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Optical coherence tomography angiography in comparison with fluorescein angiography in diabetic retinopathy

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Abstract

Background
Diabetic retinopathy (DR) is a microvascular complication of diabetes, and it is a leading cause of blindness. Fluorescein angiography (FA) is a vitally crucial diagnostic tool for evaluating fundus features of diabetic retinopathy.

Purpose
The purpose of the study was to evaluate optical coherence tomography angiography (OCTA) in eyes with diabetic maculopathy (DM) compared with the findings in fundus fluorescein angiography.

Design
It is a cross-sectional study.

Patients and methods
The study involved 40 eyes of 40 patients suffering from DM. The patients’ ages ranged from 30 to 66 years with a mean value of 51.4 ± 8.55 years, of which –28 (70%) were females and 12 (30%) were males. We compared OCTA with FA in terms of the ability to visualize the DM changes detected, such as microaneurysms, capillary nonperfusion, foveal avascular zone interruption, perifoveal changes, hemorrhages, and edema in both superficial and deep capillary plexuses.

Results
Microaneurysms were detected in all eyes in OCTA and FA. Retinal hemorrhages were detected using OCTA in deep capillary plexuses (42.5% (17/40) of eyes compared with 7.5% (3) in superficial capillary plexuses with a significant difference that may better evaluate the level of retinal hemorrhage among diabetic eyes. Areas of capillary loss obscured by fluorescein leakage on fluorescein angiography were more clearly defined on OCTA. Capillary nonperfusion showed no statistically significant difference between FA and OCTA. FA could detect intraretinal microvascular abnormalities/collaterals in eight (20%) eyes, while OCTA could detect four (10%) with \( P \) value = 0.210, which is insignificant.

Conclusion
Both FA and OCTA could detect microaneurysms in all eyes. OCTA could precisely locate their depth and origin, which is not possible in FA. OCTA showed higher accuracy in assessing capillary nonperfusion areas than FA, but with a statistically insignificant difference.

Keywords: Diabetic retinopathy, fluorescein angiography, optical coherence tomography angiography

Introduction

The most common cause of blindness in industrial countries is diabetic retinopathy (DR) [1]. As the number of patients who have diabetes and therefore DR is expected to increase, improving investigation methods of diagnosis, follow-up, and deciding the proper treatment of DR is a must [2].
One of the essential diagnostic tools of DR is fluorescein angiography (FA). FA is vital in the diagnosis and, therefore, in deciding treatment protocols of DR. FA evaluates the clinical features of the fundus of nonproliferative DR changes such as microaneurysms (MA), intraretinal microvascular abnormalities (IRMA), and retinal capillary nonperfusion. Neovascularization can be identified by remarkable leakage of the dye toward the vitreous cavity [3].

However, fluorescein dye injection can cause serious side effects even to healthy individuals. It can cause mild symptoms such as nausea, vomiting, fatigue, and significant accidents such as anaphylactic shock. Patients with diabetic maculopathy (DM) often suffer from comorbidities such as chronic renal impairment or cardiovascular disease. Therefore, dye injection must be preceded by systemic investigations [4–6].

In addition, FA images are two dimensions restricted, making it harder to distinguish intraretinal structures such as superficial capillaries and deep capillaries [7].

The optical coherence tomography angiography (OCTA) is a noninvasive and safer investigation tool compared with FA [8]. Recently, many theoretically based OCTA methods were developed and applied to fundus imaging. The newly developed OCT angiography uses a split-spectrum amplitude-decorrelation angiography algorithm that can visualize structural changes of the retina and provide 3-dimensional vascular mapping at the level of microcirculation, improving the signal-to-noise ratio of flow detection [9–16].

The study aims to evaluate optical coherence tomography angiography in eyes with DM compared with findings in fundus fluorescein angiography in terms of the ability to visualize the DM changes. We focused on MA, IRMA, macular edema, neovascularization, and perifoveal changes.

Patients and methods
This is a cross-sectional, observational study. Participants carefully read and signed informed consents before participation. The study involved 40 eyes of 40 patients suffering from DM.

The study followed the ethical values in collecting data, data analysis, and keeping honesty. All patients signed a written informed consent to participate in the study and for publication of data before enrollment in the study. All information about patients' health status, medical condition, diagnosis, prognosis, treatment, and all other information of a personal kind was kept confidential. The study gained the approval of the Institutional Review Board.

