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3-Dimensional Vascular Mapping Using Optical Coherence Tomography Angiography versus 2-Dimensional Dynamic Blood Flow Visualization Using Fluorescein Angiography in Diabetic Maculopathy

Mansour H. Ahmed[1], Azza I. Sedkey[1], Sahar I. Mohamed[1], Ibrahim A. Haroun[1*]

Ophthalmology, Faculty of Medicine, Beni-Suef University, Egypt[1]

Corresponding author: 1*

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ABSTRACT

Optical Coherence Tomography (OCT) is a non-invasive that can provide imaging of the cross-sectional structures of the retina by using low-coherence interferometry. The study was to assess of the macular area and detection of macular ischemia in diabetic maculopathy and correlate the finding observed using OCT-Angiography and Fluorescein angiography. The study included forty eyes of twenty patients with clinically significant diabetic macular edema as defined by Early Treatment Diabetic Retinopathy Study (ETDRS) without any other ocular diseases. In our study, the macula showed macular edema without signs of ischemia in 31 eyes out of 40 (77.5%) and 9 eyes out of 40 (22.5%) with macular ischemia (ischemic maculopathy). while by OCT-A we found that the macula was ischemic (Rarified FAZ) in 15 eyes out of 40 (37.5 %) in both superficial and deep capillary plexuses and this was statistically significant as P-value was less than 0.001. There was statistically significant (p-value less than 0.001) increase in FAZ diameter measured by OCT-A in relation to macular ischemia detected on FFA. There was statistically significant (p value = 0.004) decrease in para-foveal density percentage measured by OCT-A in relation to macular ischemia detected on FFA. DME is a major complication causing significant visual morbidity in diabetic patients affecting the quality of life. FFA and OCT-A are indispensable tools in the proper diagnosis and treatment of diabetic macular edema.

1. INTRODUCTION

Diabetes affects an estimated 346 million people worldwide in 2011, and the number of diabetics is projected to double between 2005 and 2030. [1]. In developing countries, diabetic macular edema (DME) has been the most common cause of vision loss. Diabetic macular ischemia (DMI) is another common cause of serious vision loss in diabetics. [2]. Diabetic macular edema (DME), a complication of diabetic retinopathy, is the most common cause of vision loss in diabetics. Discovered that about 41% of diabetic retinopathy patients had diabetic macular ischemia to some degree (DMI) [3]. An even higher incidence of macular edema has been reported in older patients with type 2diabetes [4].

These improvements aid in the activation of inflammatory mediators and the death of endothelial cells. Endothelial cell death leads to the breakdown of the BRB and may lead to increasing ischemia. The breakdown of endothelial cell tight junctions occurs in addition to cell death. [5]. In the clinical diagnosis and grading of macular edema, a thorough clinical examination is essential. Any diabetic patient should have a fundoscopy with stereopsis and high magnification to check for DME and DR [6]. The capillaries are rarefied at the level of the deep capillary vascular plexus. Changes in scale, vascular signal and morphology of plexus are evident. Also visible is the anastmosis between the deep and superficial vascular networks, which is not visible on fluorangiography. OCT-angiography does not display all microaneurysms; those that are clearly visible are usually the larger microaneurysms with residual blood flow. [7].

The macular ischemia examined by angio-OCT is much sharper than as with fluorescein angiography because there is no masking effect by dye leakage. There are some details in the angio-OCT make it possible to distinguish the recent ischemic areas from consolidated and chronic ischemic areas.

2. Patients and methods

The participants in this research were twenty patients with clinically relevant diabetic macular edema as described by the Early Treatment Diabetic Retinopathy Study (ETDRS) and no other ocular diseases. Criteria for inclusion are as follows: Non-proliferative diabetic retinopathy (mild, moderate, and severe) and proliferative diabetic retinopathy (proliferative diabetic retinopathy with diabetic maculopathy) are the three types of diabetic retinopathy. Refractive blunder: The range is -3D to +3D. Types of diabetes: This research looked at both type 1 and type 2 diabetes. Gender: Both male and female were included in the sample. Many of the patients were above the age of 16. Criteria for exclusion: Patients who have had previous ocular surgery, ocular injuries, or a history of other retinal vascular diseases such as vascular occlusive diseases, as well as patients who have had previous argon laser therapy or intra-vitreal injections.

