Foveal evaluation in diabetic patients with macular edema using optical coherence tomography angiography

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Purpose
The aim of this study was to evaluate the foveal avascular zone (FAZ) in patients with diabetic macular edema (DME) by documenting the morphological and quantitative changes by optical coherence tomography angiography (OCTA).
Patients and methods
The study included 47 eyes of 47 participants. They were allocated into two groups: 27 eyes of 27 patients having DME and 20 eyes of 20 age-matched healthy controls. All study participants were imaged using OCTA machine to assess the FAZ area and to compare the changes between patients and controls.
Results
The FAZ area was significantly enlarged in patients with DME than in controls ($P<0.001$), together with the presence of other morphological changes (microaneurysms, capillary loops, and widened intercapillary spaces). Retinal vessel densities were also reduced in patients than in controls at both the superficial and deep retinal capillary complexes.
Conclusion
Qualitative and quantitative changes do occur in patients with DME, which could be documented using the OCTA. This helps better disease staging and monitoring as well as treatment decisions.

Keywords:
diabetic macular edema, foveal avascular zone, optical coherence tomography angiography, vessel density

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Introduction

Diabetes mellitus induces serious complications like diabetic retinopathy (DR) which affects the retinal microvasculature and is among the most significant causes of visual function impairment in working-age individuals. An expected rise in the total number of patients with DR around the world between 2010 and 2030 has been estimated to be between 126.6 million and 191.0 million patients [1].

Visual impairment owing to DR affects the patient's life quality, disease management, the overall life expectancy, and the incidence of other diabetic complications [2].

Microvascular changes in DR include thickened basement membrane, damaged endothelium, and selective pericyte loss [3].

Diabetic macular edema (DME) is a significant etiology of the impaired visual function among diabetics, affecting up to 21 million of 93 million diabetics with DR around the world [4]. The overall prevalence of DME is 6.81% in diabetic patients, accounting for 12% of new cases of blindness per year [5]. The rate of visual loss in patients with DME has been reported to be a three-line loss of vision within 3 years in 24% of affected eyes [6].

Fluorescein angiography (FA) which is considered the cornerstone for fundus imaging provides two-dimensional images of the large-sized superficial retinal vessels which are mainly present in the nerve fiber layer and partly in the ganglion cell layer. However, deeper retinal vasculature remains invisible. Moreover, FA has been reported to induce life-threatening complications, yet rarely [7].

Optical coherence tomography (OCT) is an important imaging investigation since its first introduction in 1991. Optical coherence tomography angiography (OCTA) was demonstrated in 2015 to be able to demonstrate all layers of retinal blood vessels even in the deep retinal layers [8]. OCTA is a noninvasive tool that simultaneously visualizes retinal vasculature as well

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as microstructure in a three-dimensional, depth-resolved fashion without dye injection. It provides high-resolution volumetric angiograms that allow the superficial capillary plexus (SCP) and deep capillary plexus (DCP) to be studied separately [9].

In 2012, an intensity-based technique was introduced to visualize the choroidal and retinal microvasculature called split-spectrum amplitude-decorrelation angio graphy algorithm, which splits the spectrum of the OCT into narrower bands. It then averages the intensity decorrelation detected in each band [10,11].

This study aimed to assess the role of OCTA in documenting the foveal avascular zone (FAZ) area and retinal vessel density (VD) changes in cases of DME to find out biomarkers to monitor the disease status.

Patients and methods

The current study is an observational cross-sectional one that included 47 eyes of 47 participants. Study participants were allocated into two groups: 27 eyes of 27 patients having DME and 20 age-matched and sex-matched healthy controls. Patients with moderate to severe nonproliferative DR of both sexes were included, with age ranged from 30 to 60 years. Exclusion criteria were those with opaque ocular media, refractive error more than or equal to 5 D, co-existent age-related macular degeneration, inflammatory retinal disorders, macular scarring, cases with history of anti-vascular endothelial growth factor injection in the past 6 months, previous laser photocoagulation to the macula, retinal vascular occlusion, or previous ocular surgery.

Patients' data were evaluated and compared with the healthy age-matched controls for both the morphological (qualitative) changes and the size of the FAZ area as well as the quantitative retinal VD changes. Scans were captured using the AngioVue OCTA system (RTVue-XR Avanti; Optovue Inc., Fremont, California, USA), which is a 70-kHz spectral domain-OCT machine using an 840-nm wavelength scanning beam with a 70 000 A-scans/second acquisition and 5-μm in-vivo axial resolution. The automated angio-analytic software was implemented to study the changes in the microvessels of the retina at the SCP and DCP levels separately. The SCP was identified to be between 3 μm below the inner limiting membrane and 15 μm below the inner plexiform layer (IPL), whereas the DCP to be between 15 μm below the IPL and 71 μm below the IPL layer.

