How to Cite:
Ahmed, M. H., Haroun, H. E. A. E., Aboud, . S. A.- allah M., & Ahmed, S. A. E. S. . (2022). Optical coherence tomography angiography versus fluorescein angiography in diagnosis of ischemic diabetic maculopathy. *International Journal of Health Sciences*, *6*(S7), 1072–1085.
https://doi.org/10.53730/ijhs.v6nS7.11494

Optical coherence tomography angiography versus fluorescein angiography in diagnosis of ischemic diabetic maculopathy

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***Abstract*---**Objectives: To compare between the use of Fundus Fluorescein Angiography (FFA) and Optical Coherence Tomography Angiography (OCTA) in the diagnosis and quantification of diabetic macular ischemia (DMI) diagnosed according to the Early Treatment Diabetic Retinopathy Study (ETDRS) classification based on Foveal avascular zone (FAZ) parameters. Patients and Methods: The presented study is a prospective randomized observer blind observational study that included 40 eyes of 25 diabetic patients who were diagnosed as having ischemic diabetic maculopathy. Diabetic patients (type 1 or type 2) having different severities of diabetic retinopathy with and without previous treatment (laser or intravitreal injections). FA and OCTA images were independently graded by 2 observers that reached agreement regarding quantitative DMI according to established protocols. Quantitative analysis of the FAZ area was performed using custom software. Results: Demographic data of the studied cases were comparable between groups. OCTA images closely correlated with FA regarding area of FAZ (mm^2). The correlation was strongest with OCT angiography superficial imaging. Subjects with DMI presented a mean area on OCTA and FA of 0.55 ± 0.38 mm2 and 0.59 ± 0.41mm2 respectively (p= 0.082). Intraclass correlation coefficient (ICC) for the FAZ area measurements between the 2 observers on FA and OCTA was 0.902 and 0.949 respectively.

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
Manuscript submitted: 9 April 2022, Manuscript revised: 18 June 2022, Accepted for publication: 27 July 2022

Conclusion: The new OCT angiography imaging modality can replace the conventional fluorescein angiography imaging in evaluating the ischemic diabetic maculopathy as it is non-invasive repeatable with no risk; thus it can be the gold standard imaging modality in diagnosing and following up the ischemic macular complications in diabetic patients.

***Keywords*---**OCT Angiography, Fluorescein Angiography, Ischemic Diabetic Maculopathy.

Introduction

The DMI is an irreversible category of diabetic maculopathy, and its presence limits the potential benefits of treatments for DR. The DMI is characterized by the occlusion and loss of the macular capillary network or capillary drop out. This condition results in upregulation of growth factors, which contributes to the development of diabetic macular edema (DME), the most frequent sight-threatening disorder in individuals with DR ***(1).***

During the imaging study of the normal macula, an important hallmark is the capillary-free region called foveal avascular zone (FAZ). The characteristics of the FAZ were established since 1980 on the report number 11 of the ETDRS (5). Since then, numerous studies have shown an association between the presence of DMI and visual loss. Other studies have suggested the association of DMI with adverse or diminished effects on outcomes of patients with macular edema, regardless whether they were treated with intravitreal therapies or laser photocoagulation ***(1, 2).***

It is recognized that the FAZ can enlarge and can become irregular in DR and seems to become larger as the stage of retinopathy advances. Diabetic macular ischaemia is characterized by a decrease of foveal vascularization, which causes capillary network damage. It causes loss of neuroretinal tissue and early functional damage probably due to hypoxia or hyperglycaemia ***(3).***

Fluorescein angiography (FA) is the gold standard procedure for the clinical diagnosis of diabetic macular ischaemia since it was introduced in 1961. This technique typically shows large areas of retinal hypofluorescenc due to the absence of macular capillaries. The Early Treatment Diabetic Retinopathy Study (ETDRS) group included FA among the techniques that used to assess the severity of ischaemic damage. However, it requires venipuncture, and reports of anaphylaxis and death related to contrast injections, despite being rare, have been documented. In addition, the technique is time-consuming, requiring up to 10 minutes for framing acquisition ***(4, 5).*** Furthermore, imaging acquisition and analysis can be challenging due to compliance and reduced image quality by retinal hemorrhages. Another disadvantage of FA is that it delivers only two-dimensional images **(26).**

Optical Coherence Tomography Angiography (OCTA) is a new noninvasive three-dimensional cross-sectional imaging of retinal vasculature without the use of dye.

