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Optical coherence tomography angiography as a prediction tool for diabetic retinopathy

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Background
Diabetic retinopathy (DR) represents the leading cause of blindness in working-age people. It affects about one in every three diabetic patients. This visual loss can be prevented by early detection and proper management.
Purpose
The aim of this study was to assess the ability of optical coherence tomography angiography (OCTA) to detect subclinical changes in parafoveal capillaries in diabetic patients without DR.
Patients and methods
This prospective case–control study was conducted upon 50 participants who were divided into two groups: group A (25 diabetic patients without clinical manifestation of DR) and group B (25 healthy control participants of matched age and sex with group A). The two groups were compared regarding the parameters of the foveal avascular zone (FAZ) area, perimeter, and FD (flow density of retinal capillaries within 300 μm surrounding the FAZ) in addition to the parafoveal vessel density of superficial and deep capillary plexuses (SCP and DCP) on macular scans (3×3 mm) centered on the fovea by OCTA.
Results
There were statistically significant differences in FAZ area, perimeter, and FD together with parafoveal vessel density of SCP and DCP between healthy controls and diabetic patients without DR. The mean FAZ area of the healthy control group B was 0.27±0.08 mm^2 compared with 0.32±0.11 mm^2 in the diabetic group A (P=0.01). In addition, the FAZ perimeter was significantly increased (P=0.003) in the diabetic patients without DR (2.39±0.56 mm) compared with the control (2.11 ±31 mm). Statistically significant decreases of vessel density in the FD-300, SCP, and DCP were observed in diabetic patients without DR compared with controls (all $P<0.001$). Regarding the FD-300, the mean value in the control group was 49.98 ±2.67%, whereas in the diabetic group it was 48.11±0.58%. The mean VD of the SCP in the healthy control group B was 47.62±2.58% compared with 44.32±3.01% in the diabetic group. The mean VD of the DCP in the healthy control group B was 56.13±2.23% versus 50.21±2.56% in the diabetic group.
Conclusion
OCTA is an effective tool in the early detection of microvascular changes of diabetic patients with no clinical manifestations of DR. Vessel density and FAZ metrics were proven to be early biomarkers for DR before becoming clinically evident.

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

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Introduction

Diabetes mellitus (DM) is a worldwide health problem that affects about 347 million people [1]. DM is a chronic progressive disease characterized by hyperglycemia, which, if uncontrolled, will cause vascular complications either macrovascular or microvascular [2,3]. Diabetic retinopathy (DR) is mainly due to oxidative stress and hypoxia. The cycle starts with chronic hyperglycemia that causes activation of polyol, protein kinase C, and hexosamine and ends by apoptosis of vascular and neuronal cells together with the release of vascular endothelial growth factor (VEGF) leading to neovascularization and increased permeability of blood vessels [4,5]. DR is classified by the Early Treatment Diabetic Retinopathy Study into mild, moderate, and severe nonproliferative DR and proliferative diabetic retinopathy. Its main vision-threatening complications are maculopathy, vitreous hemorrhage, and tractional retinal detachment [6,7].

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Fluorescein angiography (FA) is a gold standard in the assessment of DR. FA provides two-dimensional images of the retina with the qualitative assessment of retinal vasculature. It can assess perfusion, leakage, pooling, and staining but it is invasive, time consuming, and has adverse reactions (from mild nausea to severe anaphylactic shock) [8]. FA is unable to fully visualize the deeper structures such as choroidal vasculature. Optical coherence tomography (OCT) provides rapid, noninvasive, imaging of the cross-section of the retina using a low-coherence interferometer. It captures two-dimensional, high-resolution images by optical scattering from different layers of the retina [9].

Optical coherence tomography angiography (OCTA) is a novel use of OCT to quantitatively and qualitatively assess the microvasculature of the retina and choroid without the need for dye injection and with depth resolution [10]. It depends on mapping erythrocyte movement over time by comparing sequential OCT B-scans (motion contrast) at a given cross-section [10,11]. The split-spectrum amplitude-decorrelation angiography (SSADA) of AngioVue software of RTVue XR Avanti allows visualization of the superficial capillary plexus (SCP) and the deep capillary plexus (DCP), which includes the intermediate plexus [12–14]. OCTA was able to detect with precise localization the common microvascular abnormalities of DR, such as microaneurysms, intraretinal microvascular abnormalities, neovascularization, retinal nonperfusion regions, enlarged irregular fovea avascular zone (FAZ), and venous tortuosity and loops [15–18].

