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Diabetic Macular Ischemia Diagnosis: Comparison between Optical Coherence Tomography Angiography & Fundus Fluorescein Angiography

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Abstract:

Background: OCT-A is developing as a new non-invasive rapid technique which may replace FFA as a gold standard procedure for diagnosis of DMI. **Aim of the Work:** Comparison between fluorescein angiography (FA) and optical coherence tomography angiography (OCTA) for imaging of foveal avascular zone (FAZ) in diabetic retinopathy patients (DR) affected and not affected by diabetic macular ischemia, (DMI). **Subjects and Methods:** In this prospective study, 30 eyes for 30 patients and separated by macular status as 19 eyes with DMI and 11 eyes without DMI instructed to undergo OCT-A scan, FFA. Full ophthalmological examination was done and patients signed their informed consents. **Results:** Of the 30 patients, 13 females and 17 males with a mean age of 52.63 ± 11.9 years. 17 eyes with DMI and 13 eyes without DMI have underwent full ophthalmological examination, BCVA measurement, FFA and OCT-A. BCVA was higher among eyes without DMI (0.5 ±0.2) as compared with eyes with DMI (0.25 ±0.2). Mean time for FFA was 9.4 ± 3.2 m and for OCT-A was 1.5 ± 0.8 m. OCTA can save time than FFA by 85%. 57% was affected with artifacts with OCT-A while 7% has allergic reactions to flourescien dye. Subjects with DMI presented a mean area on FA and OCTA of 0.85 ± 0.2 mm^2 and 0.79± 0.2 mm^2, respectively (p = 0.001). Patients without DMI presented a mean area on FA and OCTA of 0.39 ± 0.1 mm^2 and 0.36 ± 0.1 mm^2, respectively (p = 0.01). The ICC for the FAZ measurements between the 2 observers on FA and OCTA was 0.98 and 0.99, respectively. **Conclusion:** OCTA represents a novel technique to diagnose DMI and it may become an alternative to FA for this purpose.

Keywords: DMI, OCT-A, FFA.

1. Introduction:

Diabetic retinopathy is one of the most dangerous complications of diabetes which characterized by changes in the retina of the diabetic patient. Until now, retinal ischemia got much attention, because it has been considered the first risk factor leads to proliferative diabetic retinopathy and is a main cause of blindness worldwide. But little researches have been done to describe ischemic changes of macular region of human eye, mostly due to its difficult detection and limited options of treatment. Extensive non perfusion of retinal capillary has been diagnosed in the patients having diabetic macular ischemia (DMI) ***(Bresnick et al., 1975).***

There are two non-overlapping sources of blood supply to the retina. The outer retina is supplied by diffusion from choriocapillaries. The inner retina is supplied via the central retinal artery. Vasculature of macula consists of two plexuses of capillaries. Superficial capillary plexus is located in the nerve fiber layer or ganglion cell layer, deep capillary plexus lies within the inner nuclear layer. The foveola itself and in the immediate parafoveal retina have not superficial capillary plexus, So the fovea depends on the blood supply from choriocapillaris ***(Byeon et al., 2012).***

DMI is the enlargement of the FAZ which becomes irregular in DR and seems to be larger in the advanced stage of retinopathy. DMI is characterized by loss of the macular capillary network, its occlusion and capillary dropout. Optical coherence tomography angiography (OCTA) is a new non-invasive technique for imaging that uses motion contrast imaging to high-resolution volumetric blood flow information giving angiographic images in seconds. OCTA compares the decorrelation signal, (differences in the OCT signal intensity or amplitude) between sequential OCT B-scans taken at precisely the same cross-section in order to construct a map of blood flow. Axial bulk motion from patient movement is eliminated so sites of motion between repeated OCT b-scans represent strictly erythrocyte movement in retinal blood vessels ***(de Carlo et al., 2015).***

OCTA has the advantage that it can visualize microvasculature with depth resolution, similar to structural OCT. Volumetric data can be segmented and OCTA from different retinal layers can be projected to enable separate visualization of retinal capillary plexuses and the choriocapillaries, as well as visualizing vascular pathologies including neovascularization and alterations in retinal capillary as well as choriocapillaries structure. In addition, OCTA images can be seen in cross-section for confirming the depth location of vascular pathology ***(Spaide et al., 2015).***

Fluorescein angiography (FA) is an invasive technique that needs intravenous administration of dye and imaging up to10–30

minutes. They give two-dimensional image sets which permit dynamic visualization of blood flow and a wide field of view ***(de Carlo et al., 2015).***

