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Evaluation of multi-focal electroretinogram and optical coherence tomography angiography findings in diabetic maculopathy

Moataz Ayman Elshiekh (MSCh), Amin E Nawar (MD, FRCS), Yasser Ragab Serag (MD), Hamdy Abd El- Azim El- Koumy (MD)

Ophthalmology Department, Faculty of Medicine, Tanta University, Tanta, Egypt
Moataz.elshiekh93@yahoo.com

Abstract: Background: Diabetic maculopathy refers to two distinct eye diseases; diabetic macular oedema (DME) and diabetic ischaemic maculopathy. The two types of maculopathy are often comorbid, Ischaemic maculopathy occurs in conjunction with macular oedema and may occur even when macular oedema is mild. Diabetic macular oedema is one of the most important causes of blindness in developed countries under 70 years of age. Some studies have reported impaired function in the middle and inner layers of the retina in diabetic patients before vascular complications have been identified. Therefore, there is a need for an objective test for early detection and diagnosis of patients with abnormal retinal function due to diabetic retinopathy (DR) and DME. Multifocal electroretinography (mfERG) is important objective test identifying functional changes of the retina in early phases of DR Optical Coherence Tomography angiography (OCTA) can image vascular changes of diabetic maculopathy such as neovascularization and non-perfused areas (ischemic maculopathy). **Aim of the study:** is to evaluate the functional changes by multifocal electroretinography and the vascular changes by optical coherence tomography angiography in cases of diabetic maculopathy. **Patients and Methods:** A prospective randomized cross-sectional controlled study was done on (30 eyes) of (20 consecutive patients) with diabetic maculopathy and control group of (10 eyes) of (8 patients) with diabetic changes without macular affection and (10 eyes) of (10 participants) without ocular or systemic disease of the same age group. **Results:** The participants of the study are classified into 4 group, the 1st group included patients with non-central involving macular edema by OCT, 2nd group included patients with central involving macular edema by OCT, the 3rd group included patients with diabetic retinopathy without evident maculopathy neither by OCT nor FFA and the 4th group includes normal participants without ocular or systemic disease. The results showed statistically significant difference between the mean vascular density index (VDI) of the superficial capillary plexus (SCP) of each group (1^{st}non-center involving ME,2^{nd}center involving ME & 3^{rd}diabetic without evident maculopathy by OCT group) and the normal (4^{th}) group with higher difference is between the 2^{nd} (center involving ME) group and the normal. Also showed statistically significant difference between VDI of the deep capillary plexus (DCP) of each group (1^{st} non-center involving ME, 2^{nd} center involving ME & 3^{rd} diabetic without evident maculopathy by OCT group) and the normal (4^{th}) group with higher difference is between the 2^{nd} (center involving ME) group and the normal. The results of analysis of the average of the five rings of mfERG showed statistically significant difference between the mean of P1 amplitude of each of the 3 groups and the normal group with the highest difference between the 2nd (center involving ME) group and the normal group. Also, showed statistically significant difference between the mean of P1 latency of 1st and 2nd group and between 2nd and 3rd groups with the highest difference between the 2nd (center involving ME) group and the normal group with statistically significant difference between the mean retinal response density of each of the 3 groups and the normal group with the highest difference between the 2nd (center involving ME) group and the normal group. **Conclusion:** Both OCTA and mfERG could detect early vascular and functional impairment in cases of early diabetic maculopathy despite normal clinical examination and OCT scans.

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Keywords: Early diabetic maculopathy, Multifocal electroretinography, Optical Coherence Tomography angiography.

1. Introduction:

Diabetic retinopathy (DR) is one of the most important causes of blindness in developed countries under 70 years of age.[1] Diabetic maculopathy refers to two distinct eye diseases; diabetic macular oedema and diabetic ischaemic maculopathy. The two types of maculopathy are often comorbid, Ischaemic maculopathy occurs in conjunction with macular oedema and may occur even when macular oedema is mild.[2]

Diabetic macular Edema (DME) occurs in nearly 12% of patients with DR and causes more than 10,000 new cases of blindness per year.[3] Some studies have reported impaired function in the middle and inner layers of the retina in diabetic patients before vascular complications have been identified.[4] Therefore, there is a need for an objective test for early detection and diagnosis of patients with abnormal retinal function due to DR and DME.

