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The analysis of optical coherence tomography angiographic parameters in patients with and without clinically significant diabetic macular edema

Mehmet Demir, Cetin Akpolat, Ceylan Uslu Dogan, Gurcan Dogukan Arslan, Dilek Guven

Sisli Hamidiye Etfal Training and Research Hospital, Department of Ophthalmology, Istanbul, Turkey

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Abstract

The aim of our study was to compare the parameters of optical coherence tomography angiography between eyes with clinically significant macular edema (CSME) and without (w/o) CSME in patients diagnosed with diabetic macular edema (DME). Sixty-eight eyes of 34 patients with DME were included in the cross-sectionally designed study. The eyes of the patients with DME were divided into 2 groups, including the eyes with CSME and the eyes w/o CSME. Optical coherence tomography (OCTA) parameters, including central macular thickness, superficial and deep capillary plexus, and choriocapillaris flow area were evaluated between these two groups. Eyes with CSME had a thicker central retinal thickness (CRT), ($P \leq 0.001$) and worse visual acuity (VA), ($P=0.002$), and there was a strong negative correlation between CRT and VA among patients with CSME ($r=-0.616$, $P \leq 0.001$). We observed increases in the vessel density (VD) measurements of the superficial fovea ($P=0.006$) and deep fovea areas ($P=0.036$), whereas reductions in the VD measurements of other deeper plexuses in the comparison of eyes with CSME and w/o CSME in patients with diagnosis of DME. We did not note significant differences between FAZ metrics. OCTA could be used as a noninvasive modality to assess and compare the structural and vasculature changes in diabetic patients with or/and w/o CSME.

Keywords: Clinically significant macular edema, optical coherence tomography angiography, vessel density, diabetic macular edema

Introduction

Diabetes mellitus (DM) is a worldwide chronic and systemic health issue, including ophthalmic complications, especially diabetic retinopathy (DR) with 2 types of proliferative (PDR) and non-proliferative diabetic retinopathy (NPDR) [1,2]. DR is among the most common reasons for blindness mainly caused by diabetic macular edema (DME), which can occur at any of stage of PDR or NPDR [3]. DME defines the thickening of the retina and is a complicated result of DR in patients with improper DM control, long lasted DM and the type of DM [4]. A previous study reported that up to 7% of people with DM might develop DME [5]. Another study reported that patients with type 1 DM had a prevalence of DME ranged between 4.2% and 7.9%, while patients with type 2 DM had a prevalence of DME more largely ranged between 1.4% and 12.8% [6]. Unfortunately, DME has an increasing tendency of global prevalence due to the increasing prevalence of DM, especially in the aspect of the type 2 DM [7].

DME is a main reason for vision loss related to DR and qualifies as exudation and macular extracellular fluid accumulation caused by the increase of vascular permeability [8,9]. There are various explained mechanisms responsible for the etiopathogenesis of DME, including retinal neurodegeneration, blood–retinal barrier impairment, increased local inflammatory activity, vascular endothelial damage, vascular endothelial growth factor (VEGF) overexpression, cellular hypoxia and oxidative stress [10]. Macular edema is clinically subgrouped into clinically significant macular edema (CSME) and clinically nonsignificant macular edema based on the Early Treatment Diabetic Retinopathy Study (ETDRS).

DME could be diagnosed by fundus exam and confirmed with color stereo fundus photograph, optical coherence tomography (OCT), fundus fleurescein angiography (FFA) and optical coherence tomography angiography (OCTA). Technologic developments have offered innovations in the retinal imaging area since the

***Corresponding Author:** Cetin Akpolat, Sisli Hamidiye Etfal Training and Research Hospital, Department of Ophthalmology, Istanbul, Turkey
E-mail: akpolatcetin@yahoo.com)

invention of OCT in 1991 [11]. OCT provides a comparison with the histological microscopy of the retina. OCT has become an essential imaging method to diagnose and follow DR, particularly DME [12]. However, OCT has limitations for the assessment of retinal vasculature and blood flow [13]. Although, FFA and indocyanine green angiography (ICG) can view the dynamic changes and retinal vasculature, they have some disadvantages, including intravenous dye usage, time-consuming, the lack of 3-dimensional (3D) scans, poor image quality and handicap in quantitative calculation [14]. The presentation of OCTA has partially eliminated these problems and has provided rapid, non-invasive, high-resolution 3D scans and reliable quantification of the choroidal and retinal structures and vasculature [15-17]. One of or combination of laser photocoagulation, intravitreal anti-VEGF and corticosteroids, and surgical procedures are of the treatment options for DME [18].