The measurement areas included the FAZ, the area encompassing the central fovea where no vessels exist; fovea, the central 1 mm diameter ring; parafovea, defined as an annulus centered on the fovea with inner and outer ring diameters of 1 and 3 mm, respectively; and total image, an area of 3×3 mm^2.

We used the newly developed built-in Angio-Analytics Software, version 2017.1.0.151 (Optovue Inc.), to obtain measurements for a series of parameters in the foveal area. This software is an updated version that includes two important advances, that is, the projection artifact removal algorithm and improved FAZ delineation using the perimeter and the acircularity index (AI). As we did not have those parameters installed to our machine, at the time of conducting the study, the quantitative analysis of the FAZ area was evaluated as in previous studies without using the two additional parameters. Using the new parameters, the device automatically outlines the boundary of the FAZ along the centermost capillaries, allowing the area and perimeter of this zone to be calculated. The AI is measured using the following equation: AI=perimeter calculated/standard circular perimeter of equal area. The AI becomes larger as the shape becomes less smooth or less round.

Ethical considerations

The approval of the Institutional Review Board of Minia Faculty of Medicine Research Ethics Committee (FMREC) was obtained before commencing the study protocol, which followed the Declaration of Helsinki. All participants signed a written informed consent to participate in the study and for publication of data before enrollment in the study and after explaining the nature of the investigative procedure and all study details.

Statistical analysis

The Statistical Package of Social Sciences (version 24.0; SPSS Inc., IBM, Chicago, Illinois, USA) was adopted for tabulation and analysis of the obtained data. Quantitative data were presented as mean±SD, whereas qualitative data were expressed as number and percentage. Kolmogorov–Smirnov for normality test was used to differentiate between parametric data and nonparametric data.

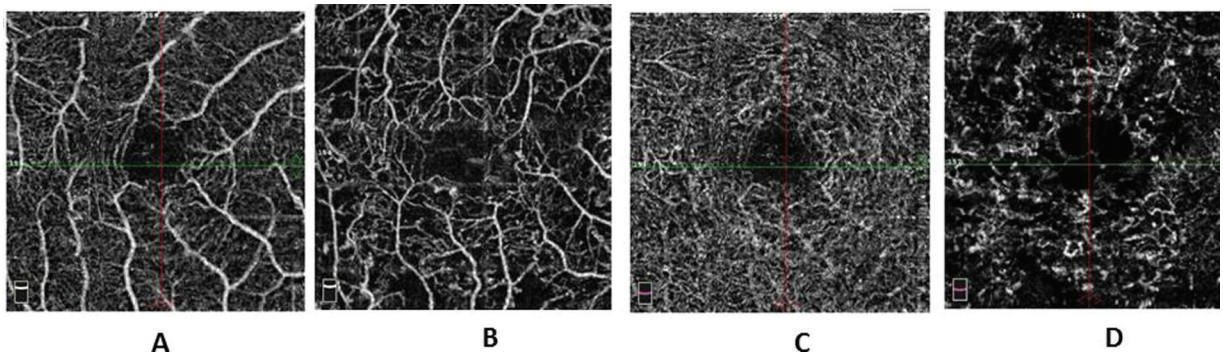
Independent sample t test was adopted for analysis of quantitative data and c^2 test and Fisher's exact test were adopted for analysis of qualitative data. P value less than 0.05 was considered significant and less than 0.001 as highly significant.

Table 1 Demographic criteria and optical coherence tomography angiography findings

Parameters	Patients with DME (*n*=27)	Controls (*n*=20)	*P*
Age (years)	55±11.5	41.48±10.3	0.06
Females (%)	55.6	60	0.28
LogMAR VA	0.85±0.39	0.06±0.17	<0.001
CMT (μm)	344.7±112.2	251.5±110.2	<0.001
FAZ area (mm^2)			
Superficial	0.48±0.22	0.29±0.12	<0.001
Deep	0.56±0.27	0.33±0.13	<0.001

CMT, central macular thickness; DME, diabetic macular edema; FAZ, foveal avascular zone; LogMAR, logarithm of the minimum angle of resolution; VA, visual acuity.

Figure 1



En face optical coherence tomography angiograms of an age-matched healthy control (a, c) and a patient with diabetic macular edema (b, d), showing macular changes in both superficial (a, b) and deep (c, d) retinal capillary plexuses.

Results

A total of 27 patients with DME (15 females and 12 males) were compared with 20 age-matched healthy controls (12 females and eight males) (Table 1).