OCTA gives clues about life exposure to hyperglycemia by studying the changes occurring in the FAZ and parafoveal vascular density. Changes in the structure or perfusion of the FAZ will affect vision. By OCTA, the normal FAZ appears as a well-defined round or oval area of absent vessel signals with no gaps, holes, or interruption of the vascular network of its border in both the superficial and deep plexuses. The longest FAZ diameter is in either the vertical or the horizontal axis [19]. The FAZ can be delineated clearly using OCTA as there is no dye leakage but shadowing from edema or hemorrhage can affect it. In diabetic eyes, the FAZ is enlarged as a result of loss of integrity of blood vessels and is irregular in shape due to gaps, holes, or notches of the capillary plexuses. FAZ disruption is correlated with DR severity [20,21]. FAZ enlargement could be considered as an index of nonperfusion and ischemia of the central retina. The vessel density (VD) varies with age, sex, and retinal thickness and volume, as reduced VD could correlate with thinner macular ganglion cell or inner plexiform layer [22,23]. VD decreases in both the DCP and SCP of diabetic patients with and without DR [24]. VD of the DCP can be used as a sensor to predict DR severity and to identify diabetic patients who are at risk to develop DR [25,26].

The aim of this study was to evaluate OCTA biomarkers for early detection of microvascular changes of diabetic patients before DR is clinically manifested by assessing the vascular density percentage of SCP and DCP and FAZ parameters (area in mm^2, perimeter in mm and FD %).

Patients and methods

This is a case–control study that was conducted upon 50 participants who were divided into two groups: group A that included 25 diabetic patients without clinical manifestation of DR and group B that included 25 healthy control participants of matched age and sex. The study was approved by the Ethics Board of Benha University, Benha, Egypt. A written informed consent was signed by all participants to be enrolled in the study and for publication of data.

Inclusion criteria for group A were patients with type 2 DM of more than 5-year duration and without clinical manifestations of DR. The exclusion criteria were advanced diabetic eye disease (vitreous hemorrhage or retinal detachment), intravitreal injection of either anti-VEGF or steroids, refractive errors more than ±5 diopters (D) in spherical equivalent, past panretinal photocoagulation, focal or grid laser, dense cataract or media opacities, glaucoma, macular edema, age-related macular degeneration, hypertensive retinopathy, central serous chorioretinopathy, and any other acquired or hereditary macular or optic nerve diseases.

For every patient, full history was taken and a complete ophthalmic examination was done. Participants were evaluated for uncorrected visual acuity, best corrected visual acuity, refractive errors (autorefractometry), slit-lamp examination of the anterior segment of the eye (cornea for clarity and sensitivity, anterior chamber for depth and content, pupil for dilation, regularity and reactivity, and lens for clarity and position), intraocular pressure measurement by Goldmann Applanation Tonometer (AT 900 HAAG-STREIT International, Koeniz, Switzerland), and dilated fundus examination by indirect ophthalmoscope.

Optical coherence tomography angiography

OCTA of the retina was done by AngioVue OCTA system (RTVue-XR Avanti; OptoVue, Fremont, California, USA) with a software algorithm (Version 2017.1 Dual Trac). The blood flow areas were detected by the SSADA algorithm that decor relate two cross-sectional 3D raster scans to improve the signal-to-noise ratio and reducing motion artifacts. Each three-dimensional volume was acquired from two horizontal and two vertical fast B-scan acquisitions, formed of 216 B-scans and picked up in 3.4 s. Each B-scan was formed of 304×304 A-scans with a scanning rate of 70,000 A-scans per second.

The scanning area was captured in 3×3 mm sections, automatically centered on the fovea using a scanning wave centered at 840 nm with a bandwidth of 45 nm. Axial and transversal saccadic motion artifacts were minimized by Motion Correction Technology (MCT) and the software ReVue.