Electroretinogram (ERG) includes different modalities like full field ERG, Focal ERG, Multifocal ERG and Pattern ERG.[5] Multifocal Electroretinogram mfERG, as described by Sutter and Tran, is a relatively new technique to record the electrical activity of the retina.[6] Multifocal electroretinography (mfERG) is important objective test identifying functional changes of the retina in early phases of DR.[7] The advantage of multifocal ERG over the older techniques, including full-field and foveal ERG, rests in its ability to record and localize retinal electrical contributions over 103 individual locations that span the central 45°.[8]

Optical Coherence Tomography (OCT) is a non-invasive, interferometric imaging modality that enables in vivo imaging of the retina in cross-section.[9] OCT angiography permits the imaging of retinal and choroidal circulation via motion contrast imaging.[10] In-contrast to OCT, OCT angiography can image vascular changes of diabetic maculopathy such as neovascularization and non-perfused areas (ischemic maculopathy).[11]

2. Patients and Methods:

The present study will include thirty eyes suffering from diabetic maculopathy attending ophthalmology outpatient clinic in Tanta University Hospital.

Inclusion criteria:

Patients with diabetic maculopathy.

Exclusion criteria:

1. Patients with any media opacity as dense cataract obscuring adequate clinical evaluation, investigations or interfering with good quality of imaging.
2. Patients with advanced diabetic eye disease as tractional retinal detachment, vitreous hemorrhage or neovascular glaucoma.
3. Patients with previous optic neuropathy such as glaucoma.
4. Uncooperative patients preventing electrophysiology testing or OCT angiography.
5. All prior ocular inflammation, retinal degeneration and dystrophy.
6. Previous procedure as Intra-vitreal injection, pan retinal photocoagulation or ocular surgery (except for cataract surgery with more than six months duration).

Statistical analysis

- Sorting and analysis of data were performed by using IBM Statistical Package for Social Sciences (SPSS); Version 25.0. Armonk, NY: IBM Corp.
- Qualitative data were described using number and percent.
- Quantitative data were presented as mean and standard deviation (SD).
- Chi-square test was used for analysis of categorical variables.
- For analysis of means of quantitative data, T-test was used.
- Analysis of variance (ANOVA) was used to analyze the differences among group means.

3. Results:

This study included 30 eyes of 20 patients with diabetic maculopathy in addition to 10 eyes of 8 patients with diabetic changes without macular affection as detected by clinical examination and 10 eyes of 5 normal participants without ocular or systemic disease.

According to the history taken from the patients, the mean of the duration of DM in the cases group is 14.15 years while the mean of duration in the group of diabetic without maculopathy is 8.75 years. According to the presence of associated systemic diseases in the cases group, 12 patients (60%) have associated HTN and 8 patients (40%) have not any associated systemic disease.

All patients have no history about any ocular intervention 6 months before the study with history of laser sessions in 6 eyes since more than 6 months, history of IVI of Anti-VEGF in 9 eyes since more than 6 months and history of IVI in 5 pseudophakic eyes since more than 6 months.

B-scan by conventional SS-OCT using (DRI OCT Triton swept source OCT, Topcon, Japan) was done to the 30 eyes of diabetic maculopathy and according to the presence of macular edema, they are classified into first 2 groups (center ME and non-

center ME) and compared macula for BCVA either with decimal notation and log MAR.