We performed the following ophthalmic examinations on all participants: best-corrected visual acuity, slit-lamp biomicroscopy, and color-fundus photography. FA was done using the device Spectralis Heidelberg Retina Angiograph + OCT (Heidelberg Engineering, Heidelberg, Germany). Both fundus-colored photography and FA were done after pupillary dilatation and intravenous injection of 5 ml of 10% fluorescein sodium injection (fluorescein 500 mg i.v. amp, Chemical Industries Development, Giza, Egypt). OCTA was based on RTVue XR Avanti (Optovue, Inc., Freemont, California, USA).

We excluded patients with severe media opacities such as dense cataracts or vitreous hemorrhage, patients with macular edema due to conditions other than DR, and patients who underwent previous ocular surgeries.

FA images
Early, intermediate, and late phases of FA images were examined. They included central and peripheral images.

The following findings were evaluated on FA images:
(1) Perifoveal capillary arcade of the capillary plexus, whether visible or not, disrupted or not.
(2) Central and peripheral nonperfused areas (areas of capillary dropout) in early phases.
(3) Dilated capillaries (telangiectatic vessels) with staining of their walls in late phases, and areas of intraretinal hemorrhages.
(4) Areas of hyperfluorescence in the macula denoting diffuse or cystoid (petaloid) macular edema, in late phases, MA.
(5) Disk hyperfluorescence (disk leakage) in late phases.
(6) Photocoagulation scars.
(7) Neovascularization elsewhere and disk neovascularization.

The parameters used in the OCTA machine
The AngioVue OCTA device (Optovue, Inc., Freemont, California, USA) was used to get amplitude-decorrelation angiography image with an A-scan rate of 70,000 scans/second, and a light source centered on 840 nm and a bandwidth of 50 nm. Every OCTA volume contained 304 × 304 A scans, with two consecutive B scans captured at fixed positions before subsequent sampling locations. The split-spectrum amplitude-decorrelation angiography algorithm was used to extract OCTA information.

Each OCTA volume was acquired in three seconds, and two orthogonal OCTA volumes were obtained to perform motion correction to reduce motion artifacts that happen due to microsaccades and fixation changes. The displayed angiography information was the mean of decorrelation values when viewed perpendicularly through the assessed thickness.

Acquisition workflow of angio retina scan
Scan size for retina was 3 × 3 mm. All were acquired with 304 × 304 A-scan per volume.

Image analysis of fundus examination for diffuse macular edema (DME), cystoid macular edema, clinically significant macular edema, nonproliferative DR (mild, moderate, or severe), and proliferative DR.

OCTA images
Angiographic analysis was done, focusing on the retina's two vascular layers: superficial capillary plexuses (SCP) and deep
capillaryplexuses (DCP). The average capillary density, central capillary density, and foveal avascular zone (FAZ).

The following findings were evaluated at the level of both plexuses: FAZ interruption. Capillary nonperfusion areas. The presence of perifoveal changes (telangiectasia, dilatation, or rarefaction), and hemorrhages. Macular edema, with further evaluation on the coregistered OCT en face intensity images and OCT B-scan images, MA, and IRMA.

The AngioVue system (Avanti OCT, Optovue, Fremont, California, USA) using the split-spectrum amplitude-decorrelation angiography algorithm can divide the retina–choroid layer into four layers: the SCP, DCP, outer retina, and choroidal vessels.

Quantitative analysis
Vessel-density measurement was performed on the selected images; the instrument automatically measured the average and foveal capillary density. The device calculated vascular density as the percentage of the area occupied by blood vessels with flow above a threshold-detection level in a selected area and depth of vessels. The investigator manually outlined the FAZ in the SCP, and the FAZ area was calculated using the software.

Qualitative analysis
Diabetic changes were also detected as MA, capillary nonperfusion, FAZ interruption, perifoveal changes, hemorrhages, and edema in both superficial and deep capillary plexuses.

Statistical analysis
Data were collected, revised, coded, and entered into the Statistical Package for the Social Sciences IBM SPSS (SPSS Statistics for Windows, Version 23.0, 2015, Armonk, New York: IBM Corp.). The quantitative data were presented as mean, standard deviations, and ranges. Qualitative variables were presented as numbers and percentages. The comparison between groups regarding qualitative data was made using the $\chi^2$ test and/or Fisher exact test when the expected count in any cell was found less than 5. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. $P$ value less than 0.05 was significant.

RESULTS
Our study involved a total of 40 eyes of 40 patients. The patients’ ages ranged from 30 to 66 years with a mean value of 51.4 ± 8.55 years, of which 28 (70%) were females, and 12 (30%) were males. Diabetes duration ranged between 5 and 23 years with a mean of 15.20 ± 5.28 years.

