

# The role of ocular coherence tomography angiography in the diagnosis of diabetic retinopathy and a comparison with the current gold standard fundus fluorescein angiography

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## ABSTRACT

**Background:** Diabetic retinopathy is a leading cause of preventable blindness in the world. Efficient and effective diagnosis and surveillance of diabetic retinopathy is of crucial importance to preserve the vision of patients. The FAZ (Foveal Avascular Zone) area is enlarged in patients of diabetic retinopathy. The purpose of this study is to evaluate the accuracy of OCT-A (Optical Coherence Tomography-Angiography) in delineating the FAZ area in cases of diabetic retinopathy and make a comparison with the findings of FFA (fundus fluorescein angiography) - the current gold standard.

**Subjects and methods:** This was a comparative analytical study carried out at a tertiary care hospital in Lahore, Pakistan. A series of 50 patients, 30 males and 20 females with a mean age of 40 years were selected from the hospital outpatient department with history of five years of diabetic retinopathy. They were classified according to the ETDRS classification system into NPDR and PDR groups. The patients were booked for OCT-A, the scans were then observed for findings with a specific focus on the area of the FAZ at the level of the superficial capillary plexus. The patients then underwent same day FFA the current gold standard modality for diabetic retinopathy, thereafter a comparison between the mean area of the FAZ in both the modalities was made & documented. Data was analyzed using SPSS version 25.0, the Independent t test was applied to compare the means of the two groups and a p value <0.05 was considered statistically significant. The diagnostic screening test accuracy evaluation was done and the Sensitivity and Specificity of each modality was determined using the ROC curve.

**Results:** The FAZ was easily distinguished by both FFA and OCT-A. The mean FAZ area was 0.62 mm<sup>2</sup> on FFA and 0.69 mm<sup>2</sup> on OCT-A. There was a statistically significant difference between the two means (p=0.002). Both the modalities had a Sensitivity of 100% at 0.44 and 0.48 cut-offs. OCT-A had a specificity of 91.9% and FFA had a Specificity of 89.2%.

**Conclusions:** OCT-A proved to be an effective and accurate modality in delineating the FAZ area and detecting macular ischemia in patients of diabetic retinopathy in comparison to the current Gold-Standard FFA.

## Keywords:

Diabetic macular ischemia, Foveal Avascular Zone, Diabetic Retinopathy, Ocular-Coherence Tomography-angiography

## INTRODUCTION

Diabetic retinopathy is the leading pathology resulting in visual loss amongst the working age adult population in the developed world.<sup>1</sup> It is characterized by diabetic macular edema, macular ischemia, and the subsequent consequences thereof including retinal neovascularization, vitreous hemorrhage and tractional retinal detachment.<sup>1</sup>

Diabetic macular ischemia, an important pathological hallmark of diabetic retinopathy, which manifests as an increase in the area of the foveal avascular zone (FAZ) in addition to parafoveal areas of capillary nonperfusion (“capillary drop-out”) has been studied to be directly linked to the visual acuity of patients of diabetic retinopathy<sup>2</sup>. Therefore it is an important feature of diabetic retinopathy that can be monitored for both the diagnosis and progression of diabetic retinopathy.<sup>2,11</sup>

Fundus Fluorescein Angiography (FFA) is an invasive dye based retinal imaging modality used to delineate areas of capillary dropout and diagnose macular ischemia in patients of diabetic retinopathy.<sup>3</sup> Despite being classically labelled as the ‘Gold Standard’

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modality in the diagnosis and surveillance of diabetic retinopathy<sup>5</sup> it is an invasive modality requiring the need for dye injection which presents serious limitations to its safety and feasibility. In addition to this FFA has its' own intrinsic limitations such as dye leakage from blood vessels that have developed microangiopathy that results in blockage of the underlying tissue fluorescence.<sup>2</sup>

One of the more recent developments in non-invasive imaging of the retina has been OCT (Optical Coherence Tomography) which has become widely accepted as a modality to obtain high resolution cross sectional scans of the retina that reveal intricate detail of the retinal layers demonstrating the presence or the absence of pathological changes, thus providing valuable information aiding in the diagnosis and surveillance of diabetic retinopathy.<sup>4</sup>

