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ORIGINAL RESEARCH

OCT-Angiography Changes in Patients with Diabetic Macular Edema Treated with Intravitreal Dexamethasone Implant

Pablo Carnota-Méndez, Carlos Méndez-Vázquez, Conchi Pérez-Gavela

Centro de Ojos de La Coruña, A Coruña, Spain

Correspondence: Pablo Carnota-Méndez, Centro de Ojos de La Coruña, Avenida, Rúa Santiago Rey Fernández Latorre, 120, A Coruña, 15006, Spain, Tel +34 981168012, Email pablokarnota@hotmail.com

Purpose: To evaluate, using optical coherence tomography angiography (OCTA), the impact of intravitreal dexamethasone (DEX) implant on quantitative vascular measurements in patients with diabetic macular edema (DME).

Methods: Prospective, randomized, and open-label study. Primary endpoints were mean changes in vessel density (VD) and vascular perfusion (VP) in superficial capillary plexus (SCP) and VP in deep capillary plexus (DCP) and peripapillary capillary plexus (PCP).

Results: Thirty-four eyes from 19 patients were included. Mean age was 67.4±7.3 years and 24 (76.5%) were men. VD in SCP in the 6 mm × 6 mm perifoveal ring was significantly decreased from 15.2±2.7 mm/mm^2 at baseline to 13.5±3.1 at month-2, p, 0.0029. VP in SCP in the 6 mm × 6 mm perifoveal ring decreased significantly from baseline to month-2 (mean change −3.8%; 95% confidence-interval: −7.7% to −1.7%, p, 0.0028). Compared to baseline, the VP in DCP was significantly reduced at month 2 in the perifoveal ring of the 6 mm × 6 mm scan (p, 0.0063), and in the parafoveal ring of the 6 mm × 6 mm scan (p, 0.0048). Foveal avascular zone (FAZ) area did not change throughout the study. Central macular thickness significantly decreased from baseline in 210.3 µm (149.9–270.8 µm) and 201.8 µm (140.4–263.3 µm), $p < 0.0001$ each at month-2 and month-3, respectively.

Conclusions: Besides functional and anatomical improvements, DEX implant significantly reduced VD and VP in DME patients.

Keywords: diabetes, diabetic macular edema, OCTA, vessels density, vascular perfusion, diabetic retinopathy

Introduction

As the prevalence of diabetes rises, the relevance of diabetic eye disease increases.[1–3] Diabetic macular edema (DME) is the leading cause of vision loss in diabetic patients. DME is a chronic, multifactorial, sight-threatening condition that critically impacts on the patient's quality of life.[4,5] The prevalence of any type of DME in Europe was 3.7%, and its pooled mean annual incidence in type-2-diabetes patients was 0.4%.[3]

Although the pathophysiology of DME is not fully understood, hyperglycemia seems to be the main risk factor involved in its development. Through several pathways, proinflammatory molecules (interleukins, adhesion molecules and other cytokines) and apoptotic factors are released. All these molecular changes lead to endothelial cells and pericytes degeneration and breakdown of the blood retinal barrier. Furthermore, a disbalance between pro- and antiangiogenic factors occurs. Thus, vascular endothelial growth factor (VEGF) is upregulated, and platelet-derived growth factor (PEDF) is downregulated. All these changes result in diabetic retinopathy (DR) and DME.[6,7]

In addition to molecular changes, vision in patients with DME can also be impaired by mechanical factors, such as epiretinal membrane and vitreomacular traction syndrome.[8]

Among the different options for treating DME, intravitreal therapy, either with VEGF inhibitors, or with sustained-released dexamethasone (DEX) implants, has emerged as the first-line treatment in center-involving DME.[9]

Fluorescein angiography (FA) first and optical coherence tomography (OCT) later have been used to assess diagnosis and follow-up of DME.

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Optical coherence tomography angiography (OCTA) has further improved the knowledge of vascular changes underlying DR and DME.[10,11]

OCTA detects the motion of erythrocytes through a series of technical improvements, in speed and sensitivity, of OCT imaging platform.[12] OCTA allows the possibility to study both qualitative and quantitative vascular changes in the four vascular plexuses that supply blood to the retina, namely the superficial (SCP) and deep (DCP) capillary plexuses, the choriocapillaris, and the radial peripapillary capillary network.[12,13]

Because DME is associated with retinal microvascular changes,[14] OCTA may be a useful tool to assess the effect of DEX implant on the retinal vascular plexuses and to evaluate the ability of this treatment to reverse diabetic pathological features. There are several studies that analyze the macular perfusion changes using OCTA in patients with DME treated with anti-VEGF drugs with inconclusive results.[15–17] On the other hand, there is evidence suggesting qualitative changes in both the SCP and DCP in DME patients treated with DEX implant.[18,19] However, no quantitative changes in OCTA measures have been found.[18]

This study aimed to evaluate the impact of DEX implant on quantitative vascular measurements, assessed by OCTA, in DME patients. Additionally, this study also aimed to evaluate the potential relationship between quantitative vascular changes and clinical, either functional or anatomic, outcomes.

Methods

Design

Prospective, non-randomized, and open-label study. The study protocol was approved by the Ethical Committee for Clinical Research of Galicia (CEIC). Informed consent was obtained from all individual participants included in the study. This study complied with the guidelines of Good Clinical Practice and adhered to the tenets of the Declaration of Helsinki.

Participants

The study was conducted on consecutive referred or recruited patients with DME, who underwent treatment with DEX implant between September 2019 and August 2020.

Inclusion criteria were type 1 or 2 diabetes and center-involving DME; age ≥50 years; baseline best-corrected visual acuity (BCVA) from 0.1 to 1.0 (logMar test); baseline central macular thickness (CMT) ≥250 μm as measured by spectral-domain OCT (SD-OCT).

Patients with macular edema secondary to other causes than diabetes mellitus; history of glaucoma or ocular hypertension (defined as intraocular pressure, IOP, > 21 mm Hg under ocular hypotensive treatment); those who underwent DEX implant in the prior 6 months or anti-VEGF drugs in the prior 3 months; and/or those who underwent any major surgical procedure, including cataract, within 6 months preceding the baseline visit, were excluded of the study.

Procedures

Study subjects underwent basic ophthalmic exams, including BCVA, IOP, slit-lamp, and fundus examination. Patients with high clinical suspicion of DME were definitely diagnosed after an SD-OCT exam. Quantitative data obtained from SD-OCT were CMT (automatic value of mean retinal thickness of the central circle of 1 mm of diameter), macular volume (MV) (automatic value of retinal volume of central 6 mm × 6 mm cube) and central choroidal thickness (CCT) (manually measured subfoveal choroidal thickness). SD-OCT biomarkers of DME were also registered. All subjects underwent an OCTA examination with the AngioPlex Cirrus 5000 (Carl Zeiss Meditec) system that uses the optical microangiography (OMAG) algorithm. OCTA imaging included macular scans of 3 mm × 3 mm and 6 mm × 6 mm centered at the fovea, and peripapillary scans of 4.5 mm × 4.5 mm centered at the disc. OCT-A scans with a signal strength index worse than 7 were discarded. Best quality images were retained for further quantitative and qualitative analysis.

Segmentation of both SCP and DCP plexuses and quantitative analyses of SCP plexus and peripapillary capillary plexus (PCP) were based on the default settings of the automated software algorithm of the AngioPlex. Quantitative analysis of DCP was performed by a custom analysis.