Twenty-six patients (65%) were on insulin, 8 patients (20%) were on oral treatment, and 6 patients (15%) were on combined oral and insulin treatment.

Among the patients with diabetes, eight (20%) had concomitant hypertension.
Comparison between the results by FA and OCTA SCP of the studied cases

FA could detect IRMA/collaterals in 8 (20%) eyes, while OCTA could detect 4 (10%) with \( P \text{ value} = 0.210 \), which is not significant.

Similarly, capillary nonperfusion showed no statistically significant difference between FA and OCTA as FA could detect 28 (70%) eyes and OCTA detected 23 (57.5%) of the cases with \( P \text{ value} = 0.244 \) [Table 1].

Macular edema was detected clinically in 40 eyes (100%), and in 40 eyes (100%) by fluorescein angiography. OCTA could detect macular edema in SCP in 12 eyes (30%), and in 21 eyes in DCP (52.5%) [Table 2].

Descriptive data found by OCTA in the studied eyes

The average capillary density (AvCD) ranged between 37.51 and 52.2 mm with a mean of 45.16 \( \pm 4.14 \), while the central capillary density (central CD) ranged between 15.24 and 47.53 mm with a mean of 27.74 \( \pm 7.14 \) and the FAZ area ranged between 0.12 and 1.07 mm\(^2\) with a mean of 0.46 \( \pm 0.21 \) (Tables 3 and 4).

(1) FAZ interruption was detected in SCP in 17 (42.5%) of the eyes compared with 20 (50%) in DCP with \( P \text{ value} = 0.057 \), which is not statistically significant.

(2) In total, 8 eyes (20%) were distorted in the SCP imaging compared with 14 (35%) in DCP imaging.

(3) Capillary nonperfusion could be detected in SCP imaging in 23 (57.5%) compared with 22 (55%) in DCP imaging with \( P \text{ value} = 0.821 \), which is nonsignificant.

(4) Perifoveal changes: in SCP imaging, rarefaction was seen in 16 (40%), dilatation in 4 (10%), rarefaction + dilatation in 11 (27.5%), and rarefaction + telangiectasia were detected in 2 (5%) of the eyes. While in DCP imaging, the results were 16 (40%), 3 (7.5%), 7 (17.5%), and 1 (2.5%) of the eyes, respectively, which are all of no statistically significant difference.

(5) Hemorrhages: only 3 (7.5%) eyes showed hemorrhages in SCP, while 17 (42.5%) of the eyes showed hemorrhages in DCP imaging with \( P \text{ value} = 0.000 \), which is a statistically high significant difference.

(6) Edema: there was a statistically significant difference with \( P \text{ value} = 0.041 \) as SCP showed 12 (30%) eyes with edema and DCP showed 21 (52.5%).

(7) MA were easily shown by SCP 40 (100%) eyes and...
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39 (97.5%) eyes by DCP with $P$ value = 0.315, which is not statistically significant.

(8) IRMA was detected by SCP in 4 (10%) eyes and by DCP in 3 (7.5%) eyes with $P$ value = 0.692, which is not significant statistically.

**DISCUSSION**

FA is an essential investigation tool in diagnosing and following DR pathological changes, and because it needs a dye injection before imaging, it is considered as an invasive tool [17].

OCTA is a noninvasive investigation that does not need dye injection [18]. It could visualize the various clinical findings associated with different stages of DM on both SCP and DCP [19].

In our study, OCTA allowed visualization of MA that were seen as focally dilated and abnormally shaped capillaries similarly with no distinction between both layers and also no distinction detected in the ability of FA and OCTA in MA detection (100% in both). OCTA might precisely locate their depth and origin as well. Salz et al. conjointly found that OCTA did have the additional benefit of localizing the precise intraretinal depth of MA [20].

These results were comparable with the study conferred by Ishibazawa, whose study enclosed 42 eyes of 25 patients with DR.

But he observed the presence of a difference between MA shown in FA and OCTA. They referred this to the histopathological configuration of MA lumen that consists of different structures such as thickened, hyalinized, fibrous, laminated, and lipid-containing basement membrane, and hypercellular or multilayered endothelial cells that cause turbulence in the blood flow within them. Therefore, they advised that the blood flow within some types of MA may not have been perfectly displayed using OCTA; additionally, he stated that around eighty percent of MA were located within the inner deep plexus [21]. Salz et al. stated that OCTA could detect MA with a higher capillary flow than MA with a slow flow [20].

OCTA could visualize IRMAs as dilated vessels near the areas of capillary loss and could detect neovascularization by the flow signal at the interior‑limiting membrane [20,22].