The FAZ shape was irregular in 13 (48.1%) eyes, oval in nine (33.3%) eyes, and round in five (18.5%) eyes of patients with DME, whereas it was oval in eight (40%) eyes and round in 12 (60%) eyes of controls ($P<0.001$). Capillary loops and dilatation together with reduced vessel rarefaction were observed in 12 (44.4%) eyes of patients with DME. Widened intercapillary spaces (capillary dry areas) and microaneurysms were observed in all DME eyes. It is worth noting that the aforementioned changes were studied separately in the SCP and DCP. They were all more pronounced in the deeper plexus.

Central macular thickness (CMT) was significantly increased in patients with DME than in controls owing to edema fluid collection (344.7±112.2 and 251.5±110.2 μm, respectively, $P<0.001$).

The normal and abnormal FAZ appearances in OCTA en-face angiogram of an age-matched control and a patient with DME are shown in Fig. 1.

Retinal capillary VD changes were calculated using the OCTA Angio-Analytics Software in the SCP and DCP. The latter was assumed to include the intermediate capillary plexus as well as the DCP because of the inability to separate them in the available segmentation software. It was found that the whole image as well as the density of the parafoveal vessels was significantly lower in patients with DME at the SCP as compared with controls ($P<0.001$). Similar findings were reported at level of the DCP in which the whole image and parafoveal VD values were significantly reduced in patients with DME when compared with the healthy controls ($P=0.001$ and $P<0.00$, respectively, Table 2).

Foveal VD was significantly lower in patients with DME than in controls at both the SCP and DCP ($P=0.02$ and 0.03, respectively, Table 2).

The FAZ was significantly positively correlated with LogMAR visual acuity (VA) at the SCP and DCP levels ($r=0.70$, $P=0.001$ and $r=0.58$, $P=0.003$, respectively), whereas it was significantly negatively correlated with parafoveal VD at the DCP level ($r=-0.52$, $P=0.006$) and with whole image VD at the SCP level ($r=-0.61$, $P=0.001$, Table 3).

Table 2 Vessel density changes

Parameters	patients with DME (*n*=27)	Controls (*n*=20)	*P*
SCP vessel density (%)			
Whole image	45.76±3.74	51.92±4.59	< 0.001
Parafoveal	43.25±3.06	52.91±5.19	< 0.001
Foveal	29.58±5.35	35.76±9.45	0.02
DCP vessel density (%)			
Whole image	45.84±3.51	49.91±5.57	0.001
Parafoveal	42.65±2.97	50.38±5.42	< 0.001
Foveal	30.12±5.53	34.17±4.87	0.03

DCP, deep capillary plexus; DME, diabetic macular edema; SCP, superficial capillary plexus.

Table 3 Correlation between foveal avascular zone area and parafoveal vessel density, LogMAR visual acuity, and whole image vessel density in patients with diabetic macular edema

FAZ area (mm^2)	Parafoveal VD %		LogMAR VA		Whole image VD %	
	R	*P*	*R*	*P*	*R*	*P*
SCP	−0.313	0.112	0.697	0.001*	−0.606	0.001*
DCC	−0.518	0.006*	0.557	0.003*	−0.329	0.094

DCC, deep capillary complex; FAZ, foveal avascular area; LogMAR, logarithm of the minimum angle of resolution; SCP, superficial capillary plexus; VA, visual acuity; VD, vessel density. *Statistically significant.

We speculate that serial OCTA quantitative measurements in longitudinal studies could settle a flow and perfusion-based severity grading scale for patients with DME and hence helps treatment decision making.

There was a negative significant correlation between LogMAR VA and the whole image VD in patients with DME at the SCP level (r=−0.58, P=0.002) and the deep retinal plexus (r=−0.70, P<0.001). There was also a significant negative correlation between the parafoveal VD and LogMAR best-corrected VA in the DME patient group at the SCP and DCP levels (r=−0.52, P=0.006 and r=−0.60, P=0.001, respectively, Table 3).

Discussion

In the current clinical study, the FAZ shape was found to be irregular in 48.1% of patients with DME, whereas it was round in 63% of control eyes. In a study by Freiberg *et al.* [8] of 22 DME eyes, they found that the FAZ was circular or oval in two eyes only and irregular in 20 eyes of patients with disintegrate vascular arcades. However, it was circular in 18 eyes and oval in 17 eyes of the 25 control eyes with intact surrounding vascular arcades.

In addition, a significant widening of the FAZ area was found in patients with DME at the SCP and DCP compared with controls. This partially agrees with Di *et al.* [12] who investigated patients with DME and demonstrated a larger FAZ area in the superficial retinal layer in the patients' group than in controls (0.41±14 and 0.36±0.06 mm^2, respectively, P=0.01). However, they did not study these changes at the deeper capillary plexus. The reported FAZ values, in the current study, were higher than values reported in other studies, as we included neither diabetic patients without DR nor patients with mild to moderate DR. All included patients had moderate to severe retinopathic changes, which could explain the higher FAZ area measurement values.

