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ORIGINAL ARTICLE

# Effects of subthreshold yellow pattern laser treatment in diabetic macular edema: Optical coherence tomography angiography study

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## Abstract

**Purpose:** The purpose of the study was to assess the effects of subthreshold yellow pattern laser (SYPL) treatment in diabetic macular edema (DME) using optical coherence tomography angiography (OCTA).

**Methods:** Thirty eyes of 30 diabetic patients diagnosed as naïve DME (central subfield thickness [CST] <400 µm) between October 2018 and January 2020 at Ege University Faculty of Medicine, Department of Ophthalmology were prospectively included in the study. Fovea sparing SYPL were performed to the macula. Comprehensive eye examination along with OCTA was performed at baseline, 1st month, and 3rd month of follow-up. Data during the follow-up were compared with the baseline.

**Results:** The mean age of the patients (15 male and 15 female) was 63.7±6.7 (48–74) years. The mean diabetes duration was 17.9±5.4 (13–27) years and mean HbA1c was 6.6±0.5 (5.7–7.7) g/dL. Best-corrected visual acuity (BCVA) did not show significant change during the follow-up (p=0.698). CST measurements were 323.7±40.1 (262–393) µm, 316.8±40.9 (268–377) µm and 318.1±39.9 (226–396) µm at baseline, 1st, and 3rd month, respectively (p=0.591). On OCTA, mean vessel density (VD) in superficial capillary plexus were 44.7±4.6 (37.4–52.3), 45.6±4.7 (38.6–54.9), and 44.6±3.9 (37.5–49.8); while mean VD in deep capillary plexus (DCP) was 43.1±4.8 (36.3–52.7), 45.3±4.8 (38.9–54.2), and 42.7±3.3 (37.4–49.3) at baseline, 1st, and 3rd month, respectively (p=0.383 and p=0.291). Foveal avascular zone area did not change significantly during the follow-up (p=0.998).

**Conclusion:** SYPL treatment in DME appears to be safe with no statistically significant difference in macular capillary perfusion, as well as no change in BCVA and CST during the 3 months of follow-up.

**Keywords:** Deep capillary plexus; diabetic macular edema; optical coherence tomography angiography; subthreshold laser; superficial capillary plexus; yellow patterns laser.

Diabetic macular edema (DME) is the most important cause of visual loss in patients with diabetic retinopathy.[1] DME prevalence is 0–3% in newly diagnosed patients, whereas 28–30% in patients who have diabetes more than 20 years.[2] At present, DME is defined by the presence of intra- and subretinal fluid and increased central subfield thickness (CST) on optical coherence tomography (OCT).[3] Anti-vascular endothelial growth factor (VEGF) agents including ranibizumab and aflibercept are the first-line treatment of DME. However, macular laser treatment also

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displays an important adjuvant therapy given its synergistic effect with anti-VEGF agents and decreased injection numbers. In addition, it may be advantageous due to its long-lasting and persistent effect despite its slower onset of action as compared to anti-VEGF agents.[4] Recently, subthreshold laser strategies have been used in the treatment of DME without causing any damage to retina pigment epithelium (RPE) and photoreceptors.[5,6] Subthreshold laser primarily affects through immunomodulation of RPE function by generating heat-shock proteins, as well as protects oxidant-antioxidant balance.[7,8] Subthreshold laser therapy is accepted as treatment alternative especially in early disease and in DME patients with good visual acuity (VA) and CST <400 μ.[9,10] In clinical practice, subthreshold laser therapy can also be considered in patients with low compliance, whom anti-VEGF agents are contraindicated and/or cannot be afforded. Nevertheless, the efficacy and the side effect profile of subthreshold laser treatment particularly at the vascular level are still yet to be determined. Recently, optical coherence tomography angiography (OCTA) was introduced as non-invasive tool which provides detailed assessment of the retinal and choroidal microcirculations without injection of dye. It utilizes endoluminal flow as an intrinsic contrast to reconstruct the microvascular network of the retina and the choroid.[11] Subthreshold laser therapy might exerts its effect through initial microvascular changes such as improved vessel densities following treatment. In addition, its safety can be determined by demonstrating any possible deterioration in the microcirculation using OCTA in the early period.