It allows the detection of the retina and choroidal structures by motion contrast and high-speed scanning, comparing the decorrelation signal between multiple sequential B-scans, and assuming that the only moving aspect is the vascular flow. The resulting decorrelation map is a reconstruction of the blood vessels with erythrocytes flowing through them ***(6, 7).*** OCTA facilitates the accurate diagnosis and follow-up of retinal vascular diseases, as morphological and perfusion characteristics can be obtained. Furthermore, early changes provoked by retinal diseases, as remodeling of the FAZ, vascular tortuosity, narrowing of capillary lumen and capillary dilation cannot be seen in the FA as in the OCTA ***(8).***

Although the clinical application of OCTA is still limited in DMI by factors like segmentation errors, the need for good patient fixation, sensitivity to mild eye movements, the lack of optimal algorithms that correct these motion artifacts, suggests that OCTA may be the gold standard for DMI within the next few years ***(9).***

Therefore, the aim of this study was to compare between the use of fundus fluorescein angiography and Optical Coherence Tomography Angiography (OCTA) in the diagnosis and quantification of diabetic macular ischemia (DMI) based on Foveal avascular zone (FAZ) parameters.

Method

Patients and Methods

This study was conducted at retina clinic of Almashreq Eye Hospital in the period from June 2018 to December 2018. After local ethical committee approval and patient's informed written consent, and in compliance with the tenets of the Declaration of ***Helsinki (World Medical Association, 2014)***, this prospective randomized observer blind observational study was conducted on 40 eyes of 25 diabetic patients who were diagnosed as having ischemic diabetic maculopathy. These patients were diagnosed by either OCTA or FFA. Diabetic patients (type 1 or type 2) having different severities of diabetic retinopathy with and without previous treatment (laser or intravitreal injections) were included in the study.

Patients with significant cataract, previous retinal arterial or venous occlusion, inherited macular dystrophy, macular degeneration or scarring due to any cause, posterior segment inflammation, and, subjects that presented motion artifacts during OCTA or poor signal strength were excluded from the study.

Signed informed consent is obtained from each subject prior to enrolment. All subjects had a comprehensive ophthalmologic examination, including best-corrected visual acuity (BCVA), intraocular pressure assessment; patients were then dilated and had +78D noncontact lens slit-lamp fundoscopy, color fundus photography, and FA and or OCT angiography. (All subjects diagnosed as having ischemic maculopathy by either OCTA or FFA had been examined by the other investigation for comparison).

All medical records from patients were reviewed and completed including age ,sex , type and duration of DM and past ocular treatment either argon laser ablation or inravitreal injections.

Acquisition and Analysis of fundus fluorescein Angiography:

Color fundus photographs were obtained and The FA images of the macula were acquired using (**ZEISS VISUCAM 224, Carl Zeiss Meditec, Dublin, CA, USA),** Standard photographs were obtained at 20–40 seconds after contrast injection**. (All patients received a standard infusion of 5mL of 20% sodium fluorescein).** From multiple early-phase FA images, the image on which the specialists were able to best identify the FAZ characteristics was selected (mostly at the arteriovenous phases) for FAZ boundries delieation and grading central macular nonperfusion area.

Acquisition and Analysis of Optical Coherence Tomography Angiography:

Optical coherent tomography angiography (OCTA) has been obtained by **(CIRRUS HD-OCT 500, (Carl Zeiss Meditec, Dublin, CA, USA)** after dilatation of the pupil, and imaging data were obtained using the split-spectrum amplitude-decorrelation angiography (SSADA) software ***(10)***. This instrument operates at **~840** nm wavelength, **27,000 - 68,000** A-scans per second, bandwidth of **50 nm**h. The tissue resolution is 5 μm and there is a 15 μm beam width. The total time has been acquired to take OCTA photos is just seconds in patient with good fixation and coordination. The scanning area was captured in 3mm × 3mm sections, and the acquired OCT volumes were centered on the fovea. For each eye analysed, a superficial flow and a deep flow image were taken. Superficial capillary plexus (SCP) angiograms were selected for our study because they provide the most reliable comparison with FA images.
All images were taken by the same well experienced technician& No image manipulation was performed prior to FAZ area measurement.

Analysis of fluorescein Angiography and Optical Coherence Tomography Angiography

We used Image J software in our study to crop all selected FFA images to approximately 3mm × 3mm areas corresponding to those captured by OCTA to enable comparison.