Table 1: Comparison of BCVA in between the groups

		Non-Center involving ME			Center involving ME			Normal macula with b scan			ANOVA		TUKEY'S Test		
											F	P-value	I & II	I & III	II & III
BCVA by decimal	Range	0.05	-	0.9	0.1	-	0.9	0.7	-	0.9	14.085	<0.001*	0.460	0.001*	<0.001*
	Mean ±SD	0.394	±	0.243	0.293	±	0.273	0.780	±	0.103					
BCVA log MAR	Range	0.1	-	1	0.1	-	1	0.1	-	0.1	12.408	<0.001*	0.136	0.006*	<0.001*
	Mean ±SD	0.444	±	0.287	0.629	±	0.305	0.100	±	0.000					

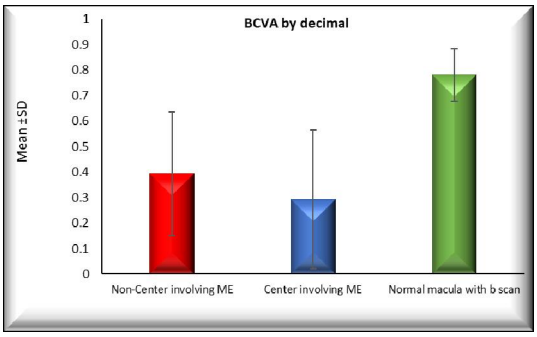

Fig. 1: Comparison of BCVA by decimal notation in the 3 groups

The result showed that the mean BCVA (decimal) in non-center ME group is 0.394, the mean BCVA in center ME is 0.293 and the mean BCVA for diabetic patients with normal macula is 0.78 with significant P-value between 1st and 3rd groups and between 2nd and 3rd groups.

Patients were examined by OCTA using (DRI OCT Triton swept source OCT, Topcon, Japan) and the vascular density index (VDI) of SCP & DCP were obtained.

The results showed statistically significant difference of the mean VDI of SCP between each group and the normal group with higher difference is between the 2nd (center involving ME) group and the normal.

Also showed statistically significant difference of the mean VDI of DCP between each group and the normal group with higher difference is between the 3rd (diabetic with normal b-scan) group and the normal.

Table 2: correlation between VDI of (SCP) and (DCP) of 1st & 2nd groups

OCT		Vascular density of SCP %	
		r	P-value
Non-Center involving ME	Vascular density of DCP %	0.438	0.089
Center involving ME		0.717	0.004*

Table 3: correlation between mfERG findings in the 5 rings and BCVA (log MAR) in the 2 groups of diabetic maculopathy:

Correlations				
	BCVA log MAR			
	Non-Center involving ME		Center involving ME	
	r	P-value	r	P-value
Ring 1 (0°-5°) Amplitude P1 (µV)	-0.553	0.026*	-0.029	0.922
Ring 1 (0°-5°) Latency P1 (mSec)	0.005	0.984	-0.406	0.150
Ring 1 (0°-5°) Retinal density (nV/Deg²)	-0.426	0.100	-0.418	0.137
Ring 2 (5°-10°) Amplitude P1 (µV)	-0.064	0.814	0.099	0.735
Ring 2 (5°-10°) Latency P1 (mSec)	0.624	0.010*	-0.072	0.807
Ring 2 (5°-10°) Retinal density (nV/Deg²)	-0.062	0.819	0.086	0.771
Ring 3 (10°-15°) Amplitude P1 (µV)	-0.159	0.556	-0.222	0.445
Ring 3 (10°-15°) Latency P1 (mSec)	0.121	0.655	0.250	0.389
Ring 3 (10°-15°) Retinal density (nV/Deg²)	-0.207	0.441	-0.129	0.659
Ring 4 (15°-20°) Amplitude P1 (µV)	0.246	0.358	-0.596	0.025*
Ring 4 (15°-20°) Latency P1 (mSec)	0.344	0.192	0.070	0.812
Ring 4 (15°-20°) Retinal density (nV/Deg²)	0.378	0.149	-0.609	0.021*
Ring 5 (20°-25°) Amplitude P1 (µV)	0.047	0.864	-0.170	0.560
Ring 5 (20°-25°) Latency P1 (mSec)	-0.042	0.877	0.116	0.692
Ring 5 (20°-25°) Retinal density (nV/Deg²)	0.076	0.780	-0.158	0.589

Multifocal ERG (mfERG) was done using (RetiMax device CSO, Pisa, Italy) for the all participants of the 4 groups and the data was obtained and analysed for P1 amplitude & latency and retinal response density.

