Correlation between Optical Coherence Tomography and Multifocal ERG Changes in Diffuse Diabetic Macular Oedema

[*]Sherif H. Emerah MD, Ehab S. El Zakzouk MD, Onsy A. Badie MD

Ophthalmology Department, Research Institute of Ophthalmology, Giza, Egypt
[*]sherifemera@yahoo.com

Abstract: Purpose: To detect and correlate retinal morphological changes measured with Optical Coherence Tomography (OCT) and functional changes recorded with Multifocal ERG (mf-ERG) in diffuse diabetic macular oedema. Materials and Methods: the study included 33 diabetic patients with diffuse macular oedema as documented by fluorescein angiography (FA). Best corrected visual acuity (BCVA) was detected for every patient. Central and pericentral macular thickness was measured by OCT. Macular functional changes were recorded with multifocal electroretinogram. Results: 85.7% of our cases with bad BCVA (worse than 0.5) had increased central foveal thickness. 71.4% of our cases with bad BCVA had increased pericentral macular thickness. There is a highly significant negative correlation between BCVA and central and pericentral macular thickness. For mfERG; we found significant changes in patients with bad BCVA and the changes were in the latency rather than amplitude. So, we did not find significant changes in mfERG in patients with good BCVA (better than 0.5). Patients with increased central and pericentral macular thickness had increased P1 latency of ring 3. Conclusion: OCT and mfERG are valuable diagnostic techniques that can help to assess morphological and functional changes in diffuse diabetic macular oedema.

[Sherif H. Emerah, Ehab S. El Zakzouk, Onsy A. Badie **Correlation between Optical Coherence Tomography and Multifocal ERG Changes in Diffuse Diabetic Macular Oedema**]. Journal of American Science 2011; 7(12): 249-253]. (ISSN: 1545-1003). http://www.americanscience.org.

Keywords: Diabetic macular oedema, mfERG, OCT.

1. Introduction

Diabetic retinopathy remains the major threat to sight in the working age population in the developed world. Furthermore, it is increasing as a major cause of blindness in other parts of the world especially in developing countries ***(Zimmet et al., 2001)***. Diabetic macular edema is a manifestation of diabetic retinopathy that produces loss of central vision. Macular edema within 1 disk diameter of the fovea is present in 9% of the diabetic population ***(Klein et al., 1984)***. Macular edema results from disruption of the blood-retinal barrier and subsequent accumulation of fluid leading to increased retinal thickness ***(Marmor, 1999)***. Macular oedema has long been clinically diagnosed and assessed by ophthalmoscopy and flourescein angiography. Newly developed devices, such as optical coherence tomography (OCT), have been shown to be powerful tools for the objective assessment of macular oedema ***(Otani et al., 1999)***.

Optical coherence tomography (OCT) is a powerful tool that has been used to assess retinal structure since 1991. This instrument emits an 820 nm near infra red illumination to generate high resolution images of the retina ***(Browning et al., 2004).***

The OCT is a diagnostic technique that provides cross sectional imaging of retinal structure and of other ocular tissues, with high accuracy and resolution. Thus, its capacity to reproduce details (10 μm) gets close to the optical microscopy, being compared to a biopsy *in vivo*. The OCT increases the ability of clinical diagnosis and imaging techniques in ancillary exams, for giving precise and reproducible results that corroborate diagnostic impressions and allow monitoring the progression of diseases, as well as the evolution of retinal responses in therapeutic interventions ***(Hannouche and de Avila, 2009).***

Multifocal electroretinography (mfERG), developed by Sutter and Tran in 1992, is a noninvasive, objective method and is used to detect the regional functional changes of the central retina by measuring the electrophysiological responses. Multifocal (mf)ERG technique allows a high-resolution mapping of the macular area of the retina ***(Sutter and Tran,1992).*** Some studies have shown the effect of diabetic retinopathy on mfERG **(*Weiner* et al., 1997)** and (***Fortune et al.,1999).***This is generally regarded as a useful diagnostic tool in a wide range of clinical conditions (e.g., in various forms of macular dystrophy, diabetic retinopathy, central retinal vein occlusion, autosomal dominant optic atrophy, cone dystrophy, and RP) ***(Kretschmann et al., 2000)***.