The quantification of macular nonperfusion in both FA and OCT angiography captured images was completed using ImageJ software **(ImageJ, National Institutes of Health, Bethesda, MD)**, as ***we used it for manually drawing the FAZs in both FFA& OCTA images then measuring these areas automatically***.

Both FFA & OCTA angiograms were graded according to the ETDRS classification by two experienced retinal specialists. They analyzed the characteristics of the capillary network in terms of FAZ area, FAZ outline and capillary loss in central area. To estimate the area of the original FAZ, FAZ boundaries **(The innermost capillaries around the fovea)** were manually delineated and the internal area

was measured automatically using Image J software. (They manually drew a circle based on shortest distance between two points of the inner borders of the damaged FAZ). **(fig.1, 2)**

Foveal avascular zone (FAZ) size was graded as follows: Grade 0, circle diameter (CD) <600 µm; Grade 1, CD 600 µm; Grade 2, CD between 600 and 1000 µm; Grade 3, CD 1000 µm or more. FAZ outline was classified as follow: Grade 0, normal; Grade 1, questionable (not smoothly round or oval); Grade 2, less than half the Original circumference destroyed; Grade 3, more than half the original circumference destroyed; Grade 4, capillary outline completely destroyed; and Grade 8, unable to grade. Capillary loss was graded as follows: Grade 0, no loss; Grade 1, questionable; Grade 2, minimal; Grade3, moderate: and Grade 4, severe ***(4).***

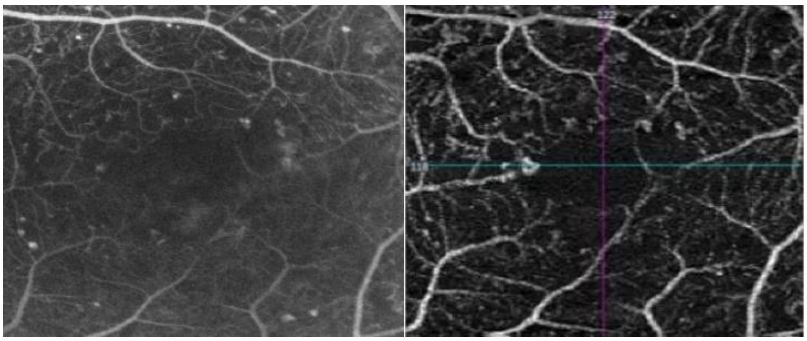

Figure 1: FFA (left) and OCTA(right) showing macular ischemia.

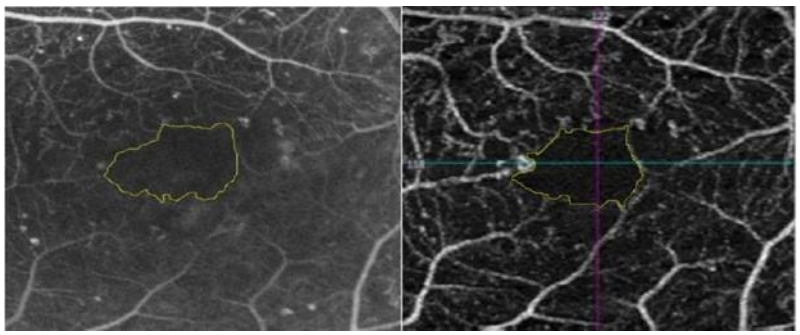

Figure 2: FFA image (the left) was cropped to get approximately the same area (3mmX3mm) taken by OCTA (the right). FAZs manually delineated in both FFA (the left) and OCTA (the right) using Image J.

Statistical Analysis: Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS, Illinois, USA) version 23. Qualitative data were presented as numbers and percentages while quantitative data were presented as mean ± standard deviations and ranges. Comparison between groups with qualitative data was done by using Chi-square test. Wilcoxon signed-rank test was used to compare area measurements performed by 2 readers on FA and OCTA 3mm× 3mm scans. Intraclass correlation coefficient (ICC) was used to estimate the agreement between individual measurements from

both readers. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. P values of <0.05 were considered statistically significant.