The four layers (the superficial retinal, deep, outer retinal, and choriocapillaries) *en face* segmentation was provided by using an automated software algorithm. The boundaries for each layer were defined as follows. For the superficial vascular layer (internal limiting membrane "ILM" to inner plexiform layer "IPL"-10 μm), the slab is extending from the ILM to 10 μm above the IPL. For the deep vascular layer (IPL-10 μm to outer plexiform layer "OPL" +10 μm), the slab is extending from 10 μm above the IPL to 10 μm below the OPL. For the outer retina (OPL+10 μm to Bruch's membrane "BRM" −10 μm), the slab is extending from10 μm below OPL to 10 μm above the BRM. For the choriocapillaries (BRM-10 μm to BRM +30 μm), the slab is extending from 10 μm above the BRM to 30 μm below the BRM.

The FAZ (the area enclosing the central fovea where there are no vessels) was evaluated by measuring the following: area (mm^2), perimeter (mm), and FD (%) (VD within 300 μm width ring surrounding the FAZ, which is calculated by dividing the number of vessel pixels by the total number of pixels then multiplied by 100%). Automated FAZ detection was provided by the AngioVue software on retinal slab (ILM to OPL +10 μm).

The parafoveal VD was evaluated in the SCP and the DCP by using the density tool of the software that calculates it automatically by measurement of the percentage of pixels occupied by flowing vessels to the total pixels within the area of analysis. The "parafovea" is an annulus centered on the fovea with inner and outer ring diameters of 1 and 3 mm, respectively and was divided into temporal, superior, nasal, and inferior quadrants.

Statistical analysis

Analysis of data was done using the Statistical Package for Social Science version 20 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were described in the form of mean and SD. Qualitative variables were described as number and percent. To compare parametric quantitative variables between the two groups, Student's *t* test was performed. A *P* value <0.05 was considered significant.

Results

Regarding the age of patients, there was no statically significant difference between the two groups (P=0.689), as the mean age of the control group B was 60.8±10.3 years and the mean age of group A was 59.9±9.8 years.

The mean of the FAZ area of the healthy control group B was 0.27±0.08 mm^2 compared with 0.32±0.11 mm^2in the diabetic group A, a statistically significant difference (*P*=0.0109, Figs 1 and 2).

There was also a statistically significant difference (*P*=0.003) regarding the FAZ perimeter as the mean FAZ perimeter was 2.11±31 mm in the control group B versus 2.39±0.56 mm in the diabetic group B (Figs 1 and 2).

The FD mean value in the control group was 49.98 ±2.67% compared with 48.11±0.58% in the diabetic group, a statistically significant difference (*P*=0.001, Figs 1 and 3).

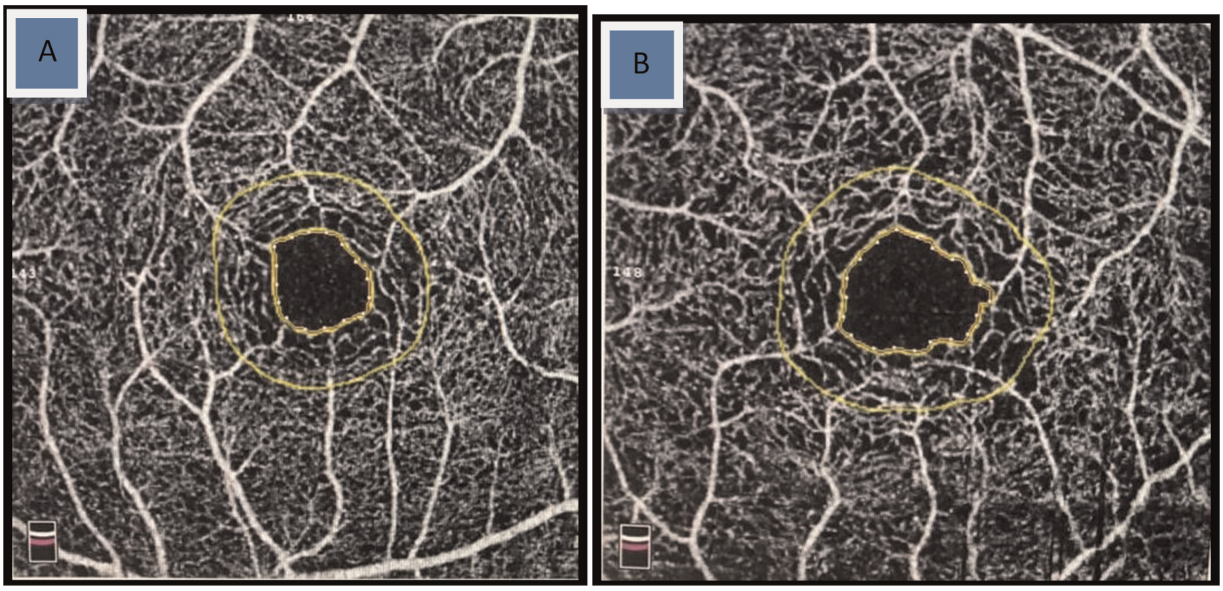
The VD results appeared to be an important biomarker in the diabetic patients as the mean VD of the SCP in the healthy control group B was 47.62±2.58%, compared with 44.32±3.01% in the diabetic group B, a statistically significant difference (*P*<0.0001, Figs 3 and 4).