However, Fluorescein angiography is considered the gold standard in retinal imaging in DR. But, it is an invasive method needing venipuncture, contrast infusion, it is a time-consuming method and provides only (2-dimensional) images. Therefore, Anaphylaxis and death reports due to contrast injections have been documented, although being rare ***(Sim et al., 2013).***

OCTA in comparison is a rapid non-invasive technique that needs volumetric angiographic details without using of dye. Each three-dimensional scan set takes about six seconds to get. The en-face images (OCT angiograms) can then be scrolled outward from the internal limiting membrane (ILM) to the choroid to visualize the individual vascular plexus and segment the inner retina, outer retina, choriocapillaries, or other area of interest ***(de Carlo et al., 2015).***

Aim of the work:

To compare using OCT angiography versus FFA in diagnosis of diabetic ischemic macula.

2. Patients & Methods:

Study design:

This is across-sectioned comparative study conducted in Ophthalmology Department at Beni Suef University.

Study population:

A total of 30 eyes belong to 30 patients including 13males and 17 females suffering from diabetes mellitus more than 10 years randomly selected.

Inclusion criteria:

Patients with type 1 & type 2 diabetes mellitus who didn't receive any treatment.

Exclusion criteria:

- Presence of cataract &media opacity.
- History of arterial or venous occlusion.
- Inherited macular dystrophies & degenerations.

Method:

In this study, 30 eyes will undergo full ophthalmological examinations including slit lamp examination, BCVA measurement, IOP measurement, fundus biomicroscopic examination and multi-modal imaging at the same day or weak without receiving any treatment in between including:

A- Optical coherence tomography angiography (OCT-A):

By using the device (Optvue s/n TFG50-232000CH-024 US) after patients were instructed to focus on a fixation target.

Parameters used in the device during procedure:

Algorithm used is SSADA, A-scan rate of the instrument is 70000 scans/second, the light source is centered on 840 nm and a band width of 45 μm, axial resolution obtained is approximately 5 μm, the beam width is 22 μm, number of A-scans required to reconstruct each B-scan is 216 A-scans, number of B-scans at each fixed position is 5 consecutive B-scans, number of locations along the slow transverse direction to form 3D data cube is 216 locations, B-scan frame rate per second is 270 frames, acquired raster scans are 4 volumetric raster scans (2 horizontal and 2 vertical). AngioVue system is provided by an orthogonal registration algorithm called Motion Correlation technology (MCT) which minimizes motion artifacts produced by involuntary saccades and changes in fixation during data acquisition. The combination of motion-corrected OCT angiogram along with the corresponding OCT intensity en face image and OCT B-scans allows direct comparison of OCT structural and functional information.

Automatic segmentation of intraretinal layers revealed: Superficial capillary plexus, 3 μm below ILM to 15 μm below IPL; deep capillary plexus 15 to 70 μm below IPL; outer retina 70 μm below IPL to 30 μm below RPE reference and finally choroidal capillary, 30 μm to 60 μm below RPE reference. Acquisition work flow of angio-retina scan: Scan size for retina is either 3 x 3, 6 x 6 or 8 x 8 mm. All are acquired with 304 x 304 A-scan per volume, thus the smaller the scan size, the higher the image quality.

B- Fluorescein fundus angiography (FFA):

By using the device (Topcon TRC-50ix s/n 175929) after pupillary dilatation and injection of 5 ml of flourescien sodium 10%

Image analysis:

For every eye images from both investigations were compared regarding time consuming for undergoing both investigations, hazards of dye using, demonstrating areas of slow blood flow, demonstrating any retinal pathology that was obscured with hge, dye pooling or media opacities with FFA, effect of artifacts on OCT-A images and sensitivity in detection of DMI.

Data analysis:

The collected data will be tabulated, coded and analysed using SPSS for windows 7, version 23, continuous variables will be presented as mean values plus or minus standard deviation (SD), and categorical variables will be presented as percentages, comparisons among data will be done using suitable statistical tests.

3. Results:

Table (1): Demographic data of the studied cases; (n=30):

	Macular Status		**TOTAL**	***P-value***
	With DMI N= 19	**Without DMI N= 11**		
Sex; N (%)				
Male	13 (68.4)	4 (36.4)	17 (56.7)	0.132[a]
Female	6 (31.6)	7 (63.6)	13 (43.3)	
Age; years				
Mean ±SD	56.89 ±10.3	45.27 ±11.5	52.63 ±11.9	**0.012[b]***
Minimum	43	38	38	
Maximum	71	68	71	

p-value ≤ 0.05 is considered significant.

[a] analyzed by Chi-Square (χ^2) test, [b] analyzed by Wilcoxon signed-rank test

There was no significant difference between with and without DMI regarding sex and there was significant difference regarding age.