The present pilot study aimed to assess the effects of subthreshold yellow pattern laser (SYPL) treatment in patients with DME using OCTA.

## Materials and Methods

The study prospectively included 30 eyes of 30 diabetic patients diagnosed as naïve DME with diabetic retinopathy (both non-proliferative and proliferative types) between October 2018 and January 2020 at Ege University Faculty of Medicine, Department of Ophthalmology, Retina Division. Inclusion criteria were age >18 years, type 2 diabetes mellitus, HbA1c ≤10%, center-involved DME with CST <400 μm and best-corrected VA (BCVA) ≥20/30 (Snellen chart). The previous treatment for DME including macular laser therapy, intravitreal injections, and/or vitrectomy, intraocular surgery and/or Nd:YAG laser therapy history within the past 6 months, glaucoma, media opacities precluding fundus examination, imaging, and/or SYPL therapy, and foveal lesions such as epiretinal membrane, hard exudates or atrophic changes which may affect the treatment response. All patients underwent comprehensive eye examination along with fundus autofluorescence (FAF), optical coherence tomography (OCT), and OCTA imaging at baseline. Then, SYPL therapy was performed using subthreshold yellow 577-nm wavelength pattern laser (Supra Scan, Quantel Medical, Cedex, France) with the Mainster Focal/Grid lens (Ocular Instruments, Bellevue, WA). Following SYPL therapy, complete eye exam, OCT, and OCTA imaging were repeated at the 1st and 3rd month of follow-up; and the data compared with the baseline.

The present pilot study was conducted in agreement with the tenets of Helsinki Declaration. Institutional Ethics Review Board of Ege University Faculty of Medicine approved the study (Approval number: 17-5.1/19). The signed written informed consent for procedures was obtained from each subject. Statistical analysis was performed with SPSS 26.0 (SPSS Inc., Chicago, IL, USA). Friedman test was utilized for the comparison of data from baseline, 1st, and 3rd month. P<0.05 was accepted as statistically significant.

### SYPL Therapy

Initially, a 100 μm diameter test spot with an exposure time of 200 ms was applied in the continuous-wave mode outside the temporal vascular arcade on an area without DME. Following the gradually increase in power and test spots were barely visible, a micropulse mode at 5% duty cycles and 50% the laser power was set. Laser therapy was performed in a 3×3 circular grid pattern mode sparing the foveal center (500 μm).

### OCTA Imaging

AngioVue OCTA (RTVue XR AVANTI; Optovue Inc, Fremont, CA) was used to obtain OCTA images and spectral domain-OCT. The AngioVue OCTA is operated at a rate of 70 000 A-scans/sec with a 840 nm wavelength light source and a bandwidth of 45 nm. Split spectrum amplitude decorrelation angiography technique was used to improve the signal-to-noise ratio, to determine flow and obtain OCTA images (6×6 mm sections centered on the fovea) and en face sections.[12] Layer segmentation (the superficial capillary plexus [SCP], deep capillary plexus [DCP], and the choriocapillaris [CC]) was performed automatically by the built-in software in the instrument. Vessel densities (VD) of SCP and DCP and foveal avascular zone (FAZ) area were determined to represent vascular integrity, thereby capillary perfusion of the macula. Non-flow and the density function of Optovue software analysis was used to measure FAZ and VD, respectively.[13] FAZ shape acircularity was also noted using the acircularity index (AI).[14] Besides, the flow mea-

surement tool of the software was utilized at the CC level to ascertain CC flow area at 3 mm radius, and to record the CC vessel flow density (VFD).