Quantitative vascular measurements of SCP were vessel density (VD) (mm of vessels per mm^2 of area) and vascular perfusion (VP) (% of area occupied by vessels). Since SCP has vessels of different caliber, VP could be influenced more by large caliber vessels. To avoid this theoretical bias, vessels are skeletonized to measure the millimeters of vessel length per area unit. Thus, vessel density is obtained. This difference between VD and VP does not occur in DCP since all vessels within this plexus have the same caliber.[20] This is the reason VD and VP were measured in the SCP but only VP was measured in the DCP in our study. In PCP, only VP was measured, since the software does not have the function of skeletonizing this plexus (Figure 1).

Vascular perfusion of DCP was obtained as follows: images obtained from the built-in software of AngioPlex were processed first with the Adobe Photoshop program (Adobe Systems Inc., Mountain View, CA). The perfusion area was calculated within a user defined circular region of interest (ROI). Perifoveal ring (3 mm of diameter, centered at the fovea) in 3 × 3 scans and perifoveal and parafoveal rings (3 mm and 6 mm of diameter, respectively, centered at the fovea) in 6 × 6 scans were obtained. The images were then consecutively converted to 8-bit grayscale images, binarized and thresholded with ImageJ software version 1.52 (National Institutes of Health, Bethesda, MD). Percentages of white and black pixels were automatically counted. Vascular perfusion was calculated by scoring the percentage of white pixels in relation to the number of total pixels.

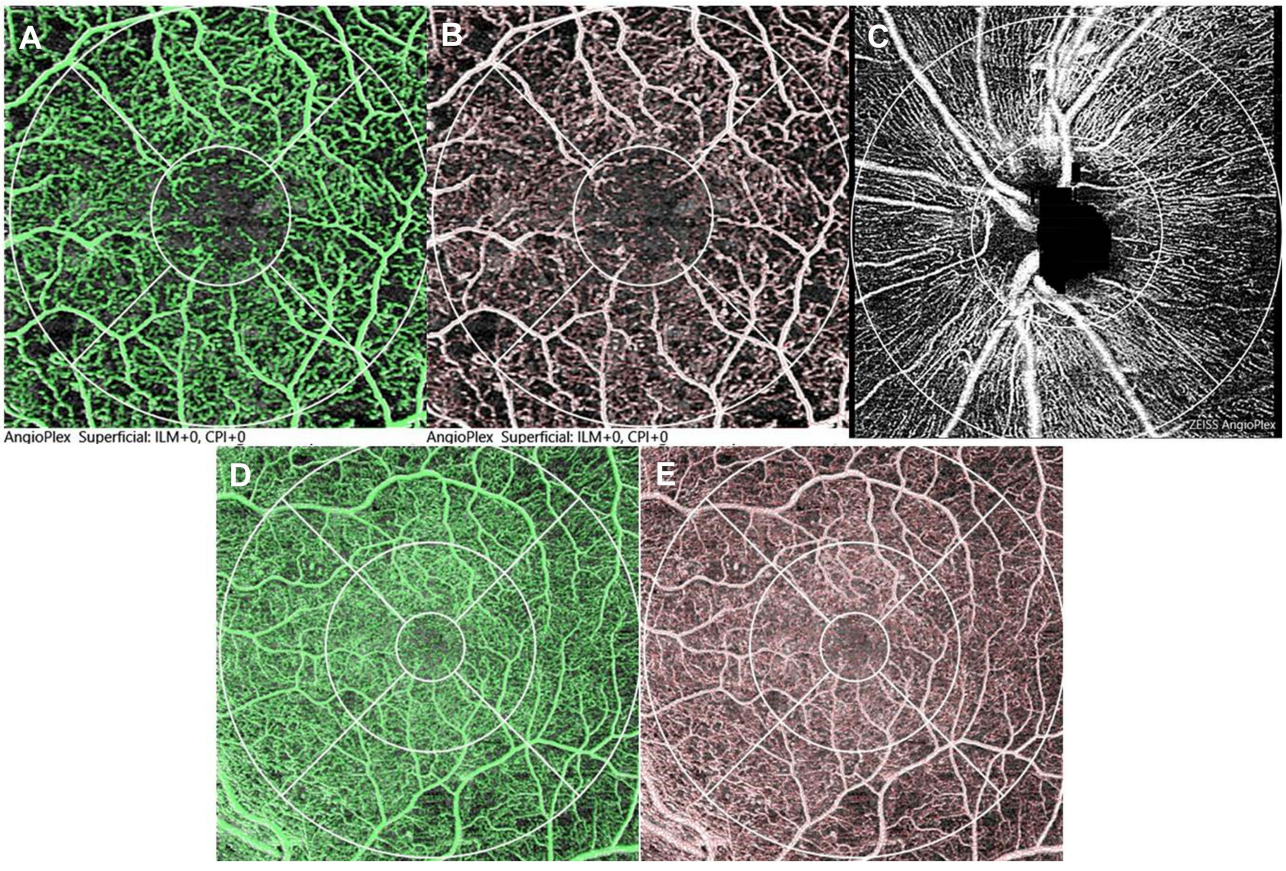

Figure 1 Optical coherence tomography angiography (OCT-A) images. (**A**) OCT-A 3 mm x 3 mm scans showing vascular perfusion (VP) (green pixels) in superficial capillary plexus (SCP). The grid shows center (1 mm diameter circle, centered in fovea) and perifoveal ring (1 mm to 3 mm from fovea). (**B**) OCT-A 3 mm x 3mm scans showing vascular density (VD) (red lines, (**B**) SCP. The grid shows center (1 mm diameter circle, centered in fovea) and perifoveal ring (1 mm to 3 mm from fovea). (**C**) OCT-A 4.5 mm x 4.5 mm scan showing VP (white pixels) in peripapillary capillary plexus. The grid shows peripapillary ring (1.5 mm to 4.5 mm from disc center). (**D**) OCT-A 6 mm x 6 mm scans showing VP (green pixels) in deep capillary plexus (DCP). The grid shows center (1 mm diameter circle, centered in fovea), perifoveal ring (1 mm to 3 mm from fovea) and parafoveal ring (3 mm to 6 mm from fovea). E. OCT-A 6 mm x 6 mm scans showing VD (red lines, (**E**) in deep capillary plexus (DCP). The grid shows center (1 mm diameter circle, centered in fovea), perifoveal ring (1 mm to 3 mm from fovea) and parafoveal ring (3 mm to 6 mm from fovea).

FAZ area and circularity index were also automatically measured with OCTA. FAZ size is smaller in DCP than in SCP. However, many OCTA devices, including AngioPlex, do not properly segment the FAZ and include the DCP FAZ within the SCP.[12] This is the reason we did not consider making a difference between FAZ in SCP and FAZ in DCP (as it is done in many papers), and we mention it simply as FAZ.

Patient Visits

This protocol included one baseline visit and three follow-up visits at months 1, 2, and 3 (± 2 weeks) after DEX implant.

Outcomes

Primary endpoints were mean changes from baseline to month-2 in VD and VP in SCP and VP in DCP in perifoveal ring in 3 mm × 3 mm scans and in perifoveal and parafoveal rings in 6 mm × 6 mm scans. Another primary endpoint was a change from baseline to month-2 in VP in PCP.

Secondary endpoints included mean changes in BCVA; CMT; MV; CCT; total VD and VP in 3 × 3 and 6 × 6 scans; mean changes in VD and VP in superior, inferior, temporal, and nasal retinal quadrants of perifoveal and parafoveal rings; and mean changes in FAZ area and circularity index.

Statistical analysis

A standard statistical analysis was performed using the MedCalc® Statistical Software version 20.013 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

Thirty-two subjects need to be included for detecting a mean difference of 1.5 mm/mm^2 in VD, with a type I error of 0.05 and a power of the 90%, assuming a standard deviation of 2.5 mm^2.

Missing data of continuous variables were allocated using an algorithm of multiple imputation.[21]

Data were tested for normal distribution using a D'Agostino-Pearson test.