Results

The study included 40 eyes with DMI (from 25 patients). Of these patients, 24% (N=6) were female and 76% (N=19) male. The mean patient age was 51.83 ± 9.74 years, and the mean time for diabetic evolution was 16.70 years. The mean visual acuity was 0.52 ± 0.27 measured on snellen charts. Mean IOP was 15.77 ± 3.89. 35% of patients had IDDM (type 1) and 65% had NIDDM (type 2). All eyes had diabetic retinopathy; 31eyes (77.5%) had PDR all of them had laser treatment with 26 eyes(65%) without neovascular activity and 5 eyes(12.5) had persistent activity after laser treatment and 9 eyes (22.5%) had sever non proliferative diabetic retinopathy (sever NPDR). (Table 1)

Table 1
Demographic data of the studied cases

		No.= 40
Age	Mean±SD	51.83 ± 9.74
	Range	25 – 70
Sex	Females	6 (24.0%)
	Males	19 (76.0%)
Site	OD	23 (57.5%)
	OS	17 (42.5%)
V.A	Mean±SD	0.52 ± 0.27
	Range	0.05 – 1
IOP (OD)	Mean±SD	15.77 ± 3.89
	Range	10 – 22

Intra-class correlation coefficient ICC for agreement in the OCTA and FA between the 2 examiners is (95% CI): for OCTA 0.949 (0.903 – 0.973) & for FA 0.902 (0.822 – 0.947) (p<.001).

Based on the OCTA, 7 eyes (17.5%) graded as grade one of macular ischemia,18 eyes (45%) as grade two, and 15 eyes (37.5%) as grade three. Similar results were obtained by the FFA; as 5 eyes (12.5%) graded as grade one, 17 eyes (42.5%) as grade two, and 18 (45%) as grade three **(table 2)**.

Table 2
Comparison between OCTA and FFA regarding grades of ischemia

Grades of ischemia	**OCTA**		**FFA**		**Test value**	**P-value**	**Sig.**
	No.	**%**	**No.**	**%**			
Grade I	7	17.50%	5	12.50%			
Grade II	18	45%	17	42.50%	0.635	0.727	NS
Grade III	15	37.50%	18	45%			

According to the OCTA and FA, the mean area of FAZ was **0.55 ± 0.38 mm², ** and **0.59 ± 0.41mm², ** respectively. And so there was no statistically significant difference in the area of FAZ measured by OCTA & FFA with p-value **>0.05 (table 3).**

Table 3
Comparison between OCTA and FFA regarding area of FAZ (mm^2)

		OCTA	**FFA**	**Test value≠**	**P- value**	**Sig.**
		No.= 40	**No.= 40**			
Area of FAZ (mm2)	Mean ± SD	0.55 ± 0.38	0.59 ± 0.41	-1.741	0.082	NS
	Range	0.18 – 1.89	0.20 – 1.88			

With Positive correlation between OCTA and FFA results according to Wilcoxon Rank test **(Fig. 3)**

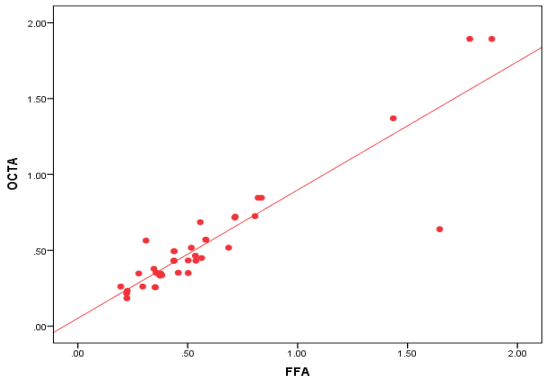

Figure 3: Positive correlation between OCTA and FFA results according to Spearman correlation in area of FAZ

There was highly statistically significant positive correlation found between age of the studied patients and area of FAZ measured by OCTA & FFA with p-value = 0.004 & 0.002 respectively (fig. 4).