2. Materials and Methods

Thirty three patients were seen at the Department of Ophthalmology at the Research

Institute of Ophthalmology. Subjects have type1 or type 2 diabetes with no history of renal failure requiring dialysis, no medical treatment of retinal disorder or any therapy that affect retinal edema. The exclusion criteria included also poor central or unsteady fixation of eyes, poor cooperation, and any other ocular diseases.

A complete ophthalmologic exam was done. After pupil dilation with 0.5% phenylephrine hydrochloride and 1% tropicamide, patients were examined with slit-lamp biomicroscopy with a 90-diopter lens. Best corrected visual acuity (BCVA) was measured for every patient.

The fluorescein angiography is performed using a digital retinal camera system (Topcon TRC-50EX; Topcon Medical Systems Inc.). One retinal colour, one early phase, one middle phase and one late phase frames were obtained from each eye ***(Figure 1)***. If the patient has diffuse macular oedema, we proceed for OCT and multifocal ERG.

All subjects were examined with the Stratus OCT (Model 3000, Carl Zeiss Meditec, software version 4.0.1). Both the fast macular thickness and regular macular thickness OCT scan protocols were performed on both eyes. Both scan protocols obtain six cross-sectional scan lines, 6 mm in length, at equally spaced angular orientations (30°) in a radial spoke pattern centred on the fovea. RT is defined by the software algorithm as the distance between the surface of the retina and the first highly reflective layer visible at the level of the outer retina and retinal pigment epithelium. An interpolated RT map is constructed from the six scan lines by the software. For analysis of the RT, the mean RT was measured: the fovea (central circle, with a diameter of 1 mm), the pericentral area (donut shaped ring with an inner diameter of 1 mm and an outer diameter of 3 mm) ***(Figure 2)***.

The electrical function of the macular area was determined by multifocal electroretinography (mERG). *The RETI-scan*™ multifocal system, produced by Roland Consult, was used for this purpose. The stimulation and recording of the mERG were performed using the m-sequence technique. Contact lens ERG-JET electrodes as well as one ground electrode in the center of forehead and two reference electrodes in the temporal region of the patient were placed. The stimulus, consisting of 61 hexagons covering a visual field of 30°, was presented on a monitor with a frame rate of 75 Hz at a distance of 28 cm from the patient's eye. Each element alternated between black and white (93% contrast, mean luminance 51.8 cd/m2). The amplifier setting was 100 μV; the lower cut off frequency was 10 Hz and the upper cut off frequency was 100 Hz. Each recording session was subdivided into 8 recording segments of approximately 47 seconds. The signals were registered with sampling intervals of 83 mseg. The results were distributed in 5 concentric rings obtaining for each ring, the response density (nV/deg^2) of P1, the P1 amplitude, N1 amplitude, and the implicit times of P1and N1. Visual acuity was satisfactory for steady fixation ***(Figure 3)***.

mfERG stimuli location and anatomic areas correspond roughly as follows: ring 1 to the fovea, ring 2 to the parafovea, ring 3 to the perifovea, ring 4 to the near periphery, and ring 5 to the central part of the middle periphery.

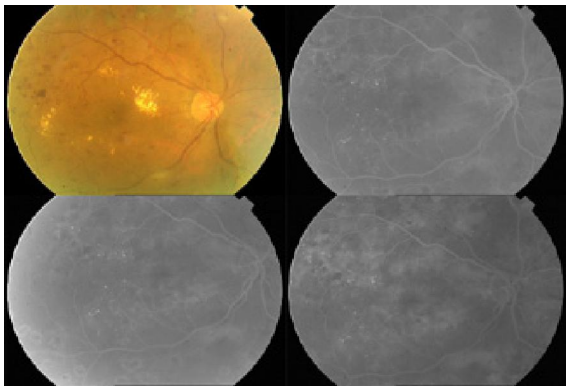

Fig.1 FFA of a diabetic patient showing diffuse macular oedema.