A repeated measures ANOVA or a Friedman's two-way analysis test, as appropriate, were used to assess changes in quantitative variables throughout the study. Post hoc analysis of pairwise comparisons was done with the Scheffé's method (ANOVA) or the Conover method (Friedman).

To explore the relationship between quantitative OCTA values (VD and VP in SCP; VP in DCP; and FAZ area) and clinical outcomes (BCVA and CMT) a partial correlation coefficient, adjusted by age and duration of diabetes, was performed.

Categorical variables were compared using a Chi-square test and a Fisher's exact test, as needed. P value of less than 0.05 was considered significant.

Results

Among the 34 subjects who fulfilled the respective demands of the inclusion and exclusion criteria, eight patients were lost to follow-up due to coronavirus disease (COVID)-19 pandemic lockdowns and restrictions, and seven had poor quality baseline OCTA images. A total of 34 eyes from 19 patients of the 34 selected patients were included in the analysis. Mean (95% confidence interval; CI) age was 67.4 (64.9 to 69.9) years and 8 (23.5%) were women. Baseline demographic and clinical characteristics are summarized in Table 1.

Table 2 shows the VD of the SCP in 3 mm × 3 mm and 6 mm × 6 mm scans. In month 2, VD in the 6 mm × 6 mm perifoveal ring was significantly lower as compared to the baseline (mean difference −1.75; 95% CI: −2.84 to −0.64, p, 0.0029). Although the values in all quadrants of the 6 mm × 6 mm perifoveal ring showed a trend ($p < 0.1000$), only the nasal quadrant was statistically significant (mean difference −1.58; 95% CI: −3.25 to −0.76, p, 0.0021) (Table 2). None of the other VD measurements (perifoveal ring in 3 × 3 scan and parafoveal ring in 6 × 6 scan) experienced significant changes, although numerical values at month 2 were lower, when compared to baseline (Table 2).

Regarding VP in SCP, there were no changes in 3 mm × 3 mm scan throughout the study, with the exception of the temporal quadrant at month 2. Nevertheless, at month 2, VP was significantly decreased in the 6 mm × 6 mm perifoveal ring in the overall (mean difference −3.79%, 95% CI: −7.70% to −1.68%, p, 0.0028) and in all the different quadrants (p, 0.0131, p, 0.0144, p, 0.0112, and p, 0.0022 at the superior, inferior, temporal, nasal quadrants, respectively) as compared

Table 1 Main Baseline Demographic and Clinical Characteristics

	Overall (n, 34)	Naïve (n, 12)	Previously Treated (n, 22)	P[a]
Age, years				
Mean (SD)	67.4 (7.3)	63.3 (7.3)	69.5 (6.5)	0.0273
95% CI	64.9 to 69.9	58.9 to 68.2	66.6 to 72.3	
Sex, n (%)				
Woman	8 (23.5)	2 (25.0)	6 (38.5)	0.4925[b]
Man	26 (76.5)	10 (75.0)	16 (61.5)	
Eye, n (%)				
Right	14 (41.2)	7 (58.3)	7 (31.8)	0.1391[b]
Left	20 (58.8)	5 (41.7)	15 (68.2)	
Duration of DM, years				
Mean (SD)	16.6 (10.7)	11.0 (5.9)	19.2 (11.5)	0.1211
95% CI	12.8 to 20.5	6.7 to 15.2	14.1 to 24.3	
Treatment of DM, n (%)				
Insulin	13 (38.2)	3 (25.0)	10 (45.5)	0.1795[c]
OAD	11 (32.4)	4 (33.3)	7 (31.8)	
Insulin + OAD	10 (29.4)	5 (41.7)	5 (22.7)	
Diabetic retinopathy, n (%)*				
MNPDR	1 (3.2)	0 (0.0)	1 (5.0)	
MoNPDR	6 (19.4)	3 (27.3)	3815.0)	0.3305[c]
SNPDR	16 (51.6)	7 (63.6)	9 (45.0)	
PDR	8 (25.8)	1 (9.1)	7 (35.0)	
VMI, n (%)				
PVD	14 (41.2)	4 (33.3)	10 (45.5)	
VMA	12 (35.3)	8 (66.7)	4 (18.1)	0.0141[c]
ERM	1 (2.9)	0 (0.0)	1 (4.5)	
Vitrectomized	7 (20.6)	0 (0.0	7 (31.8)	
Previous treatment				
None	12 (35.3)	12 (100.0)	0 (0.0)	N.A.
Anti-VEGF	4 (11.8)	0 (0.0)	4 (18.2)	
DEX implant	4 (11.8)	0 (0.0)	4 (18.2)	
Anti-VEGF+DEX implant	14 (41.2)	0 (0.0)	14 (63.6)	
DRIL, n (%)				
Yes	2 (5.9)	1 (8.3)	1 (4.5)	0.6585[b]
No	32 (94.1)	11 (91.7)	21 (95.5)	
Cysts INL, n (%)				
Yes	30 (88.2)	11 (91.7)	19 (86.4)	0.6514[b]
No	4 (11.8)	1 (8.39	3 (13.6)	
Cysts ONL, n (%)				
Yes	29 (85.3)	8 (66.7)	21 (95.5)	0.0257[b]
No	5 (14.7)	4 (33.3)	1 (4.5)	
HRF, n (%)				
Yes	19 (55.9)	5 (41.7)	10 (45.5)	0.8341[b]
No	15 (44.1)	7 (58.39	12 (54.5)	

(*Continued*)

Table 1 (Continued).

	Overall (n, 34)	Naïve (n, 12)	Previously Treated (n, 22)	P[a]
Foveal ELM integrity, n (%)				
Intact	28 (82.4)	11 (91.7)	17 (77.3)	0.4791[b]
Disruption	6 (17.6)	1 (8.39)	5 (22.7)	
Foveal EZ integrity, n (%)				
Intact	26 (76.5)	10 (83.2)	16 (72.7)	0.5446[b]
Disruption	8 (23.5)	2 (16.7)	6 (27.3)	
SRF, n (%)				
Yes	10 (29.4)	4 (33.3)	6 (27.3)	0.7150[b]
No	24 (70.6)	8 (66.79	16 (72.7)	
BCVA				
Mean (SD)	0.48 (0.17)	0.44 (0.18)	0.50 (0.16)	0.5203
95% CI	0.42 to 0.54	0.33 to 0.56	0.43 to 0.57	
CMT, µm				
Mean (SD)	445.0 (113.4)	463.1 (153.5)	435.1 (87.1)	0.6394
95% CI	405.2 to 484.6	365.6 to 560.6	396.5 to 473.8	
MV, mm^3				
Mean (SD)	12.1 (1.6)	12.7 (1.9)	11.7 (1.2)	0.0632
95% CI	11.5 to 12.6	11.5 to 14.0	11.2 to 12.3	
CCT, µm				
Mean (SD)	248.9 (97.6)	282.3 (98.7)	230.6 (94.3)	0.0774
95% CI	214.8 to 282.9	219.6 to 345.1	188.8 to 272.3	
IOP, mm Hg				
Mean (SD)	16.5 (3.6)	18.1 (3.2)	15.6 (3.5)	0.0673
95% CI	15.3 to 17.7	16.0 to 20.1	14.1 to 17.2	

Notes: *Thirty-one subjects. [a]Mann–Whitney test. [b]Fisher's exact test. [c]Chi-squared test.
Abbreviations: SD, Standard deviation; CI, Confidence interval; DM, Diabetes mellitus; OAD, Oral antidiabetics drugs; MNPDR, Mild non-proliferative diabetic retinopathy; MoNPDR, Moderate non-proliferative diabetic retinopathy; SNPDR, Severe non-proliferative diabetic retinopathy; PDR, Proliferative diabetic retinopathy; VMI, Vitreous-macular interface; PVD, Posterior vitreous detachment; VMA, Vitreous-macular adhesion; ERM, Epiretinal membrane; Anti-VEGF, Vascular endothelial growth factor inhibitors; DEX, Dexamethasone intravitreal implant, NA, Not applicable; DRIL, Disorganization of retinal inner layers; INL, Inner nuclear layer; ONL, Outer nuclear layer; HRF, Hyperreflective foci; ELM. External limiting membrane; EZ, Ellipsoid zone; SRF, Subretinal fluid; BCVA, Best-corrected visual acuity; CMT, Central macular thickness; MV, Macular volume; CCT. Central choroidal thickness; IOP, Intraocular pressure.

to baseline (Table 3). VP changes in the 6 mm × 6 mm parafoveal ring showed a trend ($p < 0.10$) in the overall and in all quadrants except in the inferior quadrant, but none of them were significant.