A correlation between the statistical analysis of the findings of each of the 5 rings of mfERG and BCVA (by log MAR) in 1st (non-center involving ME) group and 2nd (center involving ME) and the correlation showed statistically significance only in P1 amplitude in ring (1) of 1st group, P1 latency in ring (2) of the 1st group, P1 amplitude in ring (4) of the 2nd group and retinal density response in ring (4) of 2nd group.

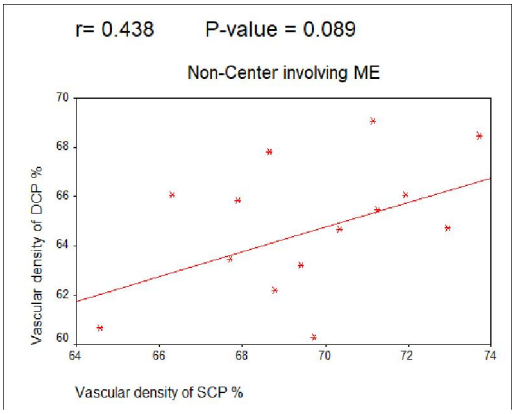

Fig. 2: correlation between the statistical analysis of the findings of each of the 5 rings of mfERG and VDI of both SCP & DCP in non-center involving ME

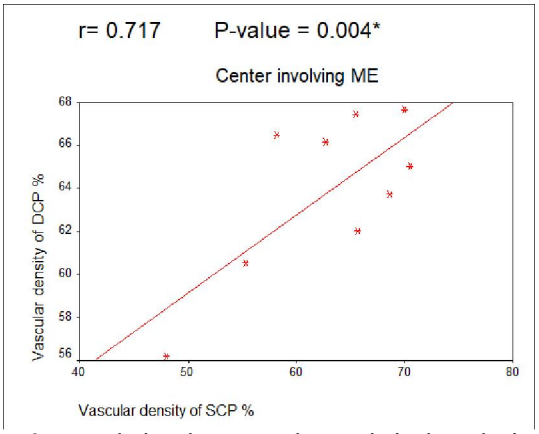

Fig. 3: correlation between the statistical analysis of the findings of each of the 5 rings of mfERG and VDI of both SCP & DCP in center involving ME

A correlation between the statistical analysis of the findings of each of the 5 rings of mfERG and VDI of both SCP & DCP in 1st (non-center involving ME) group and 2nd (center involving ME) and the correlation showed statistically significance only in the P1 latency of ring (1) of the 1st group with VDI of SCP, P1 latency of ring (2) of the 2nd group with VDI of DCP, P1 latency of ring (4) of the 1st group with VDI of SCP, P1 amplitude of ring (3) of the 2nd group with VDI of DCP and retinal density of ring (3) of the 2nd group with VDI of DCP. In addition, SFCT in affected eyes showed a positive correlation with CSF, MIM, and MOM retinal thickness of ETDRS map, but this correlation did not reach a statically significant value ($P > 0.05$).

4. Discussion:

Diabetic retinopathy (DR) is one of the most serious complication that threatens all diabetic patients either controlled or not, diabetic maculopathy is a leading cause of diminution of vision in patients with diabetic retinopathy.

In our study, BCVA was measured and converted into logMAR for all participants and the mean BCVA of 1st group was 0.444 ± 0.287, the mean of 2nd group was 0.629 ± 0.305 and the mean of 3rd group was 0.1 with statistically significant P-value between 1st and 3rd groups (0.006) and between 2nd and 3rd groups (<0.001) indicating the worst BCVA in center involving ME.

In our study, OCTA was used to segment the retina into superficial vascular plexus from the internal limiting membrane (ILM) to the outer border of the inner plexiform layer (IPL) and deep vascular plexus form outer border of the inner plexiform layer (IPL) to the outer border of outer plexiform layer (OPL) using 6x6 mm cube to detect vascular density map for both plexuses.

The results for SCP in macular edema showed that the mean VDI of 1st (non-center involving ME) group was (69.756 ± 2.433) with statistically significant difference from the normal group ($p \leq 0.001$) and the mean of 2nd (center involving ME) group was (63.542 ± 6.819) with statistically significant difference from the normal group ($p \leq 0.001$) showing that the mean VDI of center involving is less than the mean of non-center involving ME.