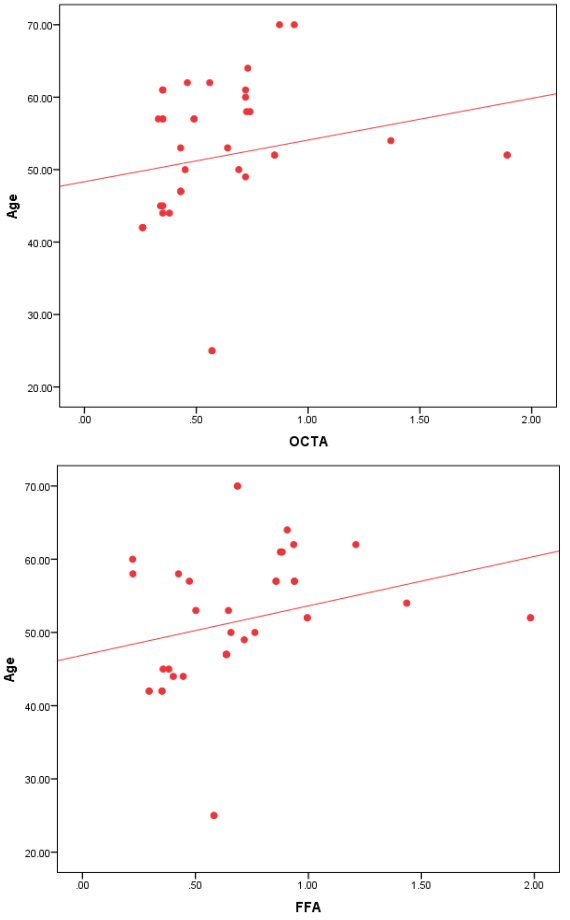

Figure 4: Positive correlation between age and OCTA and FFA results according to Spearman correlation

There was also statistically significant negative correlation found between VA of the studied patients and area of FAZ measured by OCTA & FFA with p-value = 0.008 & 0.016 **(fig. 5)**.

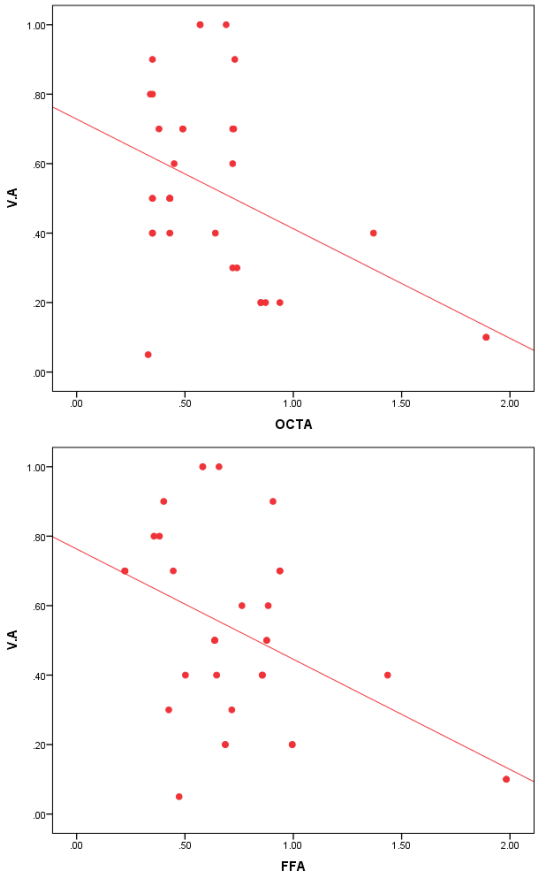

Figure 5: Negative correlation between VA and OCTA and FFA results according to Spearman correlation

There was no statistically significant correlation found between IOP of the studied patients and area of FAZ by OCTA & FFA and there was no statistically significant difference found between males and females regarding size of FAZ by OCTA and FFA.

Discussion

Diabetic macular ischemia (DMI) is associated with functional retinal damage, and its diagnosis predicts DR progression ***(7). Sim et al. (1)*** demonstrated that approximately 41% of patients with DR in a tertiary hospital setting had some degree of macular ischemia. DMI is usually associated with reduced visual acuity (VA) in the eyes with moderate to severe grades of ischemia, but VA is preserved in milder grades of ischemia ***(1, 4).***

Because antiangiogenic therapy has become one of the treatments of choice for managing DR, the diagnosis of DMI has become more important, especially because antiangiogenic therapy can obscure the clinical findings related to ischemia progression ***(11, 24).***

OCTA is a noninvasive method, obtains highly detailed 3-dimensional images without requiring injection of a contrast dye, and allows faster acquisition of images ***(5, 12).*** The OCTA performs two repeated B-scans from304 sequentially uniformly spaced locations. Each B-scan consisted of 304 A-scans for a total of 2 × 304 × 304 A-scans per acquisition. ***(5).*** Changes in the FAZ area and VD had been reported in diabetic patients even before the development of frank diabetic retinopathy using OCTA, suggesting that these alterations are potential early biomarkers for diabetic retinopathy (DR). ***(25).*** It provides an objective automated study of macular capillary nonperfusion as a potential sign of central ischemia ***(13).*** **De Carlo et al.,** also observed macular nonperfusion in a diabetic patient in a 3 mm × 3 mm OCTA that was centered on the fovea by applying a similar technology ***(14).***