All patients in this prospective randomized study had their medical histories taken, which included their age, gender, diabetes length, affected eye, and presence of systemic diseases. Complete ophthalmic assessment was done including: To test underlying vitreo-retinal pathology, previous argon laser photocoagulation, or previous vitreo-retinal surgery, best corrected visual acuity, anterior segment inspection, and posterior segment examination by (VOLK 90D lens). Investigations performed were: Fundus imaging, Fundus fluorescein angiography, Optical coherence tomography and Optical coherence tomography Angiography is a medical term for the study of blood vessels.

2.1 METHODS

All patients were subjected to the following:

1- Measurement of best corrected visual acuity: using Snellen`s chart, LogMAR acuity testing were obtained from each eye.

2- Slit limp examination: complete anterior segment evaluation was done.

3- Fundus examination: using fundus non-contact lens (VOLK 90D lens) and Keeler indirect ophthalmoscope.

4- Fundus photography: using Topcon TRC-50DX Series camera

5- Fluorescein angiography: Digital retinal camera system (Spectralis HRA2, Heidelberg Engineering, Germany) was used for FA examination after pupillary dilatation with Tropicamide 1% eye drops to evaluate the perifoveal capillary network, and type of leakage which was categorized into different types: Focal leakage: Leaking from microaneurysms or capillaries is present on FA. Diffuse leakage: was diagnosed when poorly demarcated areas of capillary leakage are present on FA. Cystoid leakage: Diffuse leakage and pooling of dye in the cystic spaces of the macula in the late phase of the angiogram. Ischemic diabetic maculopathy:

the predominant finding in patients with ischemic maculopathy was macular capillary non-perfusion (Enlarged, irregular foveal avascular zone). Mixed ischemic maculopathy: many patients with ischemic maculopathy have features of more than one type of maculopathy.

6- Optical Coherence Tomography Angiography (OCT-A): all patients were subjected to (the RTVue XR Avanti, Optovue, Inc., OCT-A) after pupillary dilatation with Tropicamide 1% eye drops: Diabetic macular edema (DME) also was classified according to retinal morphology detected at accompanied OCT images obtained during OCT-A scans into: Focal macular edema, diffuse macular edema, cystoid macular edema and subretinal fluid or neuro-sensory detachment [8].

Statistical analysis of the data: The IBM SPSS software package version 20.0 was used to analyze the data. (IBM Corp., Armonk, NY) Qualitative data were represented using percentages and numbers. The Kolmogorov-Smirnov test was used to ensure that the distribution was natural. Range (minimum and maximum), mean, standard deviation, and median were used to characterize quantitative data. The significance of the obtained results was assessed at a 5% stage.

3. Results

Our study included 40 eyes of 20 patients. Male to female ratio was 1:1. Age ranged between 49 to 70 years old. IDDM to NIDDM ratio was 1.2: 0.8.

In our study, the best corrected visual acuity (LogMar) ranged from 0.20 to 1.30 with mean visual acuity of 0.57± 0.34. There was significant relation between BCVA (LogMAr) and FAZ Diameter assessed by OCT-A (Directly proportional) with p-value less than 0.001 (Table 1).

In our study, there was significant relation between BCVA (LogMAr) and foveal density assessed by OCT-A (inversely proportional) with p- value=0.004 (Table 2).

In our study, there was significant relation between BCVA (LogMAr) and integrity of FAZ assessed by OCT-A with p value<0.001 (Table 3).