Similarly, the mean VD of the DCP in the healthy control group B was 56.13±2.23% compared with 50.21±2.56% in the diabetic group A, a statistically significant difference (*P*<0.0001, Figs 3, 5, and 6).

Discussion

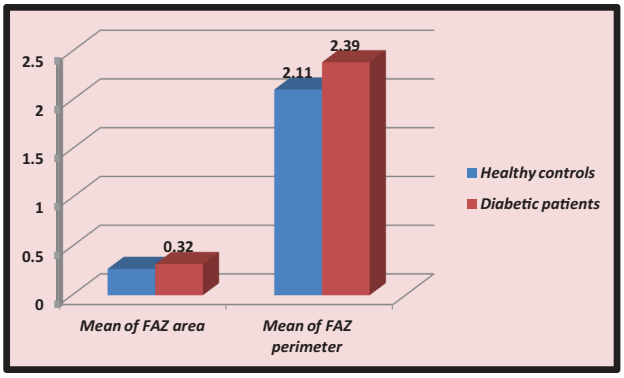
DR is one of the major causes of visual disability that can be prevented by early detection. OCTA enables us

Figure 1



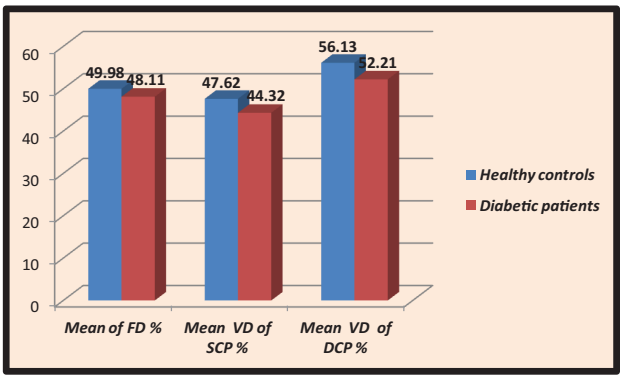
The foveal avascular zone area (mm^2), perimeter (mm), and FD (%) of a healthy control (A) and a diabetic patient (B).

Figure 2



Mean value of the foveal avascular zone area (mm^2) and perimeter (mm) of the healthy control group and the diabetic group.