CSME may develop in various retinal disorders and should be evaluated with imaging studies. In the current study, our purpose was to assess and compare the changes of OCTA parameters between the eyes with CSME and eyes without (w/o) CSME among the patients with DME.

Materials and Methods

This study was carried out in a tertiary eye clinic in accordance with the principles of the Declaration of Helsinki. The study was approved by the local medical ethics committee (Sisli Hamidiye Etfal Training and Research Hospital, 2939). Informed consent forms were signed by all participants.

Patients and Ophthalmic Examination

The patients whose both eyes with the diagnose of naive DME were included. The study was designed in a cross-sectional nature. CSME was detected clinically on biomicroscopic fundus assessment, and the diagnosis was confirmed by OCTA (spectral-domain, SD) following pupillary dilatation. CSME in patients with DME was detected within 500 μm from the central macula considering the ETDRS guideline [19], which was described according to the slit lamp biomicroscope examination as 1) retinal thickening at or within 500 μm from the central macula; or 2) hard exudate at or within 500 μm from the central macula related to adjacent retinal thickening; or 3) increase of retinal thickness in ≥1 disc area , within 1 disc diameter from the central macula. None of the patients had any other ocular disease other than DME during enrollment. Sixty-eight eyes of 34 patients with DME were divided into two groups. Eyes (40 eyes of 30 participants) with CSME were included in the CSME group and the left eyes (28 eyes of 20 patients) w/o CSME comprised the non-CSME group. A detailed ophthalmic examination was applied for all participants, including visual acuity (VA, in decimal), intraocular pressure (Pneumatic tonometry, IOP, mmHg), anterior segment exam with a slit lamp, posterior segment biomicroscopic examination, color fundus photography (Canon CF- 60DS, Canon Inc., NY), and OCTA measurements, composed of foveal avascular zone (FAZ, mm2), FAZ perimeter (mm), central retinal thickness (CRT, um), blood flow area (BFA, mm2) in choriocapillaris, and vessel density (VD, the proportion of the region occupied by vasculature in the OCTA enface scan, %) or capillary plexus density (CPD: superficial capillary plexus (SCP) and deep capillary plexus (DCP)) in superficial fovea, superficial parafovea, superficial superior hemifield (parafoveal), superficial inferior hemifield (parafoveal), deep fovea, deep parafovea, deep superior hemifield (parafoveal), and deep inferior hemifield (parafoveal) areas. Patients with glaucoma, cataract, inflammatory eye disease, previous ocular surgery within 6 months, and any kind of retinopathy other than DR were excluded. Pregnant participants and patients with any kind of cancer disease were also not included.

Measurement Protocol

The OCTA recording volumes are mostly ranged from 2×2 up to 6×6 mm. For the optimal macular image resolution, 3×3 mm volumes are usually used. We measured retinal and choroidal structures and vasculature via a SD-OCTA device (Optovue RTVue XR Avanti; Optovue, Inc, Fremont, CA, USA) with 840 nm wavelength, 20×7 μm resolution, and 70.000 A-scans per second. The measurements were performed at both the foveal and parafoveal areas for all participants. All SD-OCTA images were performed by the same experienced clinician. All scans were measured within the 3×3 mm area centered on the fovea, including FAZ area, which was calculated as the avascular area in the center of the fovea and the border of the FAZ was manually confirmed. The mean thickness of retina within 1 mm diameter ring of the macular center was described as CRT. An automated segmentation module was used within the same day of the clinal examination for the division of retinal vasculature layers, including SCP, DCP, and the choroid. Quantitatively assessed SCP was the vasculature region beginning from 3 microns under the internal limiting membrane (ILM) to 15 microns under the inner plexiform layer (IPL), and quantitatively assessed DCP was the vasculature area from the end border of SCP to 70 microns under the IPL. The VD (%) was defined as vascular area (pixels) / (region of interest – FAZ area) (pixels) ×100, and the specifies of the analysis of BFA in the choriocapillaris has been previously described (20). Manual adjustments were performed in case of scan errors. OCTA images low resolution (if the signal strength ≤5/10), motion artifacts, or incorrect auto-segmentation were not included in the analyses.