Using OCT-A, 7 eyes out of 14 (50.0%) shows no ischemic non-perfusion in the macula neither in SCP nor DCP. and 7 eyes out of 14 (50.0%) showed ischemic maculopathy. The mean FAZ diameter in this group was 0.42 ± 0.21 mm and the mean foveal capillary density was 12.09 ± 6.34%. (in the 14 eyes of severe NPDR) (Table 4).

Using OCT-A, the integrity of the superficial and deep capillary plexuses showed 25 eyes out of 40 eyes (62.5%) with intact SCP and DCP without signs of ischemic macula, and 15 eyes out of 40 eyes (37.5%) showed rarified SCP and DCP (ischemic macula) (Table 5).

In our study, according to fluorescein angiography finding, The macula showed macular edema without signs of ischemia in 31 eyes out of 40 (77.5%) and 9 eyes out of 40 (22.5%) with macular ischemia (ischemic maculopathy). while by OCT-A we found that the macula was ischemic (Rarified FAZ) in 15 eyes out of 40 (37.5 %) in both superficial and deep capillary plexuses and this was statistically significant as P value was less than 0.001. There was statistically significant (p-value less than 0.001) increase in FAZ diameter measured by OCT-A in relation to macular ischemia detected on FFA. There was statistically significant (p value = 0.004) decrease in para-foveal density percentage measured by OCT-A in relation to macular ischemia detected on FFA (Table 6).

Macular edema was classified by FFA into two groups, the first group was 19 eyes of 40 (47.5%) had focal macular edema and the second group were 21 eyes out of 40 (53.5%) had diffuse macular edema. There was statistically significant increase in FAZ diameter in the group of eyes with diffuse macular edema in relation to the other group of focal macular edema with p value of 0.039 (Table 7).

Table (1): Demographic distribution of studied eyes:

	No.	%
Sex		
Male	20	50.0
Female	20	50.0
Age (years)		
<60	21	52.5
≥60	19	47.5
Min. – Max.	49.0 –70.0	
Mean ± SD.	58.48 ±5.59	
Median	58.50	

Table (2): Descriptive analysis of the studied cases according to BCVA (LogMar)

	Min. – Max.	Mean ± SD.	Median
BCVA	0.20 –1.30	0.57 ±0.34	0.45

Table (3): Relation between FAZ integrity by OCT-A and BCVA (logMAR) (n=40)

BCVA	FAZ		U	P
	Intact (n = 31)	Ischemic (n = 9)		
Min. – Max.	0.20 –1.0	1.0 –1.30		
Mean ±SD.	0.42 ±0.21	1.10 ±0.15	3.0*	<0.001*
Median	0.40	1.0		

U: Mann Whitney test p: p value for comparing between the different categories *: Statistically significant at $p \leq 0.05$

Table (4): Distribution of the studied cases according to fluorescein angiography

Fluorescein Angiography	No.	%
FAZ		
Intact	31	77.5
Ischemic	9	22.5
Type of DR		
Mild NPDR	3	7.5
Moderate NPDR	7	17.5
Severe NPDR	16	40.0
PDR	14	35.0
Macular Edema		
Focal	19	47.5
Diffuse	21	52.5

Table (5): Distribution of the studied cases according to OCT and OCT-A

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OCT Angiography	No.	%
Macular Edema		
Focal	15	37.5
Cystoid	7	17.5
Diffuse	15	37.5
Thinning	3	7.5
FAZ Diameter (mm)		
Min. –Max.	0.137 – 0.786	
Mean ±SD.	0.351 ± 0.168	
Median	0.299	
SCP		
Intact	25	62.5
Ischemic	15	37.5
DCP		
Intact	25	62.5
Ischemic	15	37.5
Central Macular Thickness (mic)		
Min. –Max.	206.0 –468.0	
Mean ±SD.	266.4 ±50.12	
Median	249.5	
Foveal Density		
Min. –Max.	3.30 –41.80	
Mean ±SD.	14.68 ±7.71	
Median	14.70	
Para-Foveal Density		
Min. –Max.	24.80 –47.10	
Mean ±SD.	38.75 ±5.91	
Median	39.85	