## Results

The mean age of the patients (15 male and 15 female) was 63.7±6.7 (48–74) years. The mean diabetes duration was 17.9±5.4 (13–27) years; mean HbA1c was 6.6±0.5 (5.7–7.7) g/dL. The mean best-corrected visual acuity (BCVA) was 0.2±0.2 (range, 0-0.7) log MAR at baseline; 0.2±0.2 (range, 0–0.7) log MAR and 0.2±0.2 (range, 0–0.7) log MAR at 1st and 3rd month after SYPL treatment, respectively (p=0.698). No FAF signs of treatment were detected at any examination. CST were 323.7±40.1 (262–393) µm at baseline; 316.8±40.9

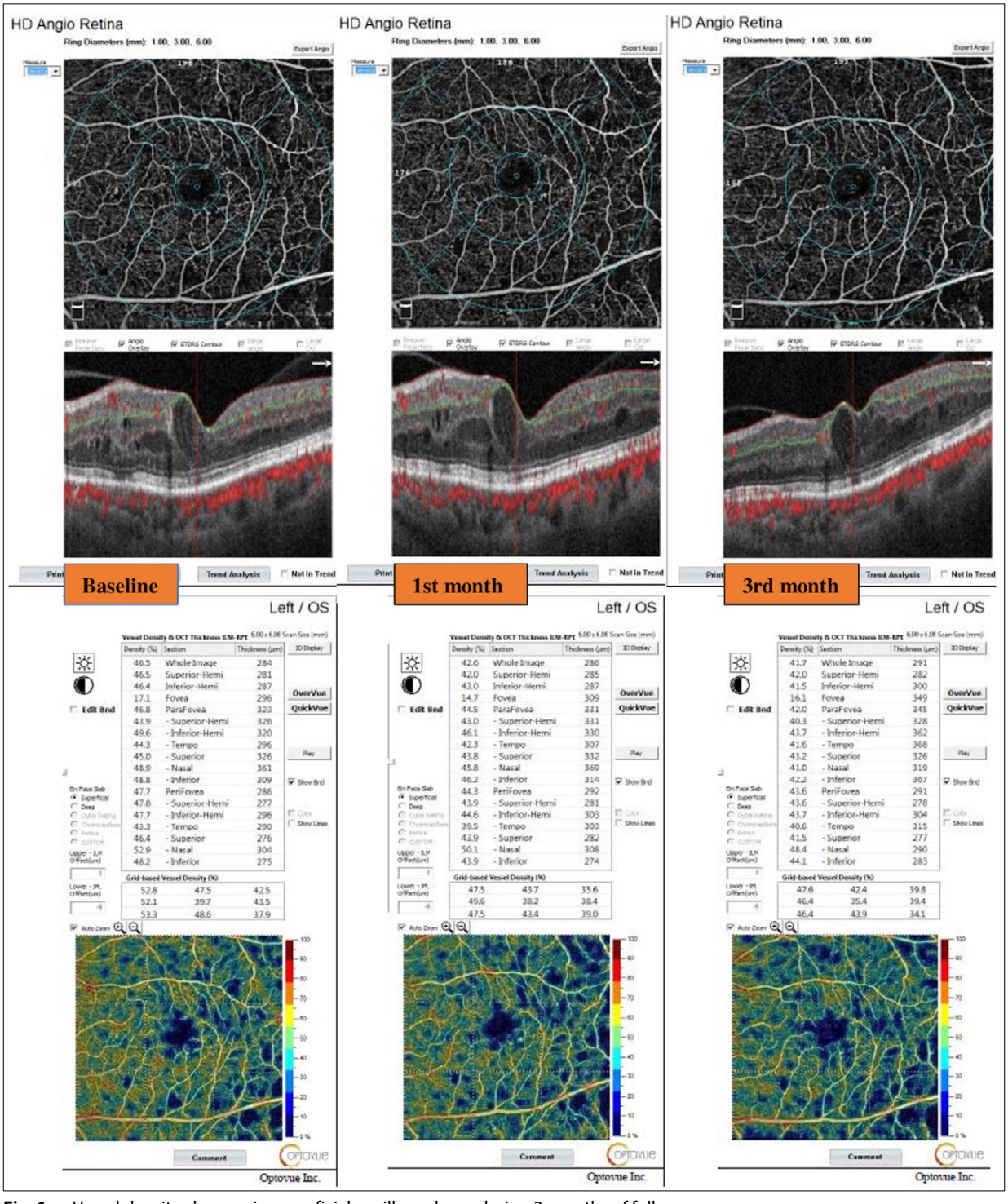


**Fig. 1.** Vessel density changes in superficial capillary plexus during 3-months of follow-up.

(268–377) µm and 318.1±39.9 (226–396) µm at 1st and 3rd month after SYPL treatment, respectively (p=0.591). On OCTA, FAZ area and AI did not change significantly during the follow-up (p=0.998). The mean VD in SCP were 44.7±4.6 (37.4–52.3), 45.6±4.7 (38.6–54.9), and 44.6±3.9 (37.5–49.8); while mean VD in DCP were 43.1±4.8 (36.3–52.7), 45.3±4.8 (38.9–54.2), and 42.7±3.3 (37.4–49.3) at baseline, 1st, and 3rd month, respectively, (p=0.383 and p=0.291, respectively) (Figs. 1 and 2). CC flow area and VFD showed increase from 18.6±1.6 (15.2–20.4) and 65.9±5.6 (53.9–71.9) to 19.3±0.9 (17.5–20.7) and 68.3±3.1 (61.7–73.1), respectively, (p=0.292 and p=0.381, respectively.). Quantitative macular capillary perfusion measurements from OCTA during the follow-up are given in Tables 1 and 2.