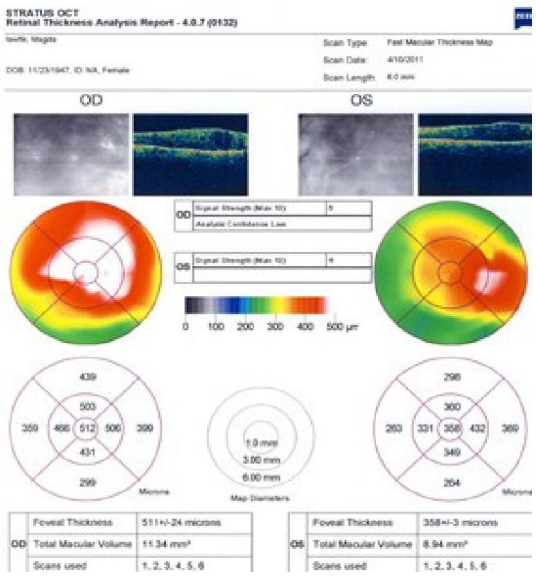

Fig.2 OCT of the same patient showing central and pericentral thickening.

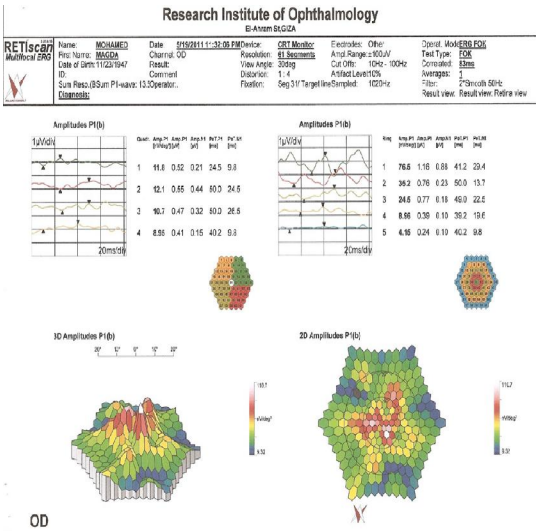

Fig.3 mfERG showing decrease amplitude and increase latency.

For data analysis, the RT was measured at the central (fovea) and pericentral macular area. For mf ERG, the amplitude of response density (nV/deg^2) of first positive peak (P1) b-wave, implicit time (latency) of b-wave (P1) and implicit time (latency)of N1 were measured using regional averages derived from 1-4 concentric rings. Best corrected visual acuity (BCVA) was detected for every patient.

The aim of this work is to detect and correlate retinal structure changes measured with (OCT) and functional changes recorded with mf ERG(P1response denisty amplitudes and P1and N1 latencies) in diffuse diabetic macular oedema.

3. Results

33 patients (6 males, 27 females) were included in this study. Their age ranged from 50 to 63 years (mean 54). Duration of diabetes ranged from 5 years to 30 years.

BCVA ranged from 0.2 to 0.8 (mean 0.38). We divided BCVA into good BCVA which is better than 0.5 and bad BCVA which is worse than 0.5

The central macular thickness (CMT) ranged from 178-512 µm with mean 276.9 µm. The pericentral macular thickness ranged from 230-477 µm with mean 303.5 µm.

85.7% of our cases with bad BCVA have increased central macular thickness compared to 0% among good BCVA and the difference is highly significant statistically. 71.4% of our cases with bad BCVA have increased pericentral macular thickness compared to 0 % among cases with good BCVA and the difference is highly significant statistically.