Statistics

The study was analyzed by SPSS for Mac version 23.0 software. Categorical features were described in frequencies and percentages, and continuous parameters were expressed as mean±standard deviation. Normal distribution of the data was confirmed by the Kolmogorov-Smirnov test. OCTA measurements were evaluated using Mann-Whitney U and independent samples t-tests. It was accepted significant if the p-value was smaller than 0.05.

Results

The average age of the 34 participants was 61.06±7.36 years. Fourteen patients (41.2%) were female, and 20 patients (58.8%) were male. Fifty-five (80.9%) of the 68 eyes were phakic and the left were pseudo-phakic (13,19.1%). Forty eyes (58.8%) were with CSME, and 28 eyes (41.2%) were w/o CSME. There was not any statistically difference in gender of patients (P=0.462) and phakic or pseudo-phakic status of the eyes (P=0.397) between the CSME and non-CSME groups.

Superficial foveal, deep foveal, and parafoveal VD numeric

parameters (Deep fovea, deep parafovea, deep superior hemifield, and deep inferior hemifield) had normal distributions, so they were analyzed by independent samples t-test and Pearson correlation formula. All other numeric parameters did not have normal distributions, so they were analyzed by Mann-Whitney U test and Spearman correlation formula. Comparisons of VA, age, and OCTA parameters between the CSME and non-CSME groups were shown in Table 1.

Table 1. The Comparison of VA, age, and OCTA measurements between the eyes with CSME and w/o CSME

Parameters	CSME Group (n=40)	Non-CSME Group (n=28)	P
VA (decimal)	0.52±0.35	0.75±0.26	0.002*
Age (years)	59.96±7.77	62.61±6.55	0.256
****Superficial Fovea (VD, %)**	20.93±9.32	15.64±6.08	0.006*
Superficial Parafovea (VD, %)	44.34±6.60	47.09±4.59	0.079
Superficial Superior Hemifield (VD, %)	42.35±7.21	44.95±4.82	0.210
Superficial Inferior Hemifield (VD, %)	44.49±5.16	47.62±6.96	0.107
****Deep Fovea (VD, %)**	36.03±10.52	31.15±8.53	0.039*
****Deep Parafovea (VD, %)**	48.37±6.06	51.46±4.74	0.022*
****Deep Superior Hemifield (VD, %)**	47.26±6.51	50.40±4.62	0.023*
****Deep Inferior Hemifield (VD, %)**	48.17±5.36	50.53±4.21	0.046*
FAZ Area (mm²)	0.45±51.34	0.32±0.13	0.334
FAZ Perimeter (mm)	2.28±1.06	2.2377±46247	0.366
CRT (um)	358.02±114.63	247.93±31.91	≤0.001*
BFA in Choriocapillaris (mm²)	1.63±0.51	1.58±0.63	0.436

** Independent samples t-test was used, * Statistically significant, w/o: Without, CSME: Clinically significant macular edema, VA: Visual acuity, OCTA: Optical coherence tomography angiography, VD: Vessel density, FAZ: Foveal avascular zone, CRT: Central retinal thickness, BFA: Blood flow area