When compared to baseline, DCP VP was significantly reduced in the perifoveal ring of the 6 mm × 6 mm scan at months 2 and 3 (Table 4). Additionally, DCP VP in the parafoveal ring of the 6 mm × 6 mm scan was significantly lower at month 2 when compared to baseline (Table 4). However, no significant changes were observed in the DCP VP in the 3 mm x 3 mm scan (Table 4).

As compared to baseline, mean (95% CI) change in PCP VP was 0.29 (−0.05 to 0.63), 0.0966; 0.11 (−0.30 to 0.53); 0.5899; and 0.02 (−0.37 to 0.41), p, 0.9218 at month 1, 2, and 3, respectively.

Mean (95% CI) FAZ area in the 3 mm × 3 mm scan was 0.28 (0.32 to 0.34) mm^2; 0.27 (0.22 to 0.33) mm^2; 0.29 (0.24 to 0.34) mm^2; and 0.28 (0.23 to 0.34) at baseline and months 1, 2, and 3, respectively (p, 0.9557; repeated measures ANOVA and the Greenhouse–Geisser correction) (Table 5). Similarly, there were no significant changes in mean (95% CI) FAZ area in the 6 mm × 6 mm scan from baseline [0.28 (0.25 to 0.31) mm^2] to month 1 [0.25 (0.22 to 0.29) mm^2, p, 0.7473]; month 2 [0.27 (0.23 to 0.31) $mm,^2$ p, 0.9337], and month 3 [0.27 (0.24 to 0.30), p, 0.7975] (Table 5).

Table 2 Overview of Vessel Density in the Superficial Capillary Plexus in 3 mm × 3 mm and 6 mm × 6 mm Scans. P Values were Calculated Using Repeated Measures ANOVA and the Greenhouse–Geisser Correction

	3 mm × 3 mm Scan[a]				P value
	Baseline	Month 1	Month 2	Month 3	
Total VD, mm /mm^2					
Mean (SE)	16.47 (0.50)	16.35 (0.46)	15.46 (0.52)	15.64 (0.48)	0.6656
Mean (95% CI) from baseline	NA	−0.12 (−1.19 to 0.94)	−1.01 (−2.44 to 0.42)	−0.83 (−2.09 to 0.42)	
P value*	NA	0.7436	0.1061	0.1107	
SUP VD, mm /mm^2					
Mean (SE)	16.12 (0.62)	16.13 (0.55)	15.36 (0.63)	15.02 (0.58)	0.7103
Mean (95% CI) from baseline	NA	0.01 (−1.59 to 1.62)	-0.76 (−2.82 to 1.30)	-1.10 (−2.52 to 0.30)	
P value*	NA	0.8816	0.2459	0.1595	
INF VD, mm /mm^2					
Mean (SE)	15.67 (0.72)	15.61 (0.64)	14.49 (0.62)	14.89 (0.66)	0.6207
Mean (95% CI) from baseline	NA	-0.06 (−1.68 to 1.56)	-1.18 (−3.14 to 0.79)	-0.78 (−2.39 to 0.84)	
P value*	NA	0.8364	0.0945	0.2450	
TEMP VD, mm /mm^2					
Mean (SE)	16.08 (0.55)	16.06 (0.49)	14.97 (0.68)	15.92 (0.42)	0.1994
Mean (95% CI) from baseline	NA	-0.02 (−1.12 to 1.07)	-1.11 (−3.05 to 0.83)	-0.16 (−1.69 to 1.36)	
P value*	NA	0.7920	0.1781	0.6568	
NAS VD, mm /mm^2					
Mean (SE)	16.57 (0.68)	16.49 (0.65)	15.90 (0.70)	15.64 (0.77)	0.8283
Mean (95% CI) from baseline	NA	-0.08 (−1.65 to 1.50)	-0.67 (−2.41 to 0.97)	-0.93 (−2.71 to 0.85)	
P value*	NA	0.7237	0.2415	0.1455	
	6 mm × 6 mm Scan				
	3 mm × 3 mm perifoveal ring (excluded the 1 mm of diameter central area).				
	Baseline	Month 1	Month 2	Month 3	
Total VD, mm /mm^2					
Mean (SE)	15.24 (0.47)	14.93 (0.51)	13.49 (0.53)	14.53 (0.59)	0.1617
Mean (95% CI) from baseline	NA	-0.31 (−1.70 to 1.09)	-1.75 (−2.84 to −0.64)	-0.71 (−2.59 to 1.19)	
P value*	NA	0.5450	0.0029	0.3043	
SUP VD, mm /mm^2					
Mean (SE)	15.03 (0.53)	14.44 (0.55)	13.43 (0.61)	14.68 (0.63)	0.1955
Mean (95% CI) from baseline	NA	-0.59 (−2.32 to 1.14)	-1.60 (−3.42 to 0.40)	-0.35 (−2.46 to 1.76)	
P value*	NA	0.3764	0.0877	0.4352	
INF VD, mm /mm^2					
Mean (SE)	14.63 (0.65)	14.63 (0.64)	13.43 (0.57)	14.04 (0.75)	0.3890
Mean (95% CI) from baseline	NA	0.00 (−1.60 to 1.60)	-1.20 (−0.54 to 2.94)	-0.59 (−2.92 to 1.73)	
P value*	NA	0.9987	0.0990	0.4044	
TEMP VD, mm /mm^2					
Mean (SE)	15.19 (0.56)	14.91 (0.56)	13.82 (0.54)	14.70 (0.74)	0.3764
Mean (95% CI) from baseline	NA	-0.28 (−1.78 to 1.22)	-1.37 (−3.22 to 0.48)	-0.49 (−2.95 to 1.97)	
P value*	NA	0.7144	0.0721	0.4364	
NAS VD, mm /mm^2					
Mean (SE)	15.56 (0.48)	15.13 (0.67)	13.68 (0.63)	15.18 (0.65)	0.0616
Mean (95% CI) from baseline	NA	-0.43 (−2.20 to 1.34)	-1.58 (−3.25 to −0.76)	-0.38 (−2.40 to 1.64)	
P value*	NA	0.5710	0.0021	0.5930	

(*Continued*)

Table 2 (Continued).