There is a highly significant negative correlation between BCVA and CMT among studied patients (P=0.000**)** (with increase in CMT thickness there is decrease of BCVA).There is a highly significant negative correlation between BCVA and percientral MT (P=0.000) (with increase in pericentral MT thickness there is decrease of BCVA) **(Table1)**.

Table (1) Correlation coefficient between VA and OCT among studied patients

N=33	VA
Central MT	r=-0.775 P=0.000**
Pericentral MT	r=-0.742 P=0.000**

** P<0.01 Highly significant

P1 latency of ring 1of the multifocal recordings in the patients with diffuse macular oedema: mean: 40.6 ms, range: 29.4–50 ms. P1 latency of ring 2: mean: 47.5 ms, range: 44.1–50 ms. P1 latency of ring 3: mean: 46.9 ms, range: 45.1–50 ms. P1 latency of ring 4: mean: 47.5 ms, range: 47.1–50 ms.

N1 latency of ring 1of the multifocal recordings in the patients with diffuse macular oedema: mean: 25.5ms, range: 17.6–30.4 ms. N1 latency of ring 2: mean: 27.2 ms, range: 19.6–30.4 ms. N1 latency of ring 3: mean: 27 ms, range: 22.5–30.4 ms. N1 latency of ring 4: mean: 28.3 ms, range: 23–30.4 ms.

81.8% of our patients have increased P1 implicit time (latency) of ring three. 90.9% of the patients have increased N1 implicit time (latency) of ring four. All patients with bad BCVA (worse than 0.5) have increased P1 latency of ring 3 compared to 50% among cases with good BCVA (better than 0.5) and the difference is highly significant statistically (0.003) **(Table 2)**.

all patients with increased central macular thickness have increased P1 latency of ring 3 compared to 60% among cases with normal foveal thickness and the difference is significant statistically (0.01) **(Table 3)**. All patients with abnormal pericentral macular thickness have increased P1 latency of ring 3 compared to 66.7% among cases with normal pericentral macular thickness and the difference is significant statistically (0.04) **(Table 4)**.

The amplitudes of P1 response density of ring 1of the multifocal recordings in the patients with diffuse macular oedema: mean: 54 nV/deg^2, range: 23–118.5 nV/deg^2. P1 response density of ring 2: mean: 27.8 nV/deg^2, range: 11.7–42.7 nV/deg^2). P1 response density of ring 3: mean: 19.3 nV/deg^2, range: 9.35–30.9 nV/deg^2. P1 response density of ring 4: mean:11.9 nV/deg^2, range: 5.83–20 nV/deg^2.

45% of our patients have decreased P1 response density of ring one and ring four. 36 % of our patients have decreased P1 response density of ring one and ring three. We did not find significant

correlation between OCT changes or BCVA with P1 response density changes in mfERG in our patients.

Table (2) Comparison between Visual acuity and time in mfERG: P1of ring 3 in milliseconds

N=33	Normal latency No. %	Increased latency No. %	P
Good VA (better than 0.5) N=12	6 50.0	6 50.0	0.003**
Bad VA (worse than 0.5) N=21		21 100.0	

** P<0.01 Highly significant

Table (3) Comparison between central MT and time in mfERG: P1of ring 3 in milliseconds

N=33	Normal latency No. %	Increased latency No. %	P
Normal CMT N=15	6 40.0	9 60.0	0.01*
Increased CMT N=18		18 100.0	

* P<0.05 significant

Table (4) Comparison between pericentral MT and time in mfERG: P1of ring 3 in milliseconds

N=33	Normal latency No. %	Increased latency No. %	P
Normal pericentral MT N=18	6 33.3	12 66.7	0.04*
Increaded pericentral MT N=15		15 100.0	

* P<0.05 significant

4. Discussion:

This clinical study was conducted to correlate retinal morphological changes measured with OCT and functional changes measured with mf-ERG in diabetic Diffuse Macular Oedema. We found significant negative correlation between BCVA and central and pericentral macular thickness. This means that visual acuity was correlated significantly with morphological changes revealed by OCT. All patients with bad BCVA (worse than 0.5) and with increased central and pericentral macular thickness have increased P1 latency of ring 3. This means that there was impairment of conduction of electrical responses in the paracentral macula in cases of diffuse diabetic macular oedema.