Correlations in the CSME Group

VA had a strong reverse correlation with CRT (r=-0.616, P≤0.001). Superficial foveal VD showed positive correlation with CRT (r=+0.490, P=0.001), but negative correlation with FAZ perimeter (r=-0.413, P=008). Superficial parafoveal VD showed a strong positive correlation with superficial superior hemifield VD (r=+0.961, P≤0.001), but negative correlations with BFA in choriocapillaris (r=-0.409, P=010). Superficial superior hemifield VD presented negative correlation with BFA in choriocapillaris (r=-0.402, P=0.010). Deep parafoveal VD presented strong positive correlations with deep superior hemifield VD (r=+0.950, P≤0.001), deep inferior hemifield VD (r=+0.923, P≤0.001), superficial parafoveal VD (r=+0.698, P≤0.001), and superficial superior hemifield VD (r=+0.653, P≤0.001) but negative correlation with FAZ perimeter (r=-0.365, P=0.021). Deep superior hemifield VD showed strong positive correlation with deep inferior hemifield (r=+0.809, P≤0.001), superficial parafoveal VD (r=+0.722, P≤0.001) and superficial superior hemifield VD (r=+0.713, P≤0.001), but negative correlation with FAZ perimeter (r=-0.431, P=0.006). Deep inferior hemifield VD presented positive correlation with superficial parafoveal VD (r=+0.554, P≤0.001) and superficial superior hemifield (r=+0.525, P=0.001), but a weak negative correlation with FAZ perimeter (r=-0.317, P=0.046). FAZ area had a strong positive correlation with FAZ perimeter (r=+0.784, P≤0.001).

Correlations in the non-CSME Group

VA showed no correlation with any parameters, including CRT. Superficial foveal VD showed positive correlation with deep foveal VD (r=+0.738, P≤0.001), whereas negative correlations with FAZ area (r=-0.723, P≤0.001) and FAZ perimeter (r=-0.724, P≤0.001). Superficial parafoveal VD showed positive correlations with superficial superior hemifield (r=+0.923, P≤0.001), superficial inferior hemifield VD (r=+0.853, P≤0.001), deep parafoveal VD (r=+0.479, P=0.010), deep superior hemifield VD (r=+0.430, P=0.022). Superficial superior hemifield VD presented positive correlation with superior inferior hemifield VD (r=+0.851, P≤0.001). Deep foveal VD showed positive correlations with deep superior hemifield VD (r=+0.416, P=0.028) and CRT (r=+0.468, P=0.012), but negative correlations with FAZ area (r=-0.863, P≤0.001) and FAZ perimeter (r=-0.872, P≤0.001). Deep parafoveal VD presented very strong positive correlations with deep superior hemifield VD (r=+0.942, P≤0.001) and deep inferior hemifield VD (r=+0.924, P≤0.001), but negative correlation with BFA in choriocapillaris (r=-0.407, P=0.031). Deep superior hemifield VD showed positive correlation with deep inferior hemifield VD (r=+0.824, P≤0.001). Deep inferior hemifield presented weak reverse correlation with CRT (r=-0.387, P=0.042). FAZ area had a very strong positive correlation with FAZ perimeter (r=+0.970, P≤0.001).

Correlations in all patients with DME

Age showed positive correlations with deep parafoveal VD (r=+0.311, P=0.010) and deep superior hemifield VD (r=+0.260, P=0.032). VA showed a negative correlation with CRT (r=-0.527, P≤0.001). CRT showed negative correlations with superficial parafoveal VD (r=-0.318, P=0.008), superficial superior hemifield VD (r=-0.253, P=0.037), and superficial inferior hemifield VD (r=-0.269, P=0.026). BFA in choriocapillaris had reverse correlation with superficial parafoveal VD (r=-0.322, P=0.007), superficial superior hemifield VD (r=-0.261, P=0.031), and superficial inferior hemifield VD (r=-0.259, P=0.033). Superficial parafoveal VD showed positive correlations with superficial superior hemifield VD (r=+0.946, P≤0.001), and superficial inferior hemifield VD (r=+0.912, P≤0.001). Superficial superior hemifield VD was positively correlated with superficial inferior hemifield VD (r=+0.878, P≤0.001). FAZ area showed a strong positive correlation with FAZ perimeter (r=+0.869, P≤0.001).

Superficial foveal VD showed a positive correlation with deep foveal VD (r=+0.690, P≤0.001). Deep parafoveal VD showed positive correlations with deep superior hemifield VD (r=+0.950, P≤0.001), and deep inferior hemifield VD (r=+0.928, P≤0.001).

Deep superior hemifield VD presented a positive correlation with deep inferior hemifield VD (r=+0.823, P≤0.001).