The 3 mm × 3 mm OCTA central sections obtained using SD-OCT allowed us to obtain a higher resolution over a small area. This area was sufficient for detecting central DMI, but it was not large enough to identify peripheral retinal nonperfusion. Using OCT angiography with SSADA in healthy participants, Wang et al. measured a mean FAZ of 0.35 ± 0.12 mm^2. In a study carried out by **Bhanushali et al.,** on 209 eyes of type 2 DR subjects and 60 eyes of normal subjects; normal eyes had significantly smaller FAZ area than DR subjects by OCTA scanning ***(15).***

In the present study FAZ area measurements obtained with OCTA in patients diagnosed with DMI were more delineated than those in FA and measured **0.55 ± 0.38 mm2** and **0. 58 ± 0.41 mm2,** respectively**, (p = 0.082).**

In the present study, statistical analysis indicated non significant difference between FAZ area measurements obtained with OCTA and FA in patients diagnosed with DMI. The ICC for the FAZ area between the 2 observers on OCTA and FA demonstrated the reproducibility and consistency of the used methodology.

These values are comparable with studies by **Miwa et al., Kashani et al., Soares et al and Dominika et al.**, on patients with DMI that showed that the FAZ areas in OCTA images in the superficial layer almost corresponded to those in FA images and thus concluded that OCTA may have clinical feasibility for evaluating this pathogenesis ***(16, 17, 18,26).***

In contrast, these values were different from those reported by **Yoon et al** in patints with DMI; **0.68 ± 0.53 mm2** and **0.58 ± 0.35 mm2,** respectively ***(19).*** That had the clinical note that FA measures are more than OCTA.

The grade of macular ischemia contributes to DR worsening; even more than systemic factors, especially over a short time of period. The reason may be as several studies have shown changes in the retinal layers; ***Byeon et al. (20) and Liew et al. (21)*** have reported damage to the foveal ganglion cell layer and loss of the inner retinal layers, by a SD-OCT, corresponding to the area of reduction of capillary perfusion. Other studies have reported thickening of the ischemic retina, especially in the intermediate layers ***(21)***. ***Sim et al. (7)*** found thinning of the

retinal nerve fiber layer, outer retina, and thickening of Haller's large vessel layer of the choroids.

In the present study a greater grade of DMI was found in association with a decrease in the visual acuity (visual acuity is negatively correlated to FAZ area measurements).

This is similar to other researches who stated that automated quantitative algorithms of OCTA allow for assessment of retinal vascular changes in eyes with ischemic diabetic retinopathy that are correlated to visual acuity especially FAZ. They concluded that OCTA may prove useful in monitoring disease progression and identifying parameters that affect visual function ***(22)***.

Smaller FAZ areas by OCTA seems to be a more scientifically acceptable measure as vascular visibility is an obvious undeniable finding. Thus, larger sample size and further improvements in OCTA would ensure the findings and eventually reduce the need for fluorescein angiography.

The main limitations of our study were the small number and inability to follow-up patients for reproducable results. Further studies should be performed to provide support for our particular results. Another problem that faced us during performing OCTA was, the artifacts, The most common reasons for artifacts were projection and segmentation errors **[29, 30].** Also motion artifacts, that originate from patient's movement or blinking. where the OCT angiography requires the patient to precisely fixate a target during image acquisition for approximately 3– 4 seconds, which is not an easy task especially for uncooperative patients and patients with low visual acuity, These artifacts result in small black or white horizontal lines. however, **De Carlo et al.,** suggested eye-tracking software which could reduce this artifact in the future, similar to what is applied in LASIK machines ***(14).*** Also some images were limited by the presence of edema that masked the flow signal from the perfused vessels and affected the data interpretation.**(31)**

Conclusion

Owing to the high level of agreement between the OCTA and the FA, the new OCT angiography imaging modality can replace the conventional fluorescein angiography imaging in evaluating the ischemic diabetic maculopathy as it is non-invasive repeatable without risk; thus it can be the gold standard imaging modality in diagnosing and following up the ischemic macular complications in diabetic patients.

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