In a recent study by Tag El-Din [13], comparing diabetic patients without evident retinopathy (subclinical DR) and healthy controls, statistically significant differences in OCTA parameters were reported. Both vascular density and perfusion density were significantly decreased in diabetic patients (P>0.001). The FAZ also showed significant changes in area value (P=0.02) and perimeter (P=0.01). However, the circularity changes were statistically insignificant (P=0.10).

In the present study, microaneurysms were found to exist in both the SCP and DCP in all cases with higher density in the deep layer. Similarly, in a study by Hasegawa *et al.* [14], which included 33 eyes of 27 diabetic patients, microaneurysms were found to be present in both layers with higher density in the DCP in comparison with the SCP.

In the current study, compared with healthy controls, the logMAR VA of patients with DME was

significantly impaired. AttaAllah *et al.* [15] reported significantly reduced VA in patients with DME (0.66 ±0.35) compared with both diabetic patients not having macular edema (0.04±0.05) and the healthy control group (0.05±0.16) ($P<0.001$).

According to the present study, the parafoveal VD was significantly reduced in the superficial as well as the deep capillary layers in cases with DME. In patients, the parafoveal VD was 42.48±3.06 and 42.34±2.35 in the superficial and the deep capillary layers, respectively, whereas in controls, it was 52.91±5.19 and 50.38±5.42, respectively. In a study by Dimitrova *et al.* [16], a significant reduction of parafoveal VD was reported in diabetics in the superficial as well as the deep capillary layers than in the control group. In the patient group, it was 44.35 ±13.31 and 31.03±16.33, respectively, whereas in the control group, it was 51.39±13.05, $P=0.04$ and 41.53 ±14.08, respectively ($P<0.01$).

In the current study, the whole image VD was significantly reduced in patients than in controls when examined in the SCP and DCP. This agrees with a recent study conducted by Al-Sheikh *et al.* [17] that included 13 eyes with DME and 40 eyes of healthy individuals. The latter study reported significantly reduced whole image VD in eyes with DME compared with controls. In patients' group, it was 0.53±0.088 and 0.62±0.070 in the superficial and the deep capillary layers, respectively, whereas in normal individuals, it was 0.71±0.038 ($P<0.001$) in the superficial retinal layer and 0.71±0.049 in the deep retinal layer ($P=0.028$).

A noteworthy issue is the lack of the software update that could automatically and accurately segment the different retinal capillary plexuses to delineate the intermediate retinal capillary plexus and the DCP separately. That is why, we measured the changes and compared them between the SCP and DCP. The latter included the intermediate retinal capillary plexus and the DCP.In the present study, the CMT was higher in patients than in controls (344.7±112.2 and 251.5±110.2). This is in accordance with a study by AttaAllah *et al.* [15] in which significant difference in CMT was found between diabetic patients and healthy controls (374.9±172.3 and 241.6±17.2, respectively, $P<0.001$).

In the current study, the FAZ area and LogMAR best-corrected VA positively correlated at both the SCP and the DCP levels. This finding was also reported in a study of Balaratnasingam *et al.* [18] ($P=0.003$).

In the present study, the whole image VD and LogMAR VA negatively correlated at a moderate level in patients with DME at both the SCP and the DCP. Similarly, Samara *et al.* [19] reported that the superficial as well as the deep whole image VD strongly negatively correlated with LogMAR VA of diabetic patients ($P<0.001$).

In conclusion, OCTA proved to be a promising noninvasive tool to accurately assess the degree of DME. It can reveal the underlying microvascular changes that could be easily masked and overlooked by the dye leakage in FA. Clear visualization of these changes helps better with accurate disease severity staging and assists appropriate treatment decisions as well. Serial OCTA quantitative measurements are highly recommended in terms of clinical settings particularly to avoid the hazardous adverse effects of dye injection or when it is contraindicated.

The limitations of the current study are the relatively small sample size, the lack of randomized longitudinal cohort design, and the follow-up of the reported changes over time.

Bulk eye motion was the main problem to obtain satisfactory scan images. Therefore, faster scanning speed and larger fixation target may be helpful, if available, in newer machines.

Future cohort studies including larger sample size are recommended to evaluate the qualitative and quantitative OCTA findings in diabetic patients to improve our understanding of this diagnostic method and how those changes could be valuable biomarkers to identify the disease staging and to guide and monitor the different treatment regimens.

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Conflicts of interest

There are no conflicts of interest.

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