Superficial parafoveal VD presented positive correlations with deep parafoveal VD (r=+0.659, P≤0.001), deep superior hemifield VD (r=+0.668, P≤0.001), and deep inferior hemifield VD (r=+0.520, P≤0.001). Superficial superior hemifield VD showed positive correlations with deep parafoveal VD (r=+0.589, P≤0.001), deep superior hemifield VD (r=+0.643, P≤0.001), and deep inferior hemifield VD (r=+0.470, P≤0.001). Superficial inferior hemifield VD had positive correlations with deep parafoveal VD (r=+0.433, P≤0.001), deep superior hemifield VD (r=+0.437, P≤0.001), and deep inferior hemifield (r=+0.357, P=0.003). FAZ area showed a positive correlation with deep foveal VD (r=+0.261, P=0.032). FAZ perimeter showed negative correlations with superficial foveal VD (r=-0.443, P≤0.001), deep foveal VD (r=-0.670, P≤0.001), deep parafoveal VD (r=-0.314, P=0.009), deep superior hemifield VD (r=-0.377, P=0.002), and deep inferior hemifield VD (r=-0.250, P=0.040). CRT presented a positive correlation with superficial foveal VD (r=0+0.527, P≤0.001). BFA in choriocapillaris showed negative correlations with deep parafoveal VD (r=-0.295, P=0.14), and deep superior hemifield VD (r=-0.244, P=0.045) (Figure 1, 2).

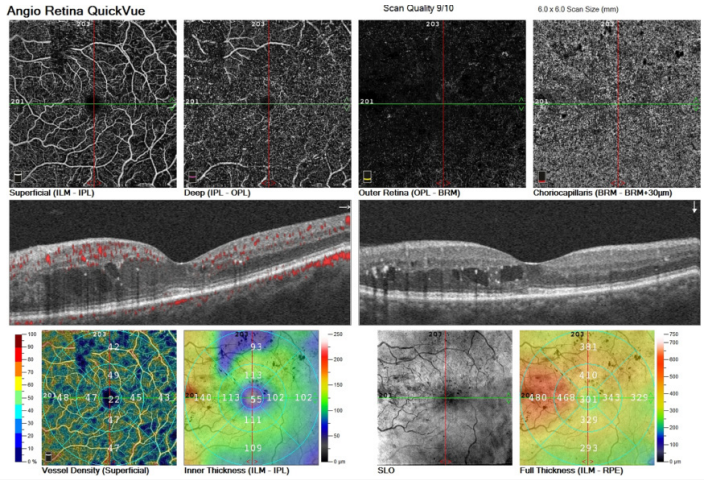

Figure 1. Optical coherence tomography angiography image representing clinically significant macular edema in a patient with diabetic macular edema

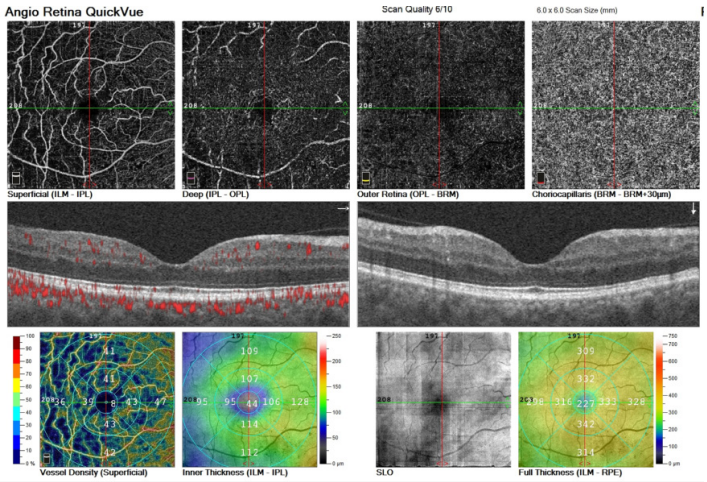

Figure 2. Optical coherence tomography angiography image representing non-CSME (clinically significant macular edema) in a patient with diabetic macular edema

Discussion

OCTA has gained agreement in the evaluation of DR and DME findings and comparing the changes between the different stages and severity of DR and DME, including patients with CSME and w/o CSME. Moreover, OCTA may offer us the opportunity to detect subclinical DR despite the contrary studies [19-21]. In the current study, we assessed the differences between OCTA measurements of eyes with CSME and w/o CSME in patients with DME. Although CSME is a clinical assessment of DME, we tried to evaluate the clinical phenomenon using a quantitative tool.