Figure 3



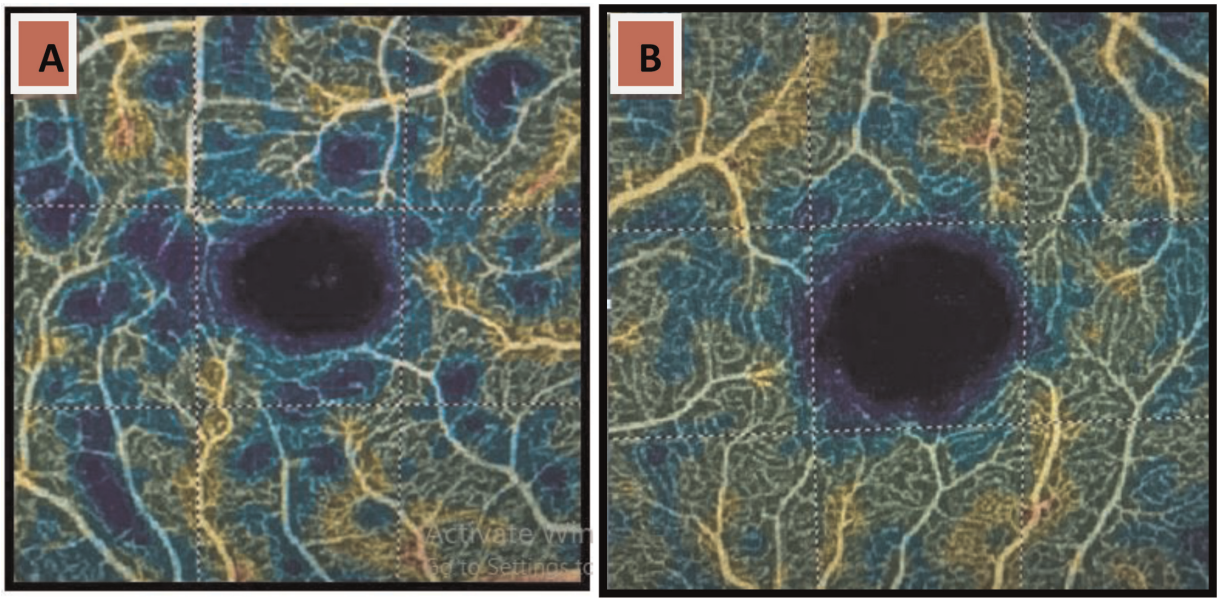
Mean value of FD% and vascular density of the superficial capillary plexus and deep capillary plexus of the healthy control group and the diabetic group.

to identify retinal microvascular changes before the onset of clinically evident retinopathy by perfect qualitative and quantitative assessment of macular perfusion with analysis of plexuses at different depths, without fluorescein injection or leakage that affect the analysis of vascular details. There is an intimate relationship between hyperglycemia and the histological changes of retinal microvasculature that can be assessed by OCTA.

Previous studies used OCTA to detect the normative data for SCP and DCP vascular density of healthy adults. Coscas *et al.* [27] performed VD mapping of healthy participants according to the age using the Angio Analytics software by OptoVue to quantify vascular density and FAZ. They found that the mean area of FAZ in all age groups was 0.28±10 mm^2 that matched with the current study results in which the mean FAZ for the control group was 0.27 ±0.08 mm^2.

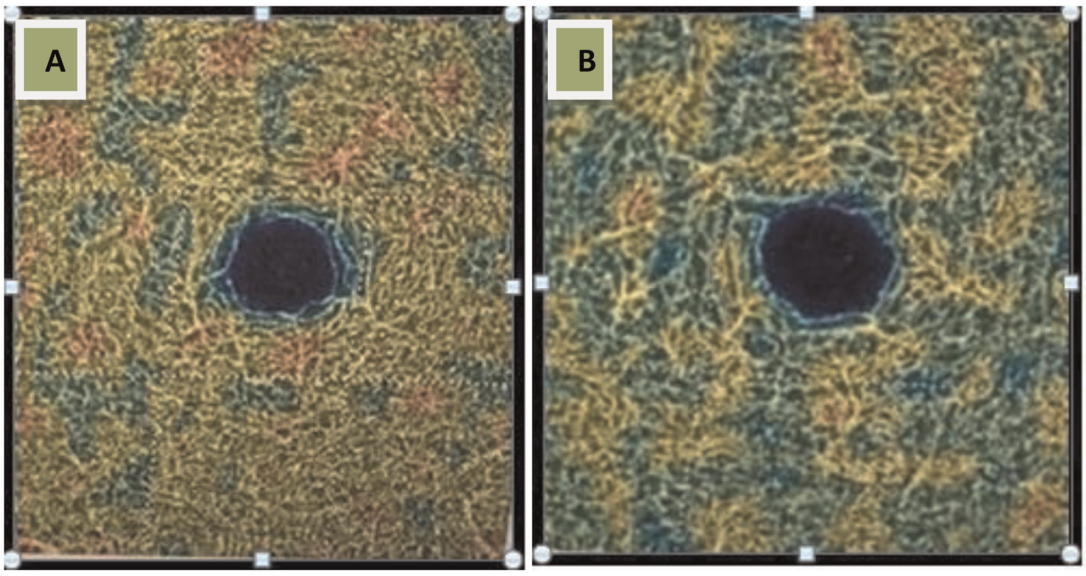
Other studies used the AngioPlex OCTA device from Carl Zeiss Meditec, Germany. Durbin *et al.* [28]

Figure 4



Vessel density of the superficial capillary plexus of a diabetic patient (A) and a healthy control (B).