So, the functional changes were significantly detected in patients with BCVA worse than 0.5 and the changes were in the latency rather than the ampilitude.

Hee et al demonstrated that the fovea as measured by OCT was significantly thicker and the best corrected visual acuity was significantly worse in diabetic eyes with diffuse macular oedema. These results are supporting the findings that the retinal thickness at the fovea is significantly correlated with the best corrected visual acuity ***(Hee et al.,1998)***.

Another study aimed to detect the correlation between the tomographic features and the visual functions of different types of diabetic macular edema. They found that fovea was significantly thicker in eyes with cystoid macular edema and in those with diffuse retinal swelling than in normal eyes. The fovea of eyes with cystoid edema was significantly thicker than the fovea of eyes with diffuse swelling. The best-corrected visual acuity and the electrical response density from the macular area were significantly reduced in eyes with diabetic macular edema, particularly in those with cystoid edema. The best-corrected visual acuity and macular response density of the multifocal ERGs were inversely correlated, and the implicit times were directly correlated with foveal thickness ***(Yamamoto et al., 2001)***.

A different study by Minzhong and associates conducted to investigate the characteristics of mf-ERG of different phases in diabetic retinopathy and its clinical significance. They found that the absolute values of N1, P1 and N2 response densities and the N1-P1 and P1-N2 response densities were attenuated ***(Minzhong et al., 2002)***.

To explore the multifocal electroretinogram in patients with non-proliferativediabetic retinopathy with clinically-significant macular edema, Farahvash and co-worker compared the latencies and amplitudes of average responses of 5 eccentric rings with normal values. They reported that local electroretinogram responses were significantly delayed and decreased in amplitude in patients with clinically-significant macular edema ***(Farahvash and Mohammadzadeh, 2006).***

Multifocal electroretinograms and optical coherence tomography were performed to investigate the macular morphology and function in patients with diabetic retinopathy (DR) without apparent visual loss, in different phases of DR patients as well as the normal control non-diabetic subjects. In patients with DR but without apparent visual loss; abnormalities of the macular morphology and function already develop. It was found that the changes of function appear to develop earlier than that of morphology ***(Wu et al., 2010)***.

To evaluate the correlation between functional and anatomical assessments in patients with central serous chorioretinopathy; mfERG records showed significant correlation of N1 and P1latencies of the paracentral rings with the central subretinal fluid

thickness. No significant correlation was observed between log MAR BCVA and any of the OCT measuerments. Correlation analysis showed that log MAR BCVA was significantly correlated with mfERG N1 amplitudes of rings1 and 2, N1 latency of ring 4 and P1 latency of ring 1 ***(Yip et al., 2010)***.

Shimada et al found that the pre-VA and the duration of the symptoms were significantly correlated with the post-VA. The central retinal thickness (CRT) was significantly correlated with the pre-VA and the post-VA. The amplitudes of macular electroretinogram were not significantly correlated with the pre-VA or post-VA. The CRT to amERG ratio (CRT/amERG) was correlated with the post-VA but not with the pre-VA. ***(Shimada et al., 2011).***

In conclusion, OCT and mfERG are valuable diagnostic techniques that can help to assess morphological and functional changes in diffuse diabetic macular oedema. Further studies are needed to detect morphological and functional changes after resolution of macular oedema either after laser treatment or intravitreal injection.