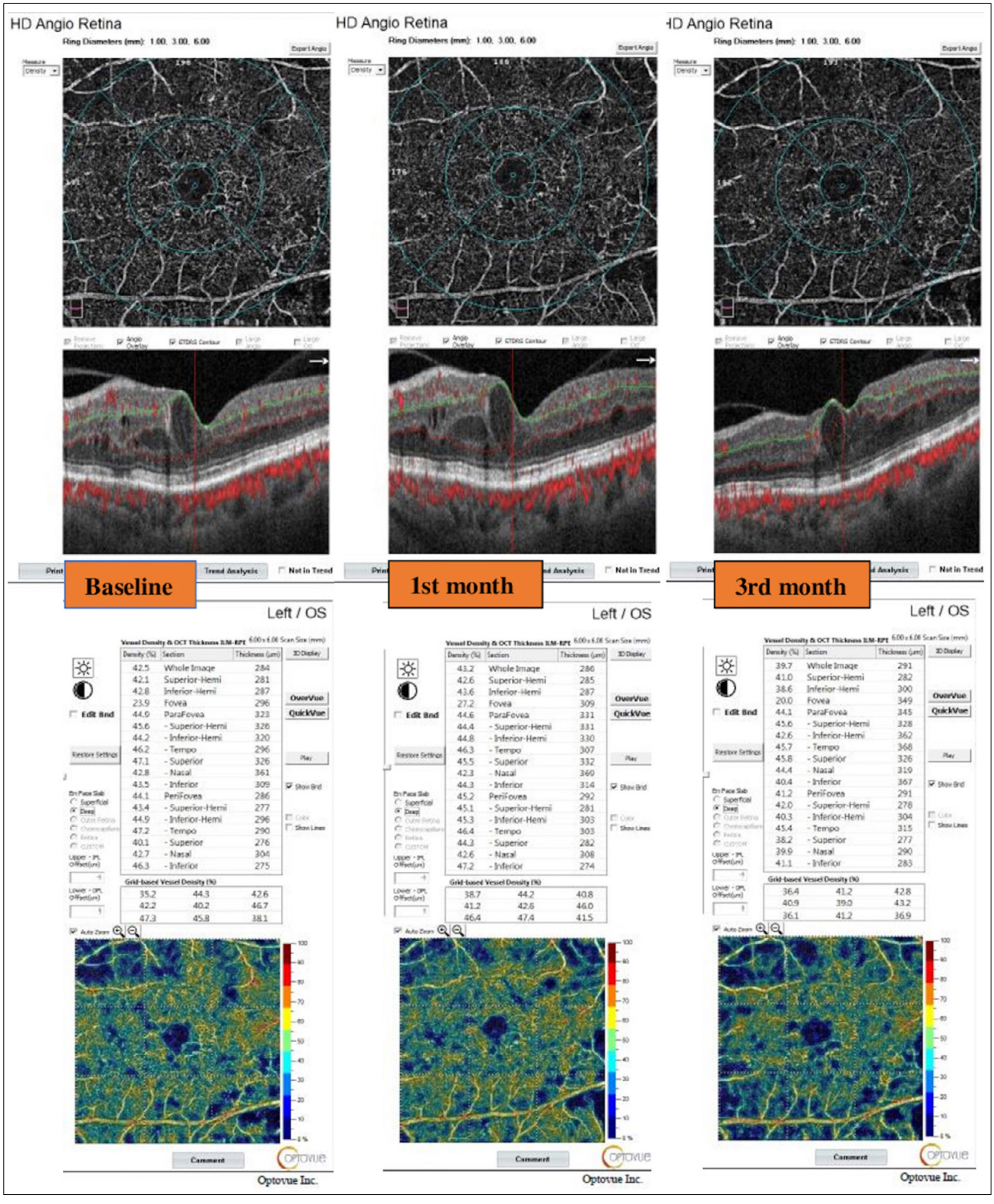


**Fig. 2.** Vessel density changes in deep capillary plexus during 3-months of follow-up.

**Table 1.** Vessel density changes in superficial and deep capillary plexuses using optical coherence tomography angiography

| | Baseline (Before SYPL) (Mean±SD, range) | 1st month (After SYPL) (Mean±SD, range) | 3rd month (After SYPL) (Mean±SD, range) | p-value (Friedman test) |
|---|---|---|---|---|
| VD in SCP (%) | | | | |
| Total | 44.9±4.9 (38.4–52.3) | 44.5±4.4 (38.6–52.4) | 44.6±4.1 (37.5–49.8) | 0.383 |
| Foveal | 19.3±8.0 (10.9–36.6) | 21.6±7.9 (11.2–35.4) | 18.7±5.1 (12.0–31.2) | 0.269 |
| Parafoveal | 44.6±6.1 (31.2–52.7) | 44.5±4.6 (39.6–53.5) | 44.4±5.4 (33.7–53.9) | 0.484 |
| Superior-hemi | 44.5±4.9 (37.0–51.4) | 43.8±4.9 (37.4–51.7) | 44.3±3.8 (37.8–49.2) | 0.662 |
| Inferior-hemi | 45.1±4.9 (38.1–52.8) | 44.8±4.4 (39.1–53.1) | 44.9±4.5 (36.4–50.7) | 0.500 |
| Temporal | 45.3±6.5 (33.4–56.4) | 43.8±5.6 (31.3–51.3) | 44.6±5.4 (32.1–51.8) | 0.545 |
| Superior | 44.7±6.7 (30.8–54.2) | 42.6±7.6 (32.8–54.4) | 44.8±6.8 (31.8–55.7) | 0.397 |
| Nasal | 42.5±7.3 (29.3–53.9) | 44.4±6.4 (33.4–53.8) | 42.1±7.5 (26.2–53.3) | 0.368 |
| Inferior | 46.7±4.6 (39.1–53.5) | 47.2±6.1 (35.0–55.0) | 46.1±5.7 (34.9–54.7) | 0.500 |
| Perifoveal | 45.1±5.2 (36.0–52.4) | 45.0±5.2 (36.5–53.2) | 44.8±4.6 (35.0–50.7) | 0.338 |
| Superior-hemi | 44.5±5.3 (35.6–52.2) | 44.6±5.5 (35.1–52.4) | 44.6±4.3 (35.7–50.0) | 0.920 |
| Inferior-hemi | 45.4±5.1 (36.4–52.6) | 45.4±5.0 (38.0–54.1) | 45.1±5.0 (34.2–51.4) | 0.558 |
| Temporal | 40.7±5.6 (28.5–47.7) | 40.9±4.2 (35.0–47.3) | 39.2±4.5 (30.1–43.9) | 0.338 |
| Superior | 44.2±5.9 (32.8–53.6) | 44.2±6.9 (31.9–53.9) | 43.9±5.3 (32.8–51.4) | 0.640 |