Previous studies published in the literature have reported that VD in OCTA showed a decreasing tendency in DR and this decrease gets worsening with DR severity, despite the discordance in the outcomes of the analysis in the deeper plexuses [22-24]. We observed opposite results in our study with an increasing tendency of VD in the superior fovea and deep fovea areas, and we noted similar results of decreasing VD in other deeper plexuses in the comparison of eyes with CSME and w/o CSME in patients with DME. As expected, worse VA values were documented in our results, which was parallel to the literature reporting poor VA with DR severity and an association between poor VA and edema [25-27].

FAZ contour can demonstrate diabetic macular ischemia grading using OCTA as well as FFA [28]. OCTA findings have demonstrated FAZ enlargement in DR cases when compared to healthy individuals and a correlation with this enlargement and the severity of DR, which has also been presented in FFA images [29, 30]. Both FAZ area and perimeter had an increasing tendency in eyes with DR compared to control eyes, supporting previous studies [31]. However, no significant FAZ area and perimeter enlargement were noted in eyes with CSME when compared to eyes w/o CSME. Our results agree with previously described studies that concluded an increase in CRT with worsening degree of DME and a strong correlation with VA and CRT in patients with DR [27,32,33].

DR may affect the retinal choroidal system in addition to the retinal vascular system. In patients with DR, the choriocapillaris layer can be quantitatively evaluated non-invasively by OCTA, and the choriocapillaris flow area may be lower than in healthy subjects [34]. A cross-sectionally designed study revealed that retinal and choriocapillaris microvasculature deteriorations were observed in OCTA findings in all stages of DR [35]. Dynamic imaging modalities presented a decrease in BFA of choriocapillaris in eyes with DR [36]. Moreover, choriocapillaris VD had a decreasing tendency in DR when compared to control subjects, supporting those choroidal vascular changes might be related with the pathogenesis of DR [37]. A study reported decreased flow density in choriocapillaris of subjects with proliferative DR and DME [38]. However, we did not find any difference in BFA of choriocapillaris between patients with CSME and w/o CSME.

Our results showed a strong negative correlation between VA and CRT in eyes with CSME (and DME independent of comparing eyes with CSME and w/o CSME), but no correlation in eyes w/o CSME, which represents the importance of macular involvement in VA. Superficial foveal VD decrease meant enlargement of FAZ perimeter in both eyes with CSME and w/o CSME. The increase in FAZ area demonstrated a similar increase in FAZ perimeter in eyes

with CSME and w/o CSME and in eyes with DME, independent of comparing eyes with CSME and w/o CSME. Superficial parafoveal VD showed a positive correlation with superficial superior hemifield in both eyes with CSME and w/o CSME. Deep parafoveal VD presented positive correlations with deep superior hemifield VD and deep inferior hemifield VD in both eyes with CSME and w/o CSME. We observed a tendency of more regular association between SCP and DCP density in eyes w/o CSME (and in eyes with DME independent of comparing eyes with CSME and w/o CSME) than in eyes with CSME, which suggests that more deteriorations in superficial and deep retinal, and choroidal microvascular network happen when worse and/or clinically significant macular edema is present.

Conclusion

In conclusion, despite limitations such as device proper algorithms, projection artifacts, and limited field of view, OCTA can provide important information regarding choroidal and retinal vascular alterations in eyes with CSME compared to eyes w/o CSME. This provides us CSME screening, therapy monitoring, and evaluation and progression of the disease severity. Overall, OCTA demonstrates the ability to increase our understanding of the retinal and choroidal microvascular alterations in eyes with CSME caused by DME and allows further promise in the revolution of disease evaluation. Considering cross-sectional nature and small sample size, studies with larger sample size and prospective nature are warranted.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Regarding consent of ethics, the study was conducted according the principles of the Declaration of Helsinki

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