Corresponding author
Sherif H. Emerah
Ophthalmology Department, Research Institute of Ophthalmology, Giza, Egypt
sherifemera@yahoo.com

References:

1. Browning DJ, McOwen MD, Bowen RM Jr *et al.* Comparison of the clinical diagnosis of diabetic macular edema with diagnosis by optical coherence tomography. Ophthalmology 2004; 111(4):712-5.
2. Farahvash MS, Mohammadzadeh S. Multifocal electroretinogram in clinically significant macular edema. Archives of Iranian Medicine 2006; 9(3): 261-65.
3. Fortune B, Schneck ME, Adams AJ. Multifocal electroretinogram delays reveal local retinal dysfunction in early diabetic retinopathy. Invest Ophthalmol Vis Sci. 1999; 40: 2638 – 2651.
4. Hannouche RZ, Avila MP.Retinal thickness measurement and evaluation of natural history of the diabetic macular edema through optical coherence tomography. Arq Bras Oftalmol 2009; 72(4):433-8.
5. Hee MR, Puliafito CA, Duker JS et al. Topography of diabetic macular edema with optical coherence tomography. Ophthalmology 1998; 105:360-70.
6. Hood DC, Seiple W, Holopigian K, Greenstein V. A comparison of the components of the multifocal and fullfield ERGs. Vis Neurosci. 1997; 14:533–544.
7. Klein R, Klein BE, Moss SE et al. The Wisconsin epidemiology study of diabetic retinopathy. IV. Diabetic macular edema. Ophthalmology. 1984 Dec;91(12):1464-74.
8. Kretschmann U, Bock M, Gockeln R, Zrenner E. Clinical applications of multifocal electroretinography. Doc Ophthalmol. 2000; 100:99–113.
9. Marmor MF. Mechanism of fluid accumulation in retinal edema. Doc Ophthalmol. 1999;97(3-4): 239-49.
10. Minzhong Y, Xin Z, Xingwu Z, Qiang Y et al. Multifocal electroretinogram in the early stages of diabetic retinopathy. Chinese medical journal, 2002,115(4): 563-66.
11. Otani T, Kishi S, Maruyama Y. Pattern of diabetic macular oedema with optical coherence tomography. Am. J Ophthalmol. 1999; 127: 688-693.
12. Palmowski AM, Sutter EE, Bearse MA, Fung W. Mapping of retinal function in diabetic retinopathy using the multifocal electroretinogram. Invest Ophthalmol Vis Sci. 1997; 38: 2586 – 2596.
13. Seeliger MW, Kretschmann U, Apfelstedt-Sylla E, Zrenner E. Implicit time topography of multifocal electroretinograms. Invest Ophthalmol Vis Sci. 1998; 39: 718 – 723.
14. Shimada Y, Sakurai S, Naito K et al. Multifocal electroretinogram and optical coherent tomography: prediction of visual outcome after epiretinal membrane removal. Clin Exp Optom. 2011 May;94(3):296-301.
15. Sutter EE, Tran D. The field topography of ERG components in man. I. The photopic luminance response. Vision Res.1992; 32:433 – 446.
16. Weiner A, Christopoulos VA, Gussler CH et al. Foveal cone function in nonproliferative diabetic retinopathy and macular edema. Invest Ophthalmol Vis Sci. 1997; 38: 1443 – 1449.
17. Wu B, Deng J, Yao C et al. Macular morphology and function in patients with diabetic retinopathy without apparent visual loss. Yan Ke Xue Bao. 2010 Aug;25(1):41-43.
18. Yamamoto S, Yamamoto T, Hayashi M, Takeuchi S. Morphological and functional analyses of diabetic macular edema by optical coherence tomography and multifocal electroretinograms. Graefes Arch Clin Exp Ophthalmol. 2001 Feb; 239(2):96-101.
19. Yip YW, Nagi JW, Fok AC et al. Correlation between functional and anatomical assessments by multifocal electroreinography and optical coherence tomography in central serous chorioretinopathy. Doc Ophthalmol. 2010 apr;120(2): 193-200.
20. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemics. Nature, 2001; 13: 414: 782-7.

12/5/2011