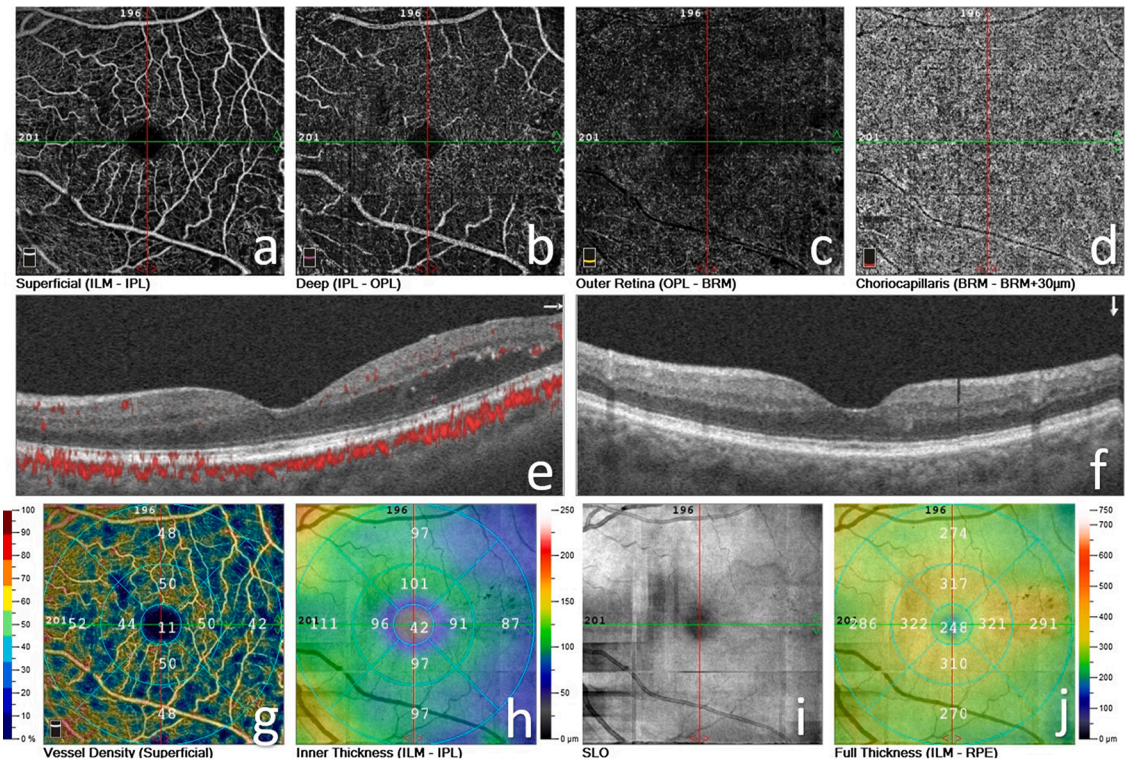


**Fig. 2.** En-face and cross-sectional images obtained by the optical coherence tomography angiography (OCTA) device display (RTVue XR Avanti with the AngioVue, Optovue, Fremont, CA): En-face OCTA images, superficial (a) and deep vascular plexus (b), outer retinal layer (OPL-Bruch membrane [BRM]) (c) and choriocapillaris (BRM-BRM + 30 microns) (d); vascular structures with flow displayed (in red color) in B-scan section (e); B-scan section from the other axis without flow display (f); en-face images, macular superficial vascular plexus density map (g), macular thickness map of inner layers (ILM-IPL) (h), scanning laser ophthalmoscopy (SLO) (i), and full-thickness macular map (ILM-RPE) (j).

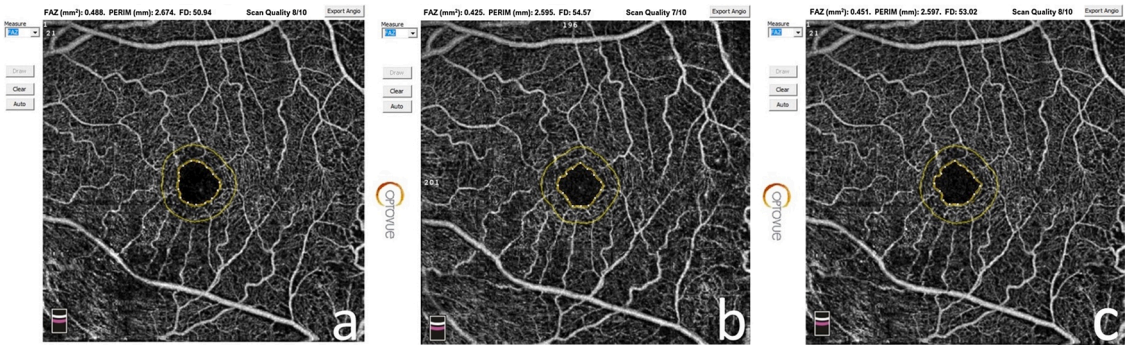

**Fig. 3.** Display of the foveal avascular zone with optical coherence tomography angiography. a) Baseline, b) One month after the PRP and c) Six months after the PRP. Note the decrease in the FAZ area one and six months after PRP. (PRP: Panretinal photocoagulation).