	6 mm × 6 mm parafoveal ring (excluded the 3 mm of diameter central area).				
Total VD, mm /mm^2					
Mean (SE)	14.69 (0.46)	14.62 (0.46)	13.72 (0.48)	14.47 (0.47)	0.2814
Mean (95% CI) from baseline	NA	-0.07 (−1.49 to 1.33)	-0.97 (−2.63 to 0.68)	-0.22 (−1.78 to 1.33)	
P value*	NA	0.8769	0.1077	0.6865	
SUP VD, mm /mm^2					
Mean (SE)	14.13 (0.46)	13.82 (0.53)	12.97 (0.63)	14.09 (0.56)	0.2133
Mean (95% CI) from baseline	NA	-0.30 (−2.03 to 1.42)	-1.16 (−3.12 to 0.80)	-0.04 (−1.86 to 1.79)	
P value*	NA	0.7729	0.1050	0.8837	
INF VD, mm /mm^2					
Mean (SE)	14.02 (0.59)	13.83 (0.59)	13.34 (0.58)	13.73 (0.63)	0.5129
Mean (95% CI) from baseline	NA	-0.19 (−1.66 to 1.28)	-0.68 (−2.49 to 1.12)	-0.29 (−2.06 to 1.48)	
P value*	NA	0.8944	0.2548	0.6067	
TEMP VD, mm /mm^2					
Mean (SE)	13.75 (0.65)	13.75 (0.63)	12.62 (0.61)	13.42 (0.71)	0.3961
Mean (95% CI) from baseline	NA	0.00 (−1.87 to 1.87)	-1.13 (−3.43 to 1.18)	-0.33 (−2.60 to 1.94)	
P value*	NA	0.9991	0.1733	0.5879	
NAS VD, mm /mm^2					
Mean (SE)	16.31 (0.59)	16.26 (0.53)	16.23 (0.47)	16.85 (0.46)	0.6735
Mean (95% CI) from baseline	NA	-0.05 (−1.96 to 1.88)	-0.08 (−2.06 to 1.90)	0.54 (−1.34 to 2.42)	
P value*	NA	0.9420	0.7771	0.4743	

Notes: [a]Conducted on the 3 mm × 3 mm perifoveal ring, which excludes the 1 mm of diameter central area. *Post hoc analysis for pairwise comparisons were done with the Scheffé's method (Bonferroni corrected).

Abbreviations: VD, Vessel density; SE, Standard error; CI, Confidence Interval; NA, Not applicable; SUP, Superior quadrant; INF, Inferior quadrant; TEM, Temporal quadrant; NAS, Nasal quadrant.

Table 3 Overview of the Vascular Perfusion (VP) in the Superficial Capillary Plexus in 3 mm × 3 mm and 6 mm × 6 mm Scans. P values were Calculated Using Repeated Measures ANOVA and the Greenhouse–Geisser Correction

	3 mm × 3mm Scan[a]				P value
	Baseline	Month 1	Month 2	Month 3	
Total VP, %					
Mean (SE)	31.26 (1.03)	31.07 (0.88)	29.60 (1.04)	29.91 (0.95)	0.2126
Mean (95% CI) from baseline	NA	-0.19 (−2.33 to 1.95)	-1.66 (−4.70 to 1.39)	-1.35 (4.00 to 1.32)	
P value*	NA	0.7751	0.0984	0.1689	
SUP VP, %					
Mean (SE)	30.92 (1.07)	30.88 (0.94)	29.60 (1.07)	29.05 (1.08)	0.4433
Mean (95% CI) from baseline	NA	-0.04 (−2.87 to 2.79)	-1.32 (−4.92 to 2.29)	-1.87 (−5.13 to 1.89)	
P value*	NA	0.9295	0.2631	0.1780	
INF VP, %					
Mean (SE)	30.28 (1.34)	30.12 (1.16)	28.26 (1.17)	29.16 (1.21)	0.1580
Mean (95% CI) from baseline	NA	-0.16 (−3.04 to 2.72)	-2.02 (−5.67 to 1.63)	-1.12 (−3.69 to 1.66)	
P value*	NA	0.8826	0.1208	0.2272	
TEMP VP, %					
Mean (SE)	31.56 (1.03)	31.21 (0.86)	29.07 (1.24)	31.36 (0.78)	0.0815
Mean (95% CI) from baseline	NA	-0.35 (−2.51 to 1.84)	-2.49 (−4.69 to −0.08)	-0.20 (−3.05 to 2.66)	
P value*	NA	0.6424	0.0433	0.8188	

(*Continued*)

Table 3 (Continued).

NAS VP, % Mean (SE) Mean (95% CI) from baseline P value*	31.86 (1.3) NA NA	31.34 (1.15) -0.52 (−3.76 to 2.72) 0.4541	30.65 (1.24) -1.21 (−4.30 to 1.88) 0.1371	30.39 (1.41) -1.47 (−5.18 to 2.24) 0.1334	0.4688
	6 mm × 6 mm Scan				
	3 mm × 3 mm perifoveal ring (excluded the 1 mm of diameter central area).				
	Baseline	**Month 1**	**Month 2**	**Month 3**	
Total VP, % Mean (SE) Mean (95% CI) from baseline P value*	36.52 (1.35) NA NA	35.72 (1.50) -0.80 (−4.75 to 3.15) 0.6126	32.73 (1.37) -3.79 (−7.70 to −1.68) 0.0028	35.51 (1.55) -1.01 (−6.50 to 4.48) 0.4525	0.0936
SUP VP, % Mean (SE) Mean (95% CI) from baseline P value*	36.38 (1.42) NA NA	35.11 (1.53) -1.27 (−4.28 to 2.07) 0.4810	32.39 (1.63) -3.99 (−8.59 to −1.08) 0.0131	35.95 (1.66) -0.43 (−6.01 to 5.15) 0.6642	0.1593
INF VP, % Mean (SE) Mean (95% CI) from baseline P value*	35.78 (1.74) NA NA	35.74 (1.64) -0.04 (−4.19 to 4.11) 0.9786	32.45 (1.50) -3.33 (−6.67 to −0.91) 0.0144	34.38 (1.98) 1.40 (−7.51 to 4.71) 0.4766	0.1054
TEMP VP, % Mean (SE) Mean (95% CI) from baseline P value*	36.58 (1.50) NA NA	35.74 (1.42) -0.84 (−4.64 to 2.95) 0.5250	32.98 (1.43) -3.60 (−8.01 to −1.11) 0.0112	35.40 (1.91) -1.18 (−7.53 to 5.17) 0.3614	0.1021
NAS VP, % Mean (SE) Mean (95% CI) from baseline P value*	37.34 (1.33) NA NA	36.22 (1.73) -1.11 (5.64 to 3.42) 0.5506	33.16 (1.65) -4.17 (−7.90 to −1.90) 0.0022	36.31 (1.72) -1.01 (−6.25 to 4.19) 0.5871	0.1502
	6 mm × 6 mm parafoveal ring (excluded the 3 mm of diameter central area).				
Total VP, % Mean (SE) Mean (95% CI) from baseline P value*	35.85 (1.32) NA NA	35.42 (1.36) -0.43 (−4.48 to 3.62) 0.8538	33.78 (1.28) -2.07 (–5.80 to 0.42) 0.0878	35.82 (1.43) -0.03 (−4.66 to 4.61) 0.9725	0.2303
SUP VP, % Mean (SE) Mean (95% CI) from baseline P value*	34.73 (1.27) NA NA	33.90 (0.147) -0.83 (−5.29 to 3.64) 0.7920	31.70 (1.64) -3.03 (−7.12 to 0.10) 0.0565	34.58 (1.48) -0.15 (−5.08 to 4.77) 0.9343	0.2206
INF VP, % Mean (SE) Mean (95% CI) from baseline P value*	34.67 (1.55) NA NA	34.25 (1.58) -0.42 (−4.26 to 3.43) 0.7910	32.86 (1.53) -1.81 (−6.55 to 2.92) 0.1267	34.01 (1.72) -0.66 (−5.44 to 4.11) 0.6332	0.3701
TEMP VP, % Mean (SE) Mean (95% CI) from baseline P value*	36.96 (1.70) NA NA	33.78 (1.62) -0.18 (−4.99 to 4.64) 0.9271	30.90 (1.59) -3.05 (−8.13 to 0.27) 0.0656	33.15 (1.80) -0.81 (−6.65 to 5.03) 0.5249	0.1039

(*Continued*)

Table 3 (Continued).