However, IRMA could be detected in our study by OCTA less than FA with a statistically insignificant difference. The result was consistent with the result conferred by Couturier et al., who additionally showed the ability of OCTA to detect them in all cases and referred this to the character of IRMA that might have a more rapid blood flow than do MA, therefore enhancing their detection by OCTA [23].

Salz et al. also found that OCTA could visualize vascular abnormalities that were not seen clinically or on FA.
This could be explained by: Unlike FA, hyperfluorescence does not occur in OCTA, which does not cause any confusion due to any leaking of dye. Alsom OCTA has a higher resolution than FA that has a lower resolution, which could not visualize the small MA [20].

In our study, OCTA visualized IRMA in SCP (10%) slightly more than in DCP (7%) with a nonstatistically significant difference.

On the other hand, Ishibazawa et al. declared better visualization of IRMA in deeper capillaries by OCTA than superficial due to the thinner thickness of the inner retina in the nonperfused areas [21].

The assessment of capillary nonperfusion areas in our study by OCTA showed slightly lower accuracy than FA but with a difference that was not statistically significant. Capillary nonperfusion was visualized as capillary nonvisible areas between retinal vessels. Couturier et al. stated that edges of capillary nonperfusion areas are highly delimited on OCTA than on FA, and some capillary nonperfusion areas detected on OCTA were visualized as perfused on FA. Moreover, he referred this to the superposition of the two-capillary complex body part and a few early outpouring on FA [24].

In our study, we evaluated the enlargement and disruption of the FAZ and capillary dropout. According to recent studies, FAZ and parfoveal vessel density have been reported nearly as good indicators of vascular dropout in DM patients [23]. OCTA could also clearly identify capillary nonperfusion in DR eyes because it could distinguish the level of capillary dropout that may indicate ischemia between superficial and deep capillary plexus [25].

We conjointly could identify the perifoveal tube changes as well as rarefaction, dilatation, and telangiectasia by OCTA with delineation and distinguishement of the level in superficial and deep capillary plexus, notably OCTA allowed higher identification of combined vascular changes in the deep layer instead of the superficial layer compared with FA that had a wider field. Nevertheless, FA’s low resolution could not focus on small microvascular pathologies [20]. Couturier et al. suggested that OCT angiography was better in detecting capillary rarefaction [23].

Couturier conjointly stated that the DCP nonperfused areas were observed in 35% of the subjects studied, whereas in our study, it may be observed in 55% of the subjects. Although OCTA could detect in our study FAZ interruption in SCP in 40 tries in DCP in five-hundredth, however, we had carefully interpreted these analyses because distorted images of FAZ were found in four-hundredth and five-hundredth in SCP and DCP, respectively, and the reason could be due to the use of one method only to observe the FAZ areas of the SCP or the DCP, which is one of the limitations of our study.

FAZ area measured by OCTA ranged between 0.12 and 1.07-mm square with a mean of 0.46 ± 0.21. The FAZ area was well visualized on OCTA in our study with better delineation than FA, and FAZ enlargement was detected altogether in the cases.

Moreover, that was similar to the result conferred by Kim et al., who revealed that OCTA could display the FAZ zone more clearly than FA, and this was conjointly reported by Al-sheikh et al. [26,27].

In our study, we evaluated edema by observing any retinal capillary displacement or disappearance. OCTA did allow not only evaluation of macular edema but also visualization of its level. In our study, we also found that OCTA images of the deep-plexus 500th (21/40) eyes showed the most apparent edema compared with the superficial-plexus 30-min (12/40) eyes, which is consistent with Coscas et al., who declared that edema might affect the DCP [28].

Notably, FA could detect DME in all cases 100 pc (40/40) compared with overall edema detection in both DCP and SCP 82% (33/40), which may be referred to as an artifact within the OCTA technique.

**Conclusion**

We were conjointly able to compare OCTA and FA images and assess the relative sensitivity of OCTA compared with FA that used to be the gold standard for evaluation of DME, but with many limitations associated with the need for dye injection. Our study showed the ability of FA and OCTA in MA detection in all eyes, but less numerous in OCTA than FA, and OCTA could precisely locate their depth and origin, which is not possible in FA. The assessment of capillary nonperfusion areas in our study by OCTA showed higher accuracy compared with FA, but with a difference that was not statistically significant.

We are hoping in the future that OCT angiography machines will provide us with imaging faster scanning speed, thus yielding images with larger scanning areas and better resolution in a trial to overcome the limited field of view.

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There are no conflicts of interest.
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