Table (6): Relation between FAZ in FFA and OCT Angiography (n= 40)

	FAZ				Test of Sig.	p
	Intact (n = 31)		Ischemic (n = 9)			
	No.	%	No.	%		
Macular Edema						
Focal	14	45.2	1	11.1		
Cystoid	6	19.4	1	11.1	χ^2=	^{FE}p
Diffuse	10	32.3	5	55.6	6.288	0.070
Thinning	1	3.2	2	22.2		
SCP						
Intact	25	80.6	0	0.0	χ^2=	^{FE}p
Ischemic	6	19.4	9	100.0	19.355*	<0.001*
DCP						
Intact	25	80.6	0	0.0	χ^2=	^{FE}p
Ischemic	6	19.4	9	100.0	19.355*	<0.001*
FAZ Diameter (mm)						
Min. – Max.	0.14 – 0.59		0.21 – 0.79		U=	
Mean ± SD.	0.29 ± 0.11		0.56 ± 0.18		36.50*	<0.001*
Median	0.26		0.58			
Central Macular Thickness (mic) by OCT						

Min. – Max. Mean ± SD. Median	206.0 – 468.0 267.1 ± 52.07 249.0	220.0 – 374.0 263.7 ± 45.47 252.0	U= 134.5	0.874
Foveal Density (OCT-A) Min. – Max. Mean ± SD. Median	6.0 – 41.80 16.46 ± 7.51 16.50	3.30 – 19.50 8.54 ± 4.89 8.30	U= 50.5*	0.003*
Para-Foveal Density Min. – Max. Mean ± SD. Median	24.80 – 47.10 40.15 ± 5.69 42.10	30.0 – 42.90 33.92 ± 3.92 32.50	t=3.065*	0.004*

χ^2: Chi square test MC: Monte Carlo FE: Fisher Exact

t: Student t-test U: Mann Whitney test

p: p value for comparing between the different categories

*: Statistically significant at $p \leq 0.05$

Table (7): Relation between Macular Edema and OCT Angiography (n= 40)

	Macular Edema				**Test of Sig.**	**P**
	Focal (n = 19)		**Diffuse (n = 21)**			
	No.	**%**	**No.**	**%**		
Macular Edema Focal Cystoid Diffuse Thinning	 15 1 0 3	 78.9 5.3 0.0 15.8	 0 6 15 0	 0.0 28.6 71.4 0.0	χ^2= 41.190*	MCp <0.001*
SCP Intact Ischemic	 14 5	 73.7 26.3	 11 10	 52.4 47.6	χ^2= 1.931	0.165
DCP Intact Ischemic	 14 5	 73.7 26.3	 11 10	 52.4 47.6	χ^2= 1.931	0.165
FAZ Diameter (mm) Min. – Max. Mean ± SD. Median	0.14 –0.61 0.30 ±0.15 0.26		0.22 –0.79 0.39 ±0.18 0.33		U= 123.0*	0.039*
Central Macular Thickness (mic) Min. – Max. Mean ± SD. Median	206.0 –360.0 240.6 ±31.68 239.0		244.0 –468.0 289.7 ±52.84 270.0		U=28.0*	<0.001*
Foveal Density Min. – Max. Mean ± SD. Median	3.30 –41.80 15.86 ±9.55 16.50		6.10 –22.50 13.60 ±5.60 12.50		U=183.5	0.668
Para-Foveal Density Min. – Max. Mean ± SD.	26.30 –46.20 39.34 ±6.13		24.80 –47.10 38.21 ±5.81		t=0.594	0.556

Median	42.70	37.70		

χ^2: Chi square test MC: Monte Carlo
t: Student t-test U: Mann Whitney test
p: p value for comparing between the different categories
*: Statistically significant at $p \leq 0.05$