NAS VP, %					
Mean (SE)	39.99 (1.60)	39.75 (1.44)	39.61 (1.31)	41.54 (1.28)	0.6499
Mean (95% CI) from baseline	NA	-0.24 (−5.36 to 4.88)	-0.37 (−5.62 to 4.87)	1.55 (−3.57 to 6.67)	
P value*	NA	0.8927	0.6027	0.4441	

[a]**Notes**: [a] Conducted on the 3 mm × 3 mm perifoveal ring, which excludes the 1 mm of diameter central area. *Post hoc analysis for pairwise comparisons were done with the Scheffé's method (Bonferroni corrected).
Abbreviations: VP, Vascular perfusion; SE, Standard error; CI, Confidence Interval; NA, Not applicable; SUP, Superior quadrant; INF, Inferior quadrant; TEM, Temporal quadrant; NAS, Nasal quadrant.

Table 4 Overview of the Vascular Perfusion in the Deep Capillary Plexus Over the Course of the Study Follow-Up. P values were Calculated Using Repeated Measures ANOVA and the Greenhouse–Geisser Correction

	3 mm × 3mm Scan[a]				**P value**
	Baseline	**Month 1**	**Month 2**	**Month 3**	
Total VP, %					
Mean (SE)	20.94 (1.61)	23.86 (1.37)	21.09 (1.17)	19.45 (0.89)	0.1165
Mean (95% CI) from baseline	NA	2.92 (−2.74 to 8.79)**	0.15 (−4.90 to 5.20)	-1.49 (−5.27 to 2.29)	
P value*	NA	0.1700	0.9327	0.2753	
	6 mm × 6 mm Scan				
	3 mm × 3 mm perifoveal ring (excluded the 1 mm of diameter central area)				
	Baseline	**Month 1**	**Month 2**	**Month 3**	
Total VP, %					
Mean (SE)	33.02 (2.01)	32.21 (1.88)**	27.70 (1.55)	28.92 (1.57)	0.0020
Mean (95% CI) from baseline	NA	-0.81 (−5.20 to 3.57)	-5.32 (−9.03 to −1.61)	-4.10 (−7.14 to −1.07)	
P value*	NA	0.6065	0.0063	0.0096	
	6 mm × 6 mm parafoveal ring (excluded the 3 mm of diameter central area)				
Total VP, %					
Mean (SE)	34.42 (1.82)	32.66 (1.78)	29.36 (1.58)†	32.14 (1.76)	0.0116
Mean (95% CI) from baseline	NA	-1.76 (−6.12 to 2.60)	-5.06 (−8.46 to −1.65)	-2.28 (−6.63 to 2.06)	
P value*	NA	0.2661	0.0048	0.1496	

Notes: [a]Perifoveal ring, excluded the 1 mm of diameter central area. *Post hoc analysis for pairwise comparisons were done with the Scheffé's method (Bonferroni corrected). **P<0.05 as compared to M2 and M3. †P<0.005 as compared to M1.
Abbreviations: VP, Vascular perfusion; SE, Standard error; CI, Confidence Interval; NA, Not applicable.

No significant changes were observed at any time-point measures of circularity index in either 3 mm × 3 mm or 6 mm × 6 mm scans.

Figure 2 summarizes the overview of VD in the 6 mm × 6 mm perifoveal ring and VP in the SCP and DCP in the 6 mm × 6 mm perifoveal ring.

BCVA significantly improved from baseline to month 1 and 2 ($p < 0.0001$, each), and 3 (p, 0.0001) (Table 6).

Mean (95% CI) CMT was significantly reduced from baseline in 124.8 (87.5 to 162.2) µm, $p < 0.0001$; 210.3 (149.9 to 270.8) µm, $p < 0.0001$; and 201.8 (140.4 to 263.3) µm, $p < 0.0001$ at months 1, 2, and 3, respectively.

Mean MV was significantly decreased at all the different time-points measured. Mean CCT decreased significantly at month 2 (Table 6).

The percentage of eyes who experienced a complete resolution of their DME at 30, 60 and 90 days after DEX administration were 32.4% (11/34); 29.4% (10/34); and 8.8% (3/34).

Table 5 Overview of the Foveal Avascular Zone (FAZ) Area and Circularity in the Superficial Plexus. And 6 mm × 6 mm Scan (B) Over the Course of the Study Follow-Up. P values were Calculated Using Repeated Measures ANOVA and the Greenhouse–Geisser Correction

	3 mm × 3mm Scan				P value
	Baseline	**Month 1**	**Month 2**	**Month 3**	
FAZ area, mm^2 Mean (SE) Mean (95% CI) from baseline P value*	 0.278 (0.03) NA NA	 0.274 (0.03) -0.004 (−0.04 to 0.04) 0.8621	 0.288 (0.02) 0.01 (−0.03 to 0.04) 0.9076	 0.283 (0.03) 0.005 (−0.03 to 0.04) 0.8762	0.9557
FAZ circularity, mm^2 Mean (SE) Mean (95% CI) from baseline P value*	 0.477 (0.026) NA NA	 0.531 (0.024) 0.054 (−0.09 to −0.01) 0.0209	 0.476 (0.024) -0.001 (−0.10 to 0.10) 0.8702	 0.471 (0.022) -0.006 (−0.08 to 0.07) 0.8730	0.1084
	6 mm × 6 mm Scan				
	Baseline	**Month 1**	**Month 2**	**Month 3**	
FAZ area, mm^2 Mean (SE) Mean (95% CI) from baseline P value*	 0.280 (0.016) NA NA	 0.253 (0.017) -0.027 (−0.08 to 0.03) 0.7473	 0.272 (0.019) -0.008 (−0.07 to 0.06) 0.9337	 0.271 (0.015) -0.009 (−0.05 to 0.03) 0.7975	0.4109
FAZ circularity, mm^2 Mean (SE) Mean (95% CI) from baseline P value*	 0.621 (0.034) NA NA	 0.653 (0.023) 0.032 (0.05 to 0.12) 0.3356	 0.608 (0.021) -0.013 (−0.10 to 0.08) 0.7855	 0.632 (0.034) 0.011 (−0.11 to 0.13) 0.8383	0.8589

Notes: *Post hoc analysis for pairwise comparisons were done with the Scheffé's method.
Abbreviations: FAZ, Foveal avascular zone; SE, Standard error; CI, Confidence Interval; NA, Not applicable.

Over the course of the study, the number of eyes who experienced a rise in IOP ≥ 10 mm Hg as compared to baseline was 2 (5.7%), 4 (11.4%), and 2 (5.7%) at month 1, 2, and 3, respectively. All the cases were successfully managed with topical hypotensive medication.