| Nasal | 48.8±4.8 (41.9–57.2) | 49.3±5.3 (38.5–56.9) | 50.6±5.0 (42.2–60.6) | 0.779 |
| Inferior | 46.2±6.0 (37.2–54.8) | 45.8±5.3 (37.2–55.5) | 45.4±5.1 (34.3–53.5) | 0.656 |
| VD in DCP (%) | | | | |
| Total | 43.1±4.8 (36.3–52.7) | 45.3±4.8 (38.9–54.2) | 42.7±3.3 (37.4–49.3) | 0.291 |
| Foveal | 28.2±8.5 (11.8–42.6) | 31.6±8.8 (21.1–52.1) | 27.1±7.3 (12.1–42.6) | 0.239 |
| Parafoveal | 46.3±4.9 (39.7–55.5) | 47.8±4.1 (41.7–56.3) | 46.8±4.1 (38.6–52.7) | 0.168 |
| Superior-hemi | 42.9±5.9 (35.4–52.5) | 45.1±5.4 (35.3–53.5) | 42.3±3.5 (35.7–48.6) | 0.775 |
| Inferior-hemi | 42.9±4.6 (36.6–52.9) | 44.3±5.4 (37.8–55.0) | 42.6±3.8 (36.8–50.0) | 0.199 |
| Temporal | 47.1±7.1 (32.1–55.4) | 47.8±7.4 (30.6–55.9) | 47.9±5.3 (33.6–54.2) | 0.284 |
| Superior | 46.0±5.9 (35.3–55.5) | 47.9±5.3 (38.4–55.5) | 44.7±5.3 (31.4–53.6) | 0.368 |
| Nasal | 45.2±7.0 (30.1–55.6) | 48.6±5.6 (40.0–57.7) | 47.1±4.8 (35.3–52.6) | 0.063 |
| Inferior | 46.8±4.8 (39.3–57.5) | 48.7±5.2 (42.0–57.9) | 47.3±5.3 (37.8–56.8) | 0.116 |
| Perifoveal | 44.7±5.8 (36.4–54.5) | 46.4±5.5 (39.8–55.9) | 43.6±4.3 (36.1–51.1) | 0.368 |
| Superior-hemi | 44.8±6.1 (34.1–54.1) | 47.4±5.3 (41.2–55.4) | 43.9±4.6 (35.8–50.3) | 0.138 |
| Inferior-hemi | 44.6±5.6 (35.6–54.5) | 45.5±6.3 (38.1–56.3) | 43.3±4.6 (36.0–51.9) | 0.174 |
| Temporal | 45.9±6.4 (34.8–57.8) | 47.1±5.9 (36.8–59.5) | 45.1±4.7 (36.6–54.3) | 0.558 |
| Superior | 44.5±6.7 (31.7–53.3) | 46.6±5.9 (39.7–55.2) | 42.2±4.7 (34.6–48.6) | 0.205 |
| Nasal | 44.8±6.3 (34.3–55.1) | 46.1±7.2 (35.6–56.9) | 44.6±5.2 (36.3–53.2) | 0.517 |
| Inferior | 43.8±5.8 (36.9–54.8) | 46.0±5.5 (39.9–55.9) | 42.4±5.2 (31.4–52.6) | 0.174 |