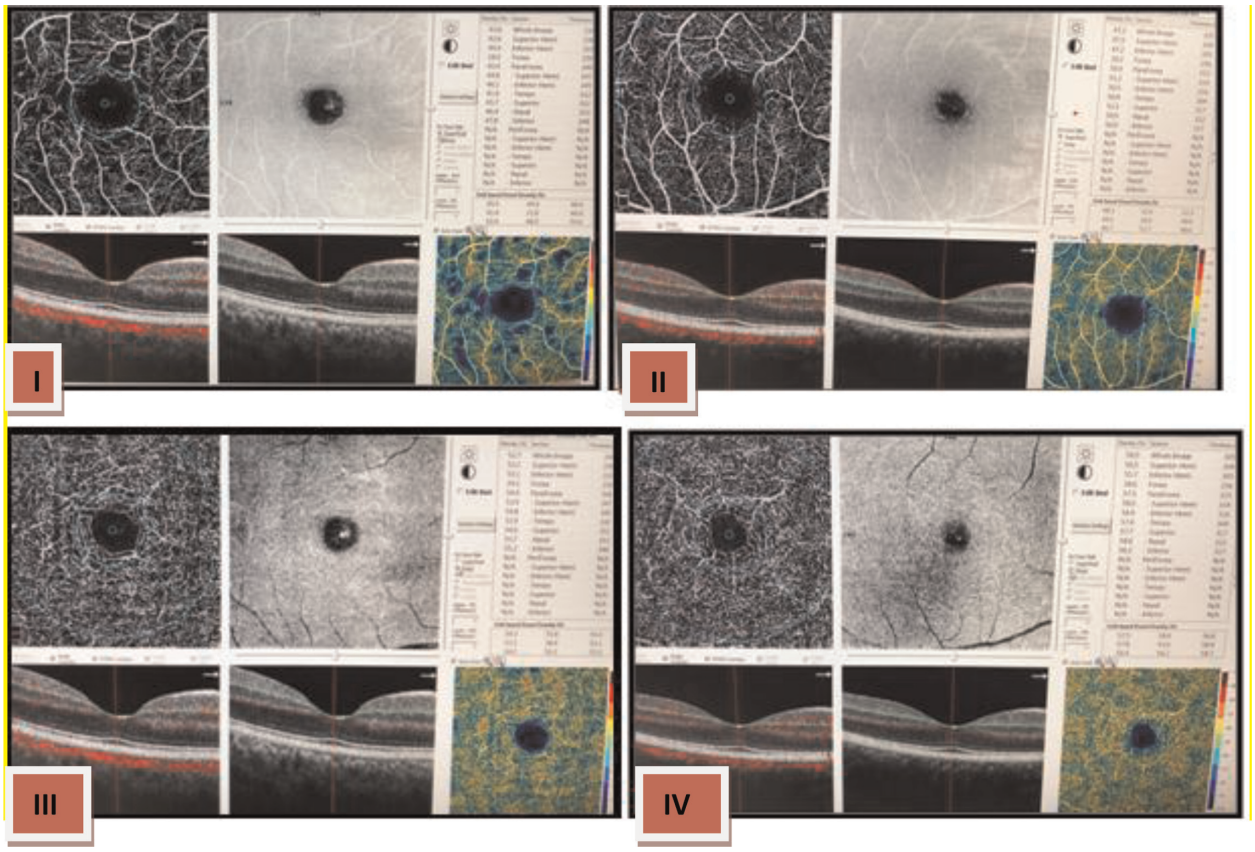
Figure 5



Vessel density of the deep capillary plexus of a healthy control (A) and a diabetic patient (B).