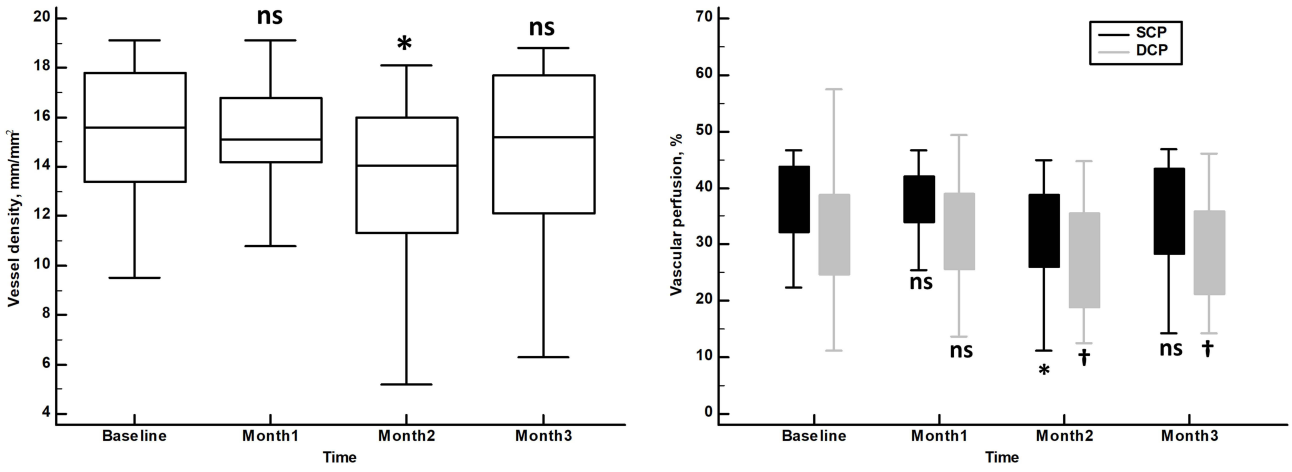

Figure 2 Vessel density in the 6 mm × 6 mm perifoveal ring (left) and vascular perfusion in the superficial capillary plexus (SCP) and deep capillary plexus (DCP) in the 6 mm × 6 mm perifoveal ring (right). Vertical bars represent 95% confidence interval. *p<0.005 as compared to baseline (Repeated measures ANOVA and the Greenhouse–Geisser correction). †<p<0.01 as compared to baseline (Repeated measures ANOVA and the Greenhouse–Geisser correction).
Abbreviations: ns, not significant; SCP, superficial capillary plexus; DCP, deep capillary plexus.

Table 6 Overview of the Best-Corrected Visual Acuity (BCVA), Macular Volume (MV), and Central Choroidal Thickness Over the Course of the Study Follow-Up. P values were Calculated Using Repeated Measures ANOVA and the Greenhouse–Geisser Correction

	Baseline	Month 1	Month 2	Month 3	P value
BCVA					
Mean (SE)	0.48 (0.03)	0.66 (0.05)	0.71 (0.05)**	0.67 (0.05)	<0.0001
Mean (95% CI) from baseline	NA	0.18 (0.09 to 0.28)	0.23 (0.13 to 0.33)	0.19 (0.09 to 0.30)	
P value*	NA	<0.0001	<0.0001	0.0001	
MV, mm^3					
Mean (SE)	12.00 (20.28)	10.89 (0.17)	10.53 (0.16)**	11.19 (0.27)	0.0001
Mean (95% CI) from baseline	NA	-1.11 (−1.49 to −0.74)	-1.47 (−1.95 to −1.00)	-0.81 (−1.37 to −0.26)	
P value*	NA	<0.0001	<0.0001	0.0016	
CCT, µm					
Mean (SE)	244.5 (17.7)	236.7 (18.0)	232.7 (17.8)	241.2 (18.4)	0.0181
Mean (95% CI) from baseline	NA	-7.7 (−20.2 to 4.7)	-11.7 (−22.1 to −1.4)	-3.3 (−14.9 to 8.4)	
P value*	NA	0.0932	0.0020	0.3105	

Notes: *Post hoc analysis for pairwise comparisons were done with the Scheffé's method (Bonferroni corrected). **P<0.05 as compared to M1.
Abbreviations: BCVA, Best-corrected visual acuity; SE, Standard error; CI, Confidence Interval; NA, Not applicable; MV, Macular volume; CCT, Central choroidal thickness.

There was a significant correlation between baseline FAZ area (in both 3 mm × 3 mm and 6 mm × 6 mm scans) and mean change in CMT, p, 0.0157 and p, 0.0014, respectively (Table 7). No other relationships between quantitative OCTA values and clinical outcomes (BCVA and CMT) were found.

No serious adverse events were reported during the study.

Discussion

The multifactorial nature of the pathophysiology of DME makes it necessary to search for tools and biomarkers that help us understand the disease.[4,5]

The OCTA is a technical device that allows the acquisition of very high-resolution images of all the vascular layers of the retina in a rapid and, unlike the standard fluorescein angiography, non-invasive fashion.[12]

Additionally, OCTA is able to provide quantitative information, such as VD and VP, which may be useful for monitoring both the course of the disease and the treatment response.[11,12,22]

VD and VP are two parameters that evaluate the retinal vessels. VP represents the area occupied by vessels divided by the selected area, while VD is the linear length of vessels divided by the selected area.[23,24]

The current study evaluated the effect of a unique DEX implant on vascular parameters of OCTA, and functional and anatomic clinical outcomes in a cohort of DME patients.

Besides the significant improvements in both functional and anatomic outcomes observed after DEX implant administration, the results of this study also found a significant reduction of the quantitative vascular parameters.

VD in the SCP in the perifoveal ring of the 6 mm × 6 mm scan analysis at month 2 was significantly decreased. This change was mainly due to the nasal quadrant, which is where the papillo-macular bundle is located. At month 2, VP in the SCP was significantly decreased from baseline in the perifoveal ring of the 6 mm × 6 mm scan in the overall and in each of the four quadrants. Additionally, we also observed an additional VP reduction in the parafoveal ring of the 6 mm × 6 mm scan from month 1 and month 2.

Regarding VP in the DCP, we found a significant reduction in the perifoveal ring of the 6 mm × 6 mm scan at months 2 and 3.

Our study did not find any changes in FAZ area in both 3 mm × 3 mm and 6 mm × 6 mm scans.

The effect of corticosteroids on retinal vessels has been previously described.[25,26] Semeraro et al,[25] in a cohort of patients with retinal vein occlusion, reported a reduction in arteriolar lumen diameter, assessed by scanning-laser Doppler

Table 7 Correlation Coefficient of Mean Changes in Best-Corrected Visual Acuity (BCVA) and Central Macular Thickness (CMT) with Baseline Vascular Parameters. Correlation Coefficient Have Been Adjusted by Age and Duration of Diabetes

	Changes in BCVA	Changes in CMT
FAZ 3 mm × 3 mm area		
Partial CC	0.042	0.52
P value	0.8560	0.0157
FAZ 6 mm × 6 mm area		
Partial CC	0.03	0.63
P value	0.9065	0.0014
VD SCP 3 mm × 3 mm perifoveal ring		
Partial CC	0.04	0.16
P value	0.8232	0.4383
VP SCP 3 mm × 3 mm perifoveal ring		
Partial CC	−0.03	0.15
P value	0.8654	0.4658
Perfusion DCP 3 mm × 3 mm perifoveal ring		
Partial CC	−0.16	−0.15
P value	0.4193	0.4490
VD SCP 6 mm × 6 mm perifoveal ring		
Partial CC	−0.08	0.12
P value	0.6906	0.5262
VD SCP 6 mm × 6 mm parafoveal ring		
Partial CC	0.02	0.15
P value	0.9352	0.4196
VP SCP 6 mm × 6 mm perifoveal ring		
Partial CC	−0.09	0.11
P value	0.6225	0.5808
VP SCP 6 mm × 6 mm parafoveal ring		
Partial CC	−0.01	0.15
P value	0.9716	0.4200
Perfusion DCP perifoveal ring*		
Partial CC	−0.07	0.20
P value	0.7378	0.2998
Perfusion DCP parafoveal ring*		
Partial CC	−0.10	0.22
P value	0.5982	0.2443

Notes: * 6 mm × 6 mm scan.
Abbreviations: BCVA, Best-corrected visual acuity; CMT, Central macular thickness; FAZ, Foveal avascular zone; CC, Correlation coefficient; VD, Vessel density; VP, Vascular perfusion; SCP, Superficial capillary plexus; DCP, Deep capillary plexus.

flowmetry, after DEX implant, which may have a positive impact on vascular leakage and macular swelling. Additionally, intravitreal triamcinolone appeared to reduce the caliber in both retinal arterioles and venules in eyes with refractory DME.[26]

Toto et al[14] did not find significant changes in VP after DEX implant in both superficial and deep capillary plexuses. However, they found a "normalization in the caliber of the deep vessels". We must take into account that OCT-A signal does not correspond to vascular caliber but to lumen. Thus, they should have better stated that "normalization in the lumen of the deep vessels" was found.