A further development and advancement to OCT is Spectral domain optical coherence tomography-angiography (OCT-A), a modality that deciphers the decorrelation signal between several simultaneous OCT B-scans resulting in a decorrelation map which gives us a three dimensional depiction of blood vessels with the red blood cell movement within them.<sup>2</sup> The FAZ area at the superficial capillary plexus is an accurate criterion for evaluating macular perfusion status.<sup>5</sup>

The objective of this study was to exhibit the true potential of OCT-A as a diagnostic tool in patients of diabetic retinopathy by demonstrating its capability in determining the status of macular perfusion depicted as foveal avascular zone area and comparing it to that shown by FFA.

Other studies that have been conducted on this subject are mostly retrospective studies with time gaps of several weeks to months between the OCT-A and FFA scans, this study in comparison was a prospective study with same-day OCT-A and FFA scans that allowed for a more just comparison between the two modalities.

## SUBJECTS AND METHODS

In this comparative analytical study, we aimed to carry out an objective assessment and comparison between FFA and OCT-A in their diagnostic capability in patients of diabetic retinopathy. The foveal avascular zone area was determined and recorded for each patient by both the modalities.

The study was conducted at LRBT Free Eye and Cancer Hospital, Lahore, Punjab. The period of the study was from the 1<sup>st</sup> of March 2021 until the 20<sup>th</sup> of October 2021. Data collection and analysis was

conducted after taking approval from the Institutional Review Board of LRBT Eye hospital (IRB/ID/65), and adhered to the tenets of the Declaration of Helsinki. Informed consent to participate in the research was taken from each patient.

The inclusion criteria for our study was: patients with a five year history of diabetes mellitus with evidence of diabetic retinopathy graded according to the EDTRS classification system. Patients of both non-proliferative diabetic retinopathy and proliferative diabetic retinopathy were included in the study.

The exclusion criteria was patients with significant cataracts and media opacities that were an impediment to successful imaging. Furthermore cases with the presence of artifacts significantly affecting image quality were also excluded from the study.

We included a total of 50 patients, 30 male and 20 female patients, the male: female ratio was 1.5:1. Patients presenting to our OPD with a five year history of diabetic retinopathy were selected. The sampling technique we applied was non-probability purposive sampling. Two independent observers graded the stage of diabetic retinopathy in each patient clinically according to the ETDRS classification system. Out of the total 50 patients, 13 patients were graded to have Proliferative diabetic retinopathy and 37 patients had Non-Proliferative diabetic retinopathy.

All the patients enrolled in our study were booked from our OPD and underwent same-day FFA and OCT-A imaging. Scans of only one eye (Right eye) of each patient was included in the study. All the FFA scans were carried out using the Canon CX-1 FFA machine. The OCT-A scans were conducted using the NIDEK RS-3000 OCTA machine.

Data was entered and analyzed using SPSS Version 25.0. The independent sample t test was used to compare the mean FAZ area measurements of FFA and OCT-A and a p-value of < 0.05 was considered statistically significant. The diagnostic screening test-accuracy evaluation was done and the Sensitivity and Specificity of each modality was determined by using the ROC curve. 95% Confidence Intervals were calculated through the Wilson Score method.

The OCT-A images were acquired with the NIDEK RS-3000 system with a scanning area of 3 by 3 mm section being captured. The images were processed by the built-in NAVIS-EX (version1.10) software. This automatically segments the scans into superficial retinal capillary plexus (SCP), deep retinal capillary plexus (DCP) and choroid capillary. We obtained the

measurements of the FAZ area at the SCP level through the aforementioned built in system software in mm<sup>2</sup>.

The FFA images were taken at the early choroidal phase which commenced at 10 seconds post-dye injection. The FAZ area was then measured using the built in Retinal Image Control Software, without any photograph alteration.