conducted a study on 50 eyes of 26 diabetic patients of different stages, and 50 eyes of 25 normal participants. They found that the mean vascular density was 22.5%, the mean FAZ area was 0.25 mm^2, and the mean perimeter was 2.05 mm in the healthy group. For the diabetic group, the mean VD was 21.2% and the FAZ area and perimeter were 0.26 mm^2 and 2.32 mm, respectively. Another study was conducted by Hisham *et al.* on 40 eyes of 20 diabetic patients without manifestations of DR and 40 eyes of 20 normal participants. They found that the mean vascular density was 20.4%, the mean FAZ area was 0.26 mm^2, and the mean perimeter was 2.18 mm in the healthy control group. For the diabetic group, the mean VD was 17.75% and the FAZ area and perimeter were 0.31 mm^2 and 2.46 mm, respectively [29]. Both studies found a statistically significant difference in all variables measured between healthy and diabetic patients with or without DR. These results matched with the present study regarding FAZ area and perimeter, but the values of VD were different as we used different software of different OCTA (SSADA of AngioVue OCTA). In addition, the study of Mary *et al.* included all stages of DR, whereas in the current study, any diabetic patient

Figure 6



I. Vessel density (VD) of the superficial capillary plexus (SCP) of a diabetic patient (average 43.6%). II. VD of the SCP of a healthy control (average 47.3%). III. VD of the deep capillary plexus (DCP) of a healthy control (average 56.3%). IV. VD of the DCP of a healthy control (average 56.3%).

showing any frank manifestation of DR was excluded. In the current study, for healthy participants, the mean VD of the SCP was 47.62±2.58%, the mean VD of the DCP was 56.13±2.203%, the mean FAZ area was 0.27 ±0.08 mm^2, and the mean perimeter was 2.11±31 mm. For diabetic patients without DR, the mean VD of the SCP was 44.32±3.01%, the mean VD of the DCP was 50.21±2.56%, the mean FAZ area was 0.32±0.11 mm^2, and the mean perimeter was 2.39±0.56 mm.

In the present study, there was a statistically significant difference in FAZ area, perimeter, and FD together with VD of the SCP and DCP between healthy controls and diabetic patients without DR. In addition, the easy operation of the device, short acquisition time, and avoidance of potentially phototoxic blue light suggest that OCTA holds promise as a tool for detection and monitoring of subclinical DR.

In this study, the FAZ showed a significant widening of its area and enlargement of the perimeter with a significant reduction in FD in diabetic patients without DR compared with the control. The FAZ is a sensitive indicator of ischemia and can be affected very early in DR. These results matched with previous studies that have shown an enlargement of the FAZ area in eyes with DR [7,19,30]. However, Goudot *et al.* [31] study did not show a difference in the FAZ area between diabetic patients without DR and nondiabetic controls.

Dimitrova *et al.* [23] demonstrated that the FAZ of the healthy eye has a well-defined round or oval shape without interruption of the vascular network in both the superficial and deep plexuses, whereas in diabetic patients, the FAZ was enlarged in both SCP and DCP. Moreover, Vujosevic *et al.* [32] found that diabetic patients of type 1 DM without DR had increased FAZ size in the DCP. In addition, De Carlo *et al.* [33] found a statistically significantly larger FAZ in the DCP in diabetic patients of type 2 DM without DR compared with controls.

Regarding VD, it was found to be a good indicator of ischemia. There was a statistically significant difference between diabetic patients without DR and control eyes in both superficial and deep plexuses. Generally, VD values gradually become lower from healthy controls to

patients with DM without DR and are well correlated with the DR stage. Carnevali *et al.* [25] found that those diabetic patients without any signs of DR have a reduction in the DCP perfusion density in comparison with controls.

These findings (enlargement of the FAZ area and perimeter and reduction of FD%, VD of SCP and DCP) point that the microcirculatory insult has a primary causative factor in the progression of the retinal impairment. The FAZ dimensions and vascular density measurements can be used as a screening tool for the assessment of macular perfusion.

On the other hand, OCTA is limited by many artifacts such as motion artifact (any motion of the patient during acquisition results in decorrelation as an inability to fixate due to poor visual acuity), projection artifact (flow signal from more superficial layers projected into deeper retinal layers of high reflectivity), and segmentation artifact (retinal edema or thinning leads to error in slab segmentations). Limitations of this study are the small sample size and its cross-sectional nature. A prospective and longitudinal study is better to be done in the future to study factors affecting the FAZ such as the axial length.

Conclusion

OCTA provides structural and topographic analysis of microvascular abnormalities that occur in diabetic patients before the onset of clinically evident retinopathy by assessment of The FAZ dimensions and vascular density. So OCTA offers an early biomarker for efficient screening of DR, before the onset of clinically evident complications

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Conflicts of interest

There are no conflicts of interest.

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