SYPL: Subthreshold yellow pattern laser; SD: Standard deviation; VD: Vessel density; SCP: Superficial capillary plexus; DCP: Deep capillary plexus.

**Table 2.** Foveal avascular area, acircularity index, choriocapillaris flow area, and vessel flow density measurements using optical coherence tomography angiography

| | Baseline (Prior to SYPL) (Mean±SD, range) | 1st month (After SYPL) (Mean±SD, range) | 3rd month (After SYPL) (Mean±SD, range) | p-value (Friedman test) |
|---|---|---|---|---|
| FAZ ($mm^2$) | 0.33±0.12 (0.14–0.59) | 0.32±0.10 (0.13–0.50) | 0.33±0.09 (0.14–0.44) | 0.998 |
| Acircularity Index | 1.18±0.08 (1.10–1.41) | 1.15±0.06 (1.07–1.28) | 1.15±0.05 (1.08–1.23) | 0.144 |
| CC flow area ($mm^2$) | | | | |
| 3 mm | 18.63±1.59 (15.24–20.36) | 19.01±1.08 (16.34–20.43) | 19.33±0.86 (17.46–20.68) | 0.292 |
| CC VFD (%) | 65.9±5.6 (53.9–71.9) | 67.2±3.8 (57.8–72.2) | 68.3±3.1 (61.7–73.1) | 0.381 |

FAZ: Foveal avascular zone; SYPL: Subthreshold yellow pattern laser; SD: Standard deviation; CC: Choriocapillaris; VFD: Vessel flow density.