The study of **Di, Gong, et al** (2016) [12] observed that the vascular density are decreased in patients with clinically significant macular edema (CSME) more than the patient with diabetic retinopathy but without CSME depending on FAZ size measurement.

The results for DCP showed that the mean VDI of 1st group was (64.639 ± 2.769) with statistically significant difference from the normal group ($p \leq 0.001$) and the mean of 2nd group was (64.044 ± 3.438) with statistically significant difference from the normal group ($p \leq 0.001$), also mean VDI of the 3rd group was (61.656 ± 3.95) with statistically significant difference from the normal group ($p \leq 0.001$) indicating early diabetic maculopathy.

It was noticed that the mean VDI of SCP is more than that of DCP which is consistent with other studies conducted by **Takase, Noriaki, et al** (2015) [13], **Gill, Aditya, et al** (2017) [14] and **Ho, Joseph** (2019) [15] showing that DCP is more affected than SCP in observed patients with diabetic maculopathy.

Multifocal ERG is used to assess the electrical function of the retina especially that of bipolar and muller cells so it is of great importance in the pathologies that affect the macula at or before the bipolar cells as retinal vascular diseases especially diabetic maculopathy [16]

The macula is divided into 5 rings from the center to the periphery as each ring represents 5°. In our study, to assess the function of the bipolar and muller cells that extend in the superficial and deep capillary plexuses, P1 amplitude by microvolt (μV), P1 latency by millisecond (mSec) and retinal response density by nV/Deg² of 1st (0-5°), 2nd (5°-10°) rings and the average of the 5 rings were analyzed.

Regarding our study, the mean P1 amplitude of ring 1 in the 2nd (central involving ME) group was (0.581 ± 0.169 μV) which is less than the 1st (non-central involving ME) group (0.673 ± 0.408) and the mean increased in the 3rd (diabetic eyes without macular edema) group (0.798 ± 0.322) with statistically significant difference (P-value ≤ 0.001) between each of the 3 groups and the normal group with the highest difference between the 2nd (center involving ME) group and the normal group.

Our analysis is agreed with other studies such as the study conducted by **Khojasteh, Hassan, et al** (2020) [17] which was a study on diabetic macular edema correlating mfERG findings with OCT finding of the 3 central rings and observed that disorganization of retinal inner layers (DRIL) was associated with decreased amplitude of both P1 and N2 at corresponding locations and also presence of cysts significantly reduce the central P1 amplitude.

In our study, the mean retinal response density in both rings are the least in central involving ME group (41.373 ± 14.311 for ring 1) (17.529 ± 7.005 for ring 2) and then in non-central involving ME (53.589 ± 34.445 for ring 1) (22.155 ± 10.78 for ring 2) with both groups are less than the patient without diabetic maculopathy (62.586 ± 28.69 for ring 1) (28.268 ± 7.994 for ring 2) with statistically significant differences (P-value ≤ 0.001) of the three groups and the normal group.

Our results are consistent with the study of **Yamamoto, Shuichi, et al** (2001) [18] that observed mfERG finding in patients with DME that classified into cystoid ME and diffuse ME comparing the results with normal participants and reported that the retinal response density of multifocal ERGs from the central part of the macula was significantly decreased in patients with DME in comparison with normal group and that the of the eyes with cystoid ME was significantly smaller than those of diffuse ME.

Conclusion:

Diabetic maculopathy results in microvascular impairment that can be detected by OCTA together with functional affection that can be detected by mfERG.

OCTA can measure the vascular density at the superficial and deep levels of the retinal capillary plexus and showed that the deep layer was affected more than the superficial one in cases of diabetic maculopathy.

The average P1 amplitude and retinal response density and those of the central rings were the most affected parameters in cases of diabetic maculopathy especially central involving ME.

Both OCTA and mfERG could detect early vascular and functional impairment in cases of early diabetic maculopathy despite normal clinical examination and OCT B-scan.

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