significantly lower than at six months after PRP and the baseline. (45.43 ± 4.27, 47.91 ± 4.26 and 49.04 ± 5.64 %; p = 0.001 and p = 0.001, respectively) (Fig. 4). No significant difference was observed for BCVA, CMT, flow area and other vascular density parameters between consecutive measurements (p > 0.05). No significant correlation was found between the difference in the FAZ area at the end of the sixth month and total laser pulses count, total power, patient age, HbA1c, baseline CMT, and visual acuity (p > 0.05).

## 4. Discussion

In the present study, significant decreases in FAZ area were observed at one and six months after the PRP treatment. In addition, a decrease was observed in vascular density of the deep vascular plexus in perifoveal region at one month after the PRP. There was no significant change in the other vascular density or flow parameters.

Mirshahi et al. [13] showed that foveal vascular density increased and the FAZ area remained unchanged after three months of PRP treatment for diabetic retinopathy in eleven eyes of six patients with very severe NPDR. However, they found that the decrease in the FAZ area; was not statistically significant. In our study, significant decreases were detected in the FAZ area at one and six months after PRP. In diabetic patients, FAZ region is recommended as a marker for screening and monitoring of the treatment, and its enlargement is considered as a poor prognosis [14–17]. The decrease in the FAZ area detected in present study may be an indicator of *ischemia control* achieved by the PRP. The underlying pathophysiology of FAZ enlargement in DRP is most likely related to microinfarction within the surrounding vascular network [15]. In this regard, Freiberg et al. suggested that OCT angiography of FAZ may be useful in identifying early microvascular abnormalities to

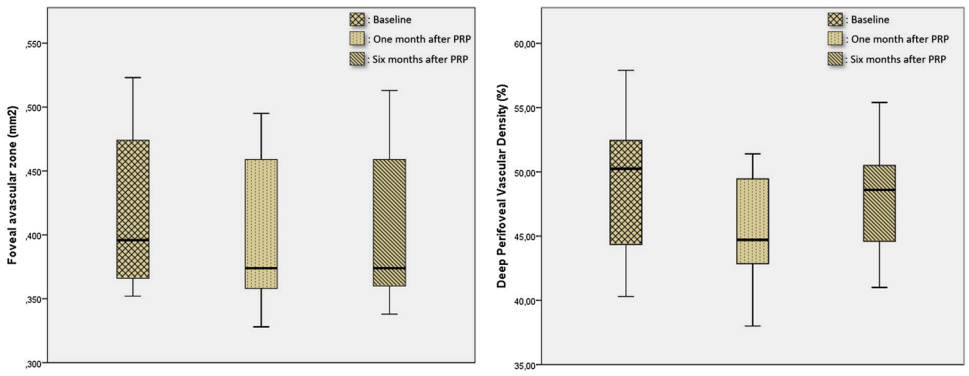


**Fig. 4.** Box-plot distribution graph of the foveal avascular zone area and deep vascular plexus density in perifoveal region at the baseline, one and six months after the PRP. (PRP: Panretinal photocoagulation).

determine the appropriate treatment target for patients based on their risk profile (HbA1c $<$ 48 mmol/mol or $<$ 53 mmol/mol) [15]. The mechanism behind the FAZ enlargement in DRP is associated with capillary closure. Furthermore, Takase et al. reported that early retinal capillary closure was transient, the significant FAZ enlargement in NPDR might be reversible [17]. A decrease in the FAZ area with the PRP treatment in NPDR patients with a large FAZ area in our study may support the situation mentioned by Takase et al. Improved oxygenation and reduction of oxidative stress because of reduction of peripheral ischemia with the PRP treatment may have contributed to this situation [13]. Unlike other studies, a decrease in vascular density seen in the perifoveal region of the deep capillary plexus may be due to laser-related early reversible inflammation or thermal damage to adjacent areas by laser beams, although no laser was applied to the macula [18–20]. The lack of significant difference in vascular density at the end of six months suggested that this occurrence was temporary. Despite these results, Lorusso et al. [21] showed that OCTA parameters were not significantly affected by peripheral laser treatment at short, medium and long-term follow-up. We attribute these different results to the patient group (n $=$ 14) with proliferative diabetic retinopathy (PDR). While there is no neovascularization in NPDR, it is present in PDR, and irreversible effects begin after the neovascular border is crossed [5,6]. Furthermore, the patients in our study (0.416 $\pm$ 0.070 mm$^2$) had a larger pre-laser FAZ area than those of Lorusso et al.'s study (0.33 $\pm$ 0.19 mm$^2$) [21]. Therefore, due to the above-mentioned reasons, the difference may have observed between the FAZ results after the laser applied by Lorusso et al. and ours.