4. Discussion

OCT angiography, including Fluorescein angiography, can detect FAZ enlargement and irregularities, as well as areas of capillary dropout [9]. FAZ was demonstrated by [10] using a 1.5 1.5 mm central foveal scan, and capillary drop out was demonstrated by [11] using a 3 3 mm scan in a diabetic patient. When compared to fluorescein angiography, [12] investigated the ability of OCT-A to detect diabetic microvascular changes. They concluded that OCT-A was more accurate than FA at detecting capillary non-perfusion and that grading for diabetic maculopathy progression could be possible. This is consistent with the findings of the current research, which showed that OCT-A was more effective than FFA in detecting macular ischemia. In diabetic retinopathy, [13] imaged and quantified neovascularization and areas of macular ischemia. The diameter of the foveal avascular zone (FAZ) and the total area of vessel non-perfusion were measured to determine the severity of macular ischemia. This is similar to the findings of our study, which used OCT-A to compare FAZ diameter in ischemic and non-ischemic maculopathy cases and found a significant increase in FAZ diameter in ischemic cases compared to non-ischemic cases.

The median diameter of FAZ in non-ischemic maculopathy cases was 0.26 mm compared with 0.58 mm in ischemic maculopathy cases. With the 6 × 6 mm OCT angiogram, it was difficult to identify microaneurysms. Higher resolution but smaller field (3 × 3 mm) OCT angiograms can identify some microaneurysms, but not reliably [11]. This difficulty is likely due to relatively low flow in micro-aneurysms and relatively low scan density used in OCT angiography. Identification of microaneurysms on angiogram may not have value in predicting the risk of progression, but their identification is a part of standard of focal laser treatment for diabetic macular edema [14]. On OCT angiography and FFA, other vascular characteristics such as arteriolar wall staining and intraretinal vascular anomalies had different appearances. This distinction, as well as the complexity of detecting microaneurysms, demonstrates the fundamental difference between how the two technologies generate their detection signal. Because the contrast in FFA is dependent on the presence of dye, pathologies that cause dye accumulation, such as a micro-aneurysm, are more clearly displayed.

The contrast in OCT angiography is determined by movement or flow. As a result, such fluorescein angiographic characteristics like staining and leakage do not have a direct equivalent in OCT angiography. Even in this limited sample, however, it was clear that the lack of leakage enables OCT angiography to detect features that would otherwise be obscured by FFA leakage. More research is required to fully comprehend the importance of these distinctions in clinical practice. Although this study demonstrated that OCT angiography can detect many of the features of diabetic retinopathy seen on FFA, conclusions regarding sensitivity and specificity of OCT angiography are difficult to draw due to the small number of patients and restricted range of disease severity. Foveal vascular density was found to be 16.5 percent in non-ischemic maculopathy cases and 8.3 percent in ischemic maculopathy cases in our research. With a p value of 0.003, there was a statistically significant decrease in foveal density in ischemic cases compared to non-ischemic cases. In conclusion, the OCT angiographic characteristics of diabetic retinopathy are shown in this analysis. Some of the advantages over fluorescein angiography include its quick acquisition time, the lack of an intravenous dye, and the ability to see tiny neovascular tufts and areas of capillary dropout that aren't blurred by leakage. This technology may be useful for routine diabetic retinopathy surveillance because of these benefits.

The narrow field of view, low resolution, and difficulty in detecting micro-aneurysms over a wide area are some of its current drawbacks. The fact that the procedure isn't yet relevant to evaluating the vascular state of the retinal periphery is also a significant roadblock to using OCT-A as the primary method of assessing diabetic retinopathy patients.

5. Conclusion

DME is a serious complication in diabetic patients that causes substantial visual morbidity and lowers their quality of life. In the proper diagnosis and treatment of diabetic macular edema, FFA and OCT-A are essential methods. These imaging techniques may also be used to assess prognostic criteria that have an effect on the final BCVA, in addition to their diagnostic function.

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