## Discussion

The present study prospectively evaluated the short-term effects of SYPL therapy in DME treatment using OCTA. The results indicated no significant change in BCVA and CST, as well as in FAZ area, VD at the level of SCP and DCP, and CC flow measurements.

In the literature, subthreshold laser therapy has been shown to be safe and effective treatment option which stabilize BCVA, decrease CST and increase retinal sensitivity without causing visible damage to retina.[15–18] Laursen et al.[18] demonstrated increase in visual functions with microperimetry despite no change in CST measurements. Vujosevic et al.[19] showed significant increase in BCVA with no significant change in CST 6 months after subthreshold micropulse yellow laser therapy. Therefore, they suggested that functional improvement may precede the thickness changes. The index study indicated stable and improving trend in BCVA during the 3 months of follow-up with no deterioration of VA in any patients. This result also supported the safety of the SYPL therapy in DME.

Previously, the effects of subthreshold laser therapy in DME were usually assessed with FAF, fluorescein angiography, and OCT.[15–18,20] There are only a few studies investigated the alterations following SYPL in DME patients using OCTA, which mostly focused on the morphological changes. Vujosevic et al.[19] studied 35 eyes with DME after subthreshold micropulse yellow laser therapy. The results showed significant decrease in number of microaneurysms and the area of cysts at the 6 months of follow-up. They suggested that those alterations become more prominent at 6 months, since some of those parameters did not change significantly at 3 months of follow-up. Vujosevic et al.[21] also showed significantly decreased number of hyperreflective spots, microaneurysms, DRIL extension and the area of cysts with no change in CST, VD, and flow parameters at 1-year of follow-up. They indicated the potential anti-inflammatory effect of subthreshold laser therapy given their preliminary data. The present study assessed the microvascular effects of SYPL in DME using OCTA quantitatively with an automated software. The mean VD particularly in DCP showed an increase at the 1st month of SYPL therapy. Similar to the results of Vusojevic et al.,[19,21] SYPL therapy appears to display its effect first at the level of DCP which is related to vulnerability of DCP to ischemia and no direct connection of DCP vessels with arterioles.[22] In addition, increasing trend in CC flow area and VFD was also noted during the follow-up. Hence, SYPL therapy may be promising in improving macular capillary perfusion. On the other hand, the insignificance of these changes may also potentiate the importance of an anti-inflammatory action of subthreshold laser therapy in DME. However, data on macular capillary perfusion obtained from OCTA images should also be interpreted with caution, as an absence of significant alterations following SYPL therapy could be related to lack of adequate sensitivity of the OCTA instrument itself and not to the insufficient modification of a specific parameter.

The study limitations were small sample size, short follow-up period, lack of identification of ischemic maculopathy, absence of control group, and assessment of only microvascular changes on OCTA. Furthermore, re-treatment with SYPL was not performed and the efficacy of re-treatment was not assessed in such a short follow-up period. Therefore, the future prospective comparative studies evaluating both microvascular and other morphological changes in a larger population along with the effect of re-treatment in the long-term will be helpful.

### Conclusion

SYPL therapy in the treatment of DME appears to be safe with no statistically significant difference in macular capillary perfusion, as well as no change in BCVA and CST during the 3 months of follow-up.

**Ethics Committee Approval:** This study was approved by Ege University Faculty of Medicine Ethics Committee (date: 16.05.2017; number: 17-5.1/19).

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions:** Concept: I.K., F.A., S.N.; Design: I.K., F.A., S.N., J.M., C.A.; Supervision: F.A., J.M., C.A.; Resource: I.K., F.A., S.N., J.M., C.A.; Materials: I.K., F.A., S.N., J.M., C.A.; Data Collection and/or Processing: I.K., S.N.; Analysis and/or Interpretation: I.K., F.A., S.N.; Literature Search: I.K., S.N.; Writing: I.K., F.A.; Critical Reviews: I.K., F.A., S.N.

**Conflict of Interest:** None declared.

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