Original Article

Multifocal Electroretinogram in Diabetic Macular Edema; Correlation with Visual Acuity and Optical Coherence Tomography

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Abstract

Purpose: To evaluate multifocal electroretinogram (mfERG) changes in eyes with diabetic macular edema (DME) and investigate any possible correlation with optical coherence tomography (OCT) features and visual acuity (VA).

Methods: Twenty-nine right eyes of 29 subjects with DME due to non-proliferative diabetic retinopathy and 30 eyes of 30 normal subjects were evaluated. All patients underwent a complete ophthalmic examination. Sixty-one scaled hexagon mfERG responses were recorded. Components of the first order kernel of N1, N2, and P1 in five concentric rings centered on the fovea, were measured in both groups. Correlation and regression analyses were performed among VA, central macular thickness (CMT) based on OCT, mfERG amplitude, and latency of the N1, N2 and P1 waves.

Results: Significant differences were observed in all mfERG parameters in five-ring regions of the retina between eyes with DME versus controls ($P < 0.05$). There were significant correlations among VA with N2 ($P = 0{,}001$, b = 0.73) and P1 amplitudes ($P = 0.001$, b = −0.84) in the central macular area, and there was a borderline association between VA and CMT ($P = 0.042$, b = 0.392).

Conclusion: Amplitudes of mfERG components (N1, P1, and N2) are significantly reduced and their latencies are delayed in eyes with DME indicating functional impairment in the outer retina. The mfERG total amplitude was significantly correlated with VA even more than CMT, therefore the combined use of OCT and mfERG for macular evaluation may better evaluate visual status in DME patients.

Keywords: Diabetes Mellitus; Diabetic Macular Edema; Multi-focal Electroretinography; Optical Coherence Tomography; Visual Acuity

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INTRODUCTION

Diabetes mellitus (DM) is a worldwide metabolic disease.[1] Diabetic retinopathy (DR) is one of the most important causes of blindness in American people under

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70 years of age.[2] The prevalence of DR is estimated to be around 37% in Iran.[3] Diabetic macular edema (DME) is the significant cause of visual loss in diabetic patients.[4] It has been shown that 20% of subjects with Type 1 DM and 14% of patients with Type 2 DM develop DME. Some studies have reported impaired function in the middle and inner layers of the retina in diabetic patients before vascular complications have been identified.[5] 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.[6] Early identification of functional changes in middle and inner retinal layers could be very helpful for development of treatments in diabetic patients.[5]

Full-field flash electroretinography and multifocal electroretinography (mfERG) are two important objective tests identifying functional changes of the retina in early phases of DR.[7] mfERG was developed by Sutter and Tran in 1992 for recording responses from many regions of the retina.[8] This objective measurement was introduced because full-field flash electroretinography records mass responses from the whole retina.[7] Optical coherence tomography (OCT) is a noninvasive technique that can reveal morphology of the retinal layers *in vivo*. OCT determines structural changes in the macula that may be correlated with measures of subjective visual function such as visual acuity and visual field.[9]

Aims of this comparative case series were firstly, to identify possible functional changes from DME using mfERG; and secondly to evaluate any correlation between mfERG parameters and OCT findings with visual acuity in order to better correlate functional and anatomical changes due to DR in the retina.

METHODS

In the present study, we compared 30 right eyes of 30 diabetic subjects with clinically significant macular edema (CSME) as the case group and 30 right eyes of 30 normal subjects as the control group. All subjects were referred from Farabi Eye Hospital and were assessed at the Visual Electrophysiology Clinic at Iran Rehabilitation College. One of the diabetic patients was excluded from the study because of failure to cooperate; so the study was done on 29 eyes. We measured best-corrected visual acuity (BCVA), dry refraction, and performed slit lamp biomicroscopy and indirect ophthalmoscopy. In addition, fluorescein angiography and OCT were conducted to confirm the diagnosis of (CSME). Next mfERG responses were recorded from many points of the retina.

Exclusion criteria were poor central or unsteady fixation, patients with proliferative retinopathy or enlargement of the foveal avascular zone, poor cooperation and other ocular diseases affecting retinal function. All participants provided informed written consent before participation. Procedures were performed in accordance with the Declaration of Helsinki.

Multifocal ERG

Metrovision system (Vision Monitor, Perenchies, France