Table (2): Diabetic history of the studied cases:

	Macular Status		**TOTAL**	***P-value***
	With DMI N= 19	**Without DMI N= 11**		
Type of DM; N (%)				
Type (1) DM	6 (31.6)	3 (27.3)	9 (30.0)	0.571[a]
Type (2) DM	13 (68.4)	8 (72.7)	21 (70.0)	
Age; years				
Mean ±SD	16.84 ±3.7	15.27 ±5.3	16.27 ±4.3	0.344[b]
Minimum	10	10	10	
Maximum	22	23	23	
Glycosylated Hb				
Mean ±SD	7.54 ±0.9	6.71 ±1.2	7.23 ±1.1	**0.042[b]***
Minimum	6	5.70	5.70	
Maximum	9	9	9	

p-value ≤ 0.05 is considered significant.

a analyzed by Chi-Square ($\chi 2$) test, b analyzed by Wilcoxon signed-rank test,

There was no significant difference between with and without DMI regarding type of diabetes mellitus and age while there was significant difference regarding glycosylated Hb.

Table (3): General and ophthalmological examination of the studied cases:

	Macular Status		**TOTAL**	***P-value***
	With DMI N= 19	**Without DMI N= 11**		
Eye; N (%)				
Rt. Eye	9 (47.4)	6 (54.5)	15 (50)	0.500[a]
Lt. Eye	10 (52.76)	5 (45.5)	15 (50)	
BCVA				
Mean ±SD	0.5 ±0.2	0.23 ±0.2	0.25 ±0.2	0.796[b]
Minimum	0.3	0.05	0.05	
Maximum	0.70	0.70	0.70	
IOP				
Mean ±SD	16.11 ±2.4	15.81 ±1.8	16.00 ±2.2	0.735[b]
Minimum	12	14	12	
Maximum	21	19	21	
Lens				
Pseudophakic	9 (47.4)	1 (9.1)	10 (33.3)	**0.037[a]***
Phakic	10 (52.6)	10 (90.9)	20 (66.7)	
HTN				
No	12 (63.2)	7 (63.6)	19 (63.3)	0.646[a]
Yes	7 (36.8)	4 (36.4)	11 (36.7)	

p-value ≤ 0.05 is considered significant.

a analyzed by Chi-Square ($\chi 2$) test, b analyzed by Wilcoxon signed-rank test,

There was no significant difference between with and without DMI regarding eye, BCVA and IOP while there was significant difference regarding lens and HTN.

Table (4): Diabetic macular ischemia diagnosis using optical coherence tomography (OCT) and fluorescence angiography (FA); (N= 30):

	Macular Status		**TOTAL**	***P-value***
	With DMI N= 19	**Without DMI N= 11**		
OCT Angiography				
Mean ±SD	0.79 ±0.2	0.36 ±0.1	16.00 ±2.2	**0.001***
Minimum	0.52	0.28	12	
Maximum	0.95	0.49	21	
Fundus Fluorescein Angiography				
Mean ±SD	0.85 ±0.2	0.39 ±0.1	0.97 ±1.6	**0.001***
Minimum	0.54	0.32	0.10	
Maximum	1.06	0.52	5.00	
P-value	0.534	0.513		

****p-value ≤ 0.05 is considered significant by Wilcoxon signed-rank test,***

There was significant difference between with and without DMI regarding OCT angiography and fundus fluroescein angiography.

Table (5): The results of ROC curve analysis of FFA and OCTA in the studied cases:

	AUC	**P-value**	**SE**	**95% CI**	**Sensitivity**	**Specificity**	**Cutoff value**
FFA	0.999	0.001*	0.000	0.999 – 1.000	95%	100%	≥ 0.5
OCTA	0.999	0.001*	0.000	0.999 – 1.000	84%	100%	≥ 0.5

AUC= Area under the curve, SE= Standard Error, CI= Confidence interval of AUC.

Intra-class correlation coefficient (ICC) was used to estimate the agreement between individual measurements from optical coherence tomography (OCT) and fluorescence angiography (FA); The ICCs for FAZ area measurements between 2 observers with respect to FA and OCTA were 0.98 (CI: 0.97–0.99) and 0.99 (CI: 0.98–0.99), respectively, demonstrating the reproducibility and consistency of the methodology.