## RESULTS

A total of 50 patients were included in this study, with mean age of  $40 \pm 15$  (range: 25-55years). There were 30 males (60%) and 20 females (40%) in the study. Thirty seven patients (74%) had non-proliferative diabetic retinopathy whereas 13 patients (26%) were graded to have proliferative diabetic retinopathy by two independent observers according to ETDRS classification system.

The mean FAZ area was calculated for both the FFA and OCT-A groups. The mean FAZ area on FFA was 0.6204 mm<sup>2</sup> (95% CI: 0.58-0.65) and the mean FAZ area on OCT-A was 0.696 mm<sup>2</sup> (95% CI: 0.65-0.73)

A statistically significant difference between the mean FFA and OCT-A FAZ areas was identified ( $p = 0.002$ ). The mean FAZ area results detected by both FFA and OCT-A in patients of non-proliferative diabetic retinopathy and proliferative diabetic retinopathy separately are shown in Table 2.

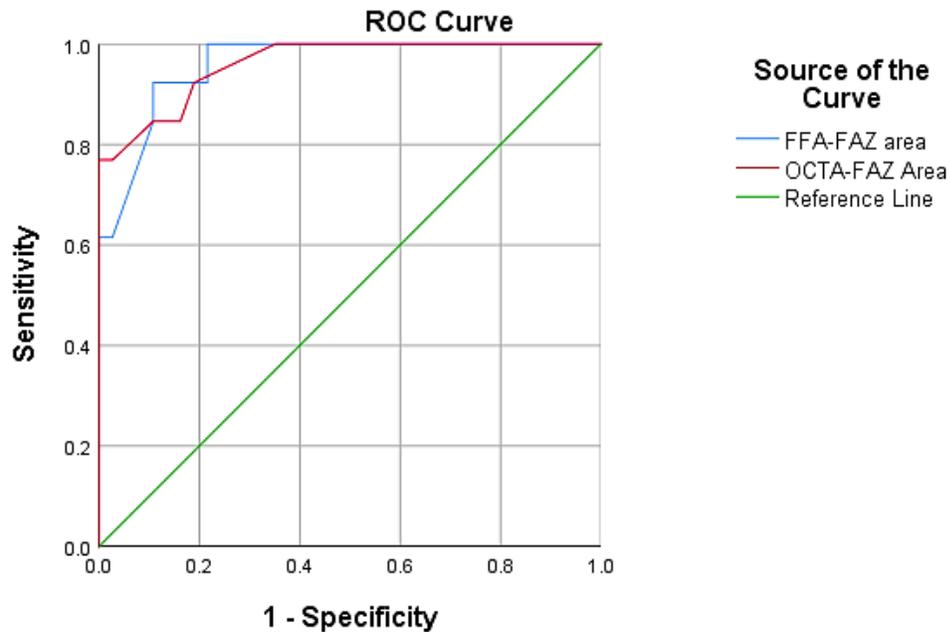
The diagnostic accuracy of both the modalities was calculated using the ROC curve. Both the modalities gave a Sensitivity of 100% at 0.44 and 0.48 cut-offs. OCT-A demonstrated a Specificity of 91.9% (95% CI: 78.7-97.2) and FFA gave a Specificity of 89.2% (95% CI: 75.3-95.7).

Table 1. Shows the Mean FAZ area with FFA and OCT -A

Parameters	N	Mean	Std. Deviation	95% CI	p-value
FFA-FAZ Area (mm <sup>2</sup> )	50	0.6204	0.13220	0.58-0.65	0.002
OCTA-FAZ Area (mm <sup>2</sup> )	50	0.6966	0.13523	0.65-0.73	

Table 2. Mean FAZ area by FFA and OCT-A in PDR and NPDR

Modality	Stage of Diabetic Retinopathy	N	Mean -FAZ area mm <sup>2</sup>	Std. Deviation	p-value
FFA	PDR	13	0.7738	0.08761	0.002
	NPDR	37	0.5665	0.09869	
OCT-A	PDR	13	0.8562	0.11673	0.001
	NPDR	37	0.6405	0.08904	



Diagonal segments are produced by ties.