In agreement with their results, we did not observe significant changes in total VD or VP (SCP and DCP) in the 3 mm x 3 mm and 6 mm x 6 mm scans. Nevertheless, at month 2, VD, VP in SCP and VP in DCP in the 6 mm x 6 mm perifoveal ring showed a significant decrease as compared to baseline.

Changes in VD and VP may be due either to an indirect or to a direct effect of DEX. DEX reduces DME, with the subsequent reduction in central retinal thickness, which could modify the vessels distribution (indirect effect). On the other hand, as mentioned above, DEX implant can reduce the vascular diameter (direct effect).[25,26] However, this would explain a reduction in VP but not in VD.

If changes in VD were caused by a purely mechanical effect of reducing edema (indirect effect), there would be a relationship between CMT reduction and VD changes. However, our study did not find any relationship between changes in CMT and changes in VD (r: 0.037, p, 0.8342). Thus, indirect effect is not the most likely explanation for changes in VD and VP.

Regarding the direct effect, it has been previously suggested that retinal arteriolar and venular calibers are larger in patients with DR.[27] On the other hand, it has been reported that VP is decreased in both SCP and DCP in patients with DR and the higher the DR degree the lower the VP measured with OCTA.[28,29] This may indicate that capillary loss that occurs in DR has a greater impact on VP than the increase in the caliber of large and medium vessels. Since there is evidence suggesting that vessel caliber enlargement in diabetes is related to inflammation,[30] it would make sense to suppose that DEX implant reduces VP, by reducing vessels diameter and, specifically, vessels lumen. However, variations in vessels lumen would impact on VP, but not in VD (where it does not matter if vessels are thick or thin).

In our study, VP reduction seems to be associated with changes in VD. There was a significant relationship between the changes in VD and changes in VP in SCP in the 3 mm x 3 mm scan (r: 0.992, 95% CI: 0.983 to 0.996; $p < 0.0001$) and in the 6 mm x 6 mm scan (r: 0.997, 95% CI: 0.993 to 0.998; $p < 0.0001$).

The underlying mechanism behind VD reduction is not so clear. The phenomenon of suspended scattering particles in motion (SSPiM) could be a plausible explanation for our results. This phenomenon is frequently observed in vascular cystic macular edema, in which some cysts have hyperreflective material as seen by OCT. This material is composed of particles with a Brownian movement that give a false-positive signal in OCTA.[31] The presence of SSPiM may lead to an overestimation of VP and VD.[32] This type of cysts is potentially more sensitive to steroids than to anti-VEGF (as other types of lipid exudation as hard exudates or hyperreflective foci). A reduction or disappearance of these hyperreflective cysts after DEX treatment would result in a reduction of the OCTA flow signal.

Retinal hypoxia, caused by either obstruction or loss of retinal capillaries, seems to be the responsible for the high levels of VEGF and several inflammatory cytokines, which are critical in the pathogenesis of DR and DME.[6–8] These inflammatory molecules cause a significant increase in leukocyte adhesion to the retinal microvasculature (leukostasis), which appears to have a central role in the development of DR and DME.[6–8] The capillary blockage secondary to leukostasis would lead to the development of non-perfusion areas, especially in the DCP.[33,34]

Intravitreal corticosteroids block the production of inflammatory mediators, and inhibit leukostasis.[35,36] Inhibition of leukostasis would lead to the opening of capillaries and the subsequent increase in perfusion.[6]

However, the reduction in VD and VP observed in the current study did not confirm this assumption. Based on the results of our study, it may be hypothesized that despite DEX implant might be able to open capillaries, capillary loss associated with DR and DME seems to be due to permanent vascular occlusion instead of leukostasis.[14,30]

Our study found different outcomes in the 3 mm × 3 mm and the 6 mm × 6 mm scans in both SCP and DCP. These findings are in agreement with those of Lei et al, who reported differences in VD depending on the pattern (3 mm × 3 mm or 6 mm × 6 mm) and the location (inner or outer) of the scans.[37]

This study did not find any change in FAZ area.

We found a significant direct relationship between baseline FAZ size and CMT reduction after DEX. Such a relationship was not observed between FAZ size and BCVA changes. A larger baseline FAZ size reflects a greater macular vascular compromise. This could lead to a greater baseline CMT and therefore a greater decrease in edema after treatment. None of the other OCTA parameters had any relationship with either functional or anatomic outcomes.

In addition to the vascular effects, DEX implant significantly improved both functional and anatomic outcomes. These findings do not differ from the currently available scientific evidence.[38–42]

Our study showed a significant improvement in BCVA and anatomic outcomes 1 month after DEX. However, VD and VP did not show any change until month 2.

Additionally, at month 3, most quantitative vascular parameters showed similar values to baseline, despite BCVA and anatomic outcomes still remained better than at baseline. The relevance of these findings critically depends on whether vascular parameters behavior may predict the evolution of the DME. Further research is needed to elucidate the predictive ability of OCTA parameters to detect the recurrence of DME.

Regarding safety, 8 (22.9%) eyes had a raise in IOP ≥ 10 mm Hg as compared to baseline. In all cases, increased IOP was managed with topical medication and none required surgery. These results are in line with those reported in other studies.[38–41]

Finally, it should be mentioned that eight patients were lost of follow-up because the COVID-19 pandemic lockdowns and restrictions. Due to COVID-19 outbreak over the last 2 years, the strategies adopted by the different Governments for reducing the risk of infection spreading have dramatically disrupted the provision of health care resulting from deferral of routine aesthetic procedures.[43] In the current times of pandemic, DEX implant may entail an advantage over routine monthly anti-VEGF therapy because it avoids visits to medical centers,[44,45] but this is beyond the objective of our study.

The current study has a few limitations. The first one is the lack of a reproducibility assessment before starting the study. Nevertheless, it should be taken into consideration that repeatability and reproducibility of OCTA are high, although might be affected by different artifacts, especially in pathologic conditions such as DME.[37,46,47] Another limitation is its open-label design. However, data have been analyzed by an independent statistician, who was blind to the intervention. Finally, we evaluated a heterogeneous cohort of DME, which may artifact the results. Nevertheless, our cohort reflects the reality of routine clinical practice, which may add clinical relevance to this paper.

Conclusions

Despite these limitations, the results of this study suggested that a single DEX implant may modify quantitative vascular parameters assessed by OCTA. In addition to the functional and anatomic improvements, DEX implant significantly reduced vessel density and vascular perfusion in patients with DME. Further research is needed, particularly prospective, multicenter, and long-term follow-up studies, to better assess the role of DEX in vascular remodeling, the role of the phenomenon of SSPiM in this process, and the role of OCTA parameters as potential biomarkers in DME outcomes.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author [PCM], upon reasonable request.

Statement of Ethics

"All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Ethical Committee for Clinical Research of Galicia (CEIC). Informed consent was obtained from all individual participants included in the study.

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Author Contributions

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