4. Discussion:

Diabetic retinopathy is a microangiopathy that can develop DMI. ETDRS Research Group connected the severity of macular nonperfusion to the potential for progression in DR. In fact, in DR, the advanced deterioration of macular perfusion is the basis for macular ischemia, and developing a method to perceive perfusion maps may allow correlations between central ischemia and the different stages of DR ***(Novais et al., 2016).***

FAZ enlargement is known to occur in patients with diabetic retinopathy, although the FAZ area varies considerably in normal study subjects ***(Arend et al., 1991).*** Despite this variability, FA remains the gold standard for evaluating the retinal perfusion status and for detecting macular ischemia in patients with diabetic retinopathy ***(Conarth et al., 2005).***

Recent advances in imaging have made it possible to analyze morphological changes of the retina in various retinal diseases. Optical coherence tomography angiography (OCT-A) is an important tool being used to evaluate the retinal status and to predict the visual outcome.

The objective of our study was to investigate the correlation between ischemic macular changes as detected by FFA and structural changes on spectral-domain optical coherence tomography angiography (SD-OCT-A) in patients with diabetic macular ischemia (DMI).

To test this correlation, ***Garcia et al. (2016)*** analyzed the data of 30 eyes of 25 patients with Diabetic retinopathy 19 eyes with DMI and 11 eyes without DMI who had underwent FA and Spectral-domain OCT-A. Thirty four eyes from 34 patients, including 20 (58.82%) females and 14 (41.18%) males, were enrolled and separated according macular status.

Twenty-four eyes from 24 patients were placed in the group of patients with DMI, including 15 (62.5%) females and 9 (37.5%) males. Ten eyes with DMI (41.66%) had PDR. The mean (±SD) age of the DMI population was 61.20 ± 6.95 years. The group without DMI comprised 10 patients, including 5 (50%) females and 5 (50%) males. One patient (10%) had PDR. The mean age of this group was 64.09 ± 4.14 years ***(Garcia et al., 2016).***

In our study; thirty eyes were examined from 30 patients and separated by macular status as 19 eyes with DMI and 11 eyes without DMI, the studied patients were distributed as 17 (57.6%) males and 13 (43.3%) females without any statistically significant difference between males and females in relation to macular status. Age of the studied cases was ranged from 38 to 71 years old with an average of 52.63 ±11.9 (SD), studied cases with DMI were significantly older as compared with cases without DMI (p-value =0.012).

In ***Klein et al. (1984)*** study the prevalence of diabetic retinopathy varied from 28.8% in persons who had diabetes for less than five years to 77.8% in persons who had diabetes for 15 or more years. The rate of proliferative diabetic retinopathy varied from 2.0% in persons who had diabetes for less than five years to 15.5% in persons who had diabetes for 15 or more years.

By using the Cox regression model, the severity of retinopathy was found to be related to longer duration of diabetes, younger age at diagnosis, higher glycosylated hemoglobin levels, higher systolic BP, use of insulin, presence of proteinuria, and small body mass.

In our study Duration of DM was ranged from 10 to 23 years with an average of 16.27 ±4.3 (SD), without a statistically significant difference between diabetes duration and macular status.

Glycosylated Hb was significantly higher among cases with DMI as compared with patients without DMI where the mean glycosylated Hb levels were (7.54 vs. 6.71) in patients with and without DMI respectively; (p-value= 0.045).

As expected, the median FAZ area increased with grade of ETDRS-DMI severity. Median FAZ areas were 0.19 mm^2 (interquartile range [IQR], 0.13–0.25) in "none"; 0.25 mm^2 (IQR, 0.18–0.32) in "questionable"; 0.27 mm^2 (IQR, 0.19–0.38) in "mild"; 0.32 mm^2 (IQR, 0.25–0.54) in "moderate"; and 0.78 mm^2 (IQR: 0.60–1.32) in "severe" ETDRS-DMI grades. Highly significant differences in median FAZ area were seen across all subgroups of DMI, with the exception of "questionable" versus "mild" ETDRS-DMI grades ***(Sim et al., 2013).***

In contrary, the work conducted by ***Lee et al. (2013)*** which studied OCT and FFA images of 35 eyes of 33 patients, done in University of Ulsan College of Medicine, Korea, showed that the horizontal and vertical extent of IS-OS disruption statistically correlated with FAZ enlargement in ischemic DME patients (P = 0.001, and P = 0.049 respectively) ***(Lee et al., 2013).***

In our study the results showed that OCTA allowed better visualization of parafoveal macular vasculature and was more sensitive to central macular vascular changes as compared to FFA. The study concluded that deep retinal vascular plexus OCTA images can identify microaneurysms better than superficial retinal vascular plexus OCTA images and FFA images. The study also observed that the FAZ appeared to be larger in FFA images than OCTA images.