Fawzi et al. [22] showed that an overall increase in the adjusted flow index of superficial, median and deep capillary plexus in the macula following the PRP in patients with PDR, in line with their mathematical model. In our study, only the choriocapillaris and outer retinal flow area were able to be measured, and no difference was detected. However, we think that a decrease we detected in the FAZ area may be compatible with their findings. Increased blood flow may indicate a decreased ischemia.

Soman et al. [23] showed a temporary drop in visual acuity and an increase in central foveal thickness after the PRP. Similarly, it has been reported that developing new macular edema or an increase in existing macular edema may occur following the PRP treatment. [24]. However, Lorusso et al. [21] reported that both foveal and parafoveal macular thicknesses did not significantly change after the PRP. Similarly, in our study, no change in CMT was observed.

Since a large FAZ area may be a sign of severe ischemic change, we performed the PRP treatment in a single session. However, there is no evidence as to whether this condition is recommended. Laser treatment can be applied in a single session, with relatively new laser types (especially using pattern lasers) or conventionally. Nevertheless, the application of treatment with multiple sessions is recommended for pain control, protection from contact lens-induced corneal edema, reducing the risk of choroidal effusion and choroidal detachment [25].

The main strengths of the present pilot study is that it included a cohort of NPDR patients with a larger FAZ area compared to the other studies in which the patients were treated with the PRP. In addition to macular vascular density measurements, choriocapillaris, outer retinal flow, BCVA and CMT were also determined. Samara et al. [26] reported that the average FAZ area of healthy eyes was variable with 0.266 mm$^2$ $\pm$ 0.097 mm$^2$. On the other hand, Takase et al. [17] showed that the average FAZ area was 0.25 $\pm$ 0.06 mm$^2$ in healthy eyes, whereas it was 0.37 $\pm$ 0.07 mm$^2$ in diabetic eyes without retinopathy, and 0.38 $\pm$ 0.11 mm$^2$ in eyes with DRP. Therefore, to include patients with a larger than average FAZ area in our study, the patients with $>$ 0.350 mm were selected for the study. To the best of our knowledge, the present article is the first prospective OCTA pilot study that revealing that the PRP decreases the large FAZ area in patients with severe NPDR. Determining the effect of PRP-induced ischemia reduction on the macular microvascular process may be useful in elucidating and understanding the pathophysiological processes associated with the PRP.

One of the limitations of the present pilot study is that the study was conducted on only a small sample of patients (n $=$ 24) with naive severe NPDR without CSDME. Results may vary in patients with PDR or CSDME. The patients in our study were using only oral metformin for DM treatment, so it is likely that the results may differ in insulin users [27]. In this study, performing conventional PRP laser therapy in a single session may have affected the results. In addition, the formation of secondary macular edema due to LPC may affect the results. However, no new macular edema confirmed with CMT was observed in any of the patients after the PRP in our study. The PRP treatment in intermittent sessions and using other types of lasers, except the conventional method, may change the results. Thus, appropriate further studies are needed.

In conclusion, the present study revealed that the PRP treatment to the peripheral ischemic retina led to changes in microvascular morphology in NPDR patients with a large FAZ area. In our patient group, a statistically significant decrease in the FAZ area was determined at the first and sixth months after the PRP. More studies are needed to investigate the anti-ischemic effects of PRP in different retinal diseases and the FAZ areas.

## Ethics

Institutional review board approval was obtained from the local ethics committee (2011-KAEK-2) (Approval code: 20.09.2019/10–283).

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## Disclosure statement

All authors certify that they have no affiliations with or involvement in any organization with any financial interest or non-financial interest in the subject matter or materials discussed in this article.

## Authorship and contributions

All authors attest that they meet the current ICMJE criteria for authorship. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Declaration of Competing Interest

The authors report no conflict of interest for this research. The authors alone are responsible for the content and writing of this article.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pdpdt.2021.102298.

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