Figure 1. Receiver operating characteristic curve

The ROC curve (Figure 1) shows the trade-off between sensitivity and specificity. The closer the curve is to the top-left corner, as is demonstrated in this result, the better the performance whereas the closer the curve comes to the 45-degree diagonal of the ROC space the less accurate the test<sup>12</sup>. The ROC curve for OCT-A and FFA showed good performance and high accuracy of the diagnostic modalities. The average time consumed in carrying out the scans was 15 ( $\pm$ 5) minutes on FFA, while on OCT-A it was 5 ( $\pm$  2) minutes.

## DISCUSSION

Through this study we objectively compared the diagnostic capability of OCT-A and FFA by documenting the FAZ area delineated by each modality and applied various statistical tools of analysis to the acquired data.

Other studies in the past on this subject, despite having their limitations of being retrospective in nature with significant time gaps between the scans of the two modalities, have compared the measurements of the mean FAZ area between the two modalities. Work by Alberto et al.<sup>2</sup> arrived at a p-value <0.001 demonstrating a low agreement between the FAZ area obtained through FFA and OCT-A scans. In contrast work by Garcia et al.<sup>6</sup> concluded a reasonable level of agreement between the two modalities in FAZ area measurement in patients of diabetic macular ischemia. Our study showed a statistically significant difference between the mean FAZ area obtained through FFA and OCT-A scans (p-value=0.002). The FAZ areas obtained through the OCT-A scans were larger than those obtained through FFA. The diagnostic accuracy of both the modalities was comparable, both having a sensitivity of 100% while OCT-A demonstrated a greater specificity (91.9%) than FFA (89.2%).

In addition to this the OCT-A modality showed greater user-friendliness by being non-invasive and free in need of dye injection. One of the challenges in general encountered while taking OCT-A scans was that of motion artifacts. This included the appearance of lines and dots usually white in color often due to the unwanted movement and the non-compliance of the patients undergoing the scans.<sup>7, 12-14</sup> Another dimension of comparison was the time duration of the OCT-A scans which was 2-3 minutes on average whereas in comparison FFA scans take 15-20 minutes on average<sup>8</sup>. The non-invasiveness and much shorter duration and higher safety profile of OCT-A all make it a worthy first line modality in the investigation of patients with

diabetic retinopathy for the assessment of diabetic macular ischemia.

These results are promising considering the fact that FFA being an invasive procedure with reports of several procedure related complications, rare ones such as anaphylactic reactions<sup>15</sup>, and more common ones such as nausea and vomiting<sup>16-18</sup>. Therefore the availability of an alternative reliable diagnostic modality such as OCT-A is highly advantageous for both the clinicians and the patients.

One of the more significant weaknesses of our study includes utilizing only the superficial capillary plexus (SCP) in the OCT-A scans for the assessment and measurement of the FAZ area. It is pertinent to mention recent studies comparing the SCP with the deep capillary plexus (DCP) have concluded that the **vasculature density and its' measurements at the DCP** is influenced by the presence of macular edema, while the SCP is independent of such factors.<sup>9,19-22</sup>

A possible improvement and advancement to our study could be an analysis of other features of diabetic retinopathy through both the modalities in addition to the FAZ area. Other areas of clinical significance in monitoring diabetic retinopathy include the quantification of peripheral capillary dropout which can be picked up on both the modalities<sup>23</sup>. Another feature is the presence of micro-aneurysms which is an early feature of diabetic retinopathy and can be delineated on both the modalities.<sup>24-25</sup>

## CONCLUSIONS

OCT-A has demonstrated high Sensitivity and Specificity for delineating the FAZ area in patients of diabetic retinopathy. OCT-A is an effective modality in the diagnosis of diabetic macular ischemia in patients of diabetic retinopathy in comparison to the current gold-standard FFA, **in addition to its' advantages of being a non-invasive modality with a more user-friendly experience with less scan times when compared to FFA.** In the near future it could potentially be a significant alternative to and possible replacement to the current **'Gold Standard' FFA.**

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