In our study, Foveal Avascular Zone (FAZ) was assessed in all studied eyes using optical coherence tomography (OCT) and fluorescence angiography (FA). Eyes with DMI presented a mean FA of 0.85 ±0.2 mm^2, while eyes without DMI presented a mean FA of 0.39 ±0.1 mm^2. With a statistically

significant difference between eyes with DMI and eyes without (p-value =0.001).

OCTA angiogram analysis demonstrated a mean of 0.79 ±0.2 mm^2 among eyes with DMI while eyes without DMI demonstrated a mean OCTA of 0.36 ±0.1mm^2. With a statistically significant difference between eyes with DMI and eyes without (p-value =0.001).

A study on patients with diabetic macular ischemia quantified the FAZ area in both FA and OCTA images. The study showed that FAZ area was similar in between FA and OCTA images ***(Garcia et al., 2016).*** This observation was similar to our data, which showed that FAZ area was similar between OCTA and FFA images.

Significant differences in VA were observed between moderate and severe ETDRS-DMI grades compared with all other grades. Relationship between FAZ Size and Visual Acuity. Overall, we found no evidence any correlation between VA and FAZ area (mm2). However, when the data were stratified by severity of ischemia, quantile regression models revealed a statistically significant association between VA and FAZ area (mm2) in all quantiles for eyes with moderate and severe ETDRS-DMI grades ***(Sim et al., 2013).***

Significant correlations were observed between VA and the FAZ area (r=0.36, P=0.02), papillomacular ischemia area (r= 0.613, P=0.01), but not with the temporal ischemia area (r= 0.22, P=0.29). These relationships are consistent with findings from our previous study and edema, we observed a positive correlation between VA and total retinal thickness (r=0.52, P=0.001) and outer retinal thickness measurements (r=0.33, P=0.04) at the FCS.

Interestingly, in eyes with macular ischemia, but without edema, we observed the converse, where VA was correlated negatively with total retinal thickness (r=0.37, P=0.004) and outer retinal thickness measurements (r=0.44, P= 0.001) at the FCS. There were no significant associations in the analysis of ‘‘all eyes,’’ or between VA and inner retinal thicknesses measurement.

In our study, Best corrected visual acuity (BCVA) was higher among eyes without DMI (0.5 ±0.2) as compared with eyes with DMI (0.23 ±0.2) but whit[l] a statistically significant difference; (p-value >0.05). Intra Ocular Pressure (IOP) was higher among eyes with DMI (16.11 ±2.4) as compared with eyes without DMI (15.81 ±1.8) but whiteout a statistically significant difference; (p-value >0.05).

Fluorescein angiography is still considered the gold standard in retinal imaging on DR. its images are less liable to show artifacts than OCTA, However, it is an invasive method requiring venipuncture and contrast infusion; it is a time-consuming test and provides only 2-dimensional images reports of anaphylaxis related to contrast

injections have been documented, despite being rare.

OCTA is a noninvasive method obtains highly detailed 3-dimensional images without requiring injection of a contrast dye allows faster acquisition of images. OCTA performed using a split-spectrum amplitude-decorrelation angiography (SSADA) algorithm has already been shown to be useful for imaging microvascular changes in DR. Cole 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. 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. High-resolution OCT imaging allows measuring thickness of segmented retinal layers in angiographically apparent ischemic DR. Future OCTA devices improvements may provide clinicians the ability to obtain wider field images with better resolution.

De Carlo et al. (2015) stated that FFA imaging consume time up to 10-30 minutes, while OCT-A scan time is a matter of seconds. ***Spaide et al. (2015)*** stated that FFA due to use of dye is a time consumer unlike OCT-A which is a label-free angiography. Each 3D scan of OCT-A can take about 6 seconds.

We have also to keep in mind that FFA requires time for dilatation about 30-50 minutes unlike OCT-A which doesn't require dilatation. IV administration of dye with FFA is painful to the patient and time consuming.

The present study demonstrates that fluorescein angiography and OCTA provide similar results when used to diagnose macular ischemia in diabetic patients. With further improvements, OCTA may eventually reduce the need for fluorescein angiography.

5. Conclusion:

OCT-A is a new non-invasive procedure which is capable of visualization of diabetic macular ischemia. OCT-A isn't requiring much time during procedure or time for pupillay dilatation. It's not painful due to cannula application for dye with FFA.

Avoiding dye complications will help patients who suffer from dye allergic reactions or can't tolerate dye metabolism as in kidney failure patients. OCTA may provide images with higher details regarding macular status, becoming a good imaging technique for the diagnosis of DMI, and may become an alternative to FA for this purpose. The results also offer improved quantification of FAZ area in diabetic patients without DMI when compared to diabetic subjects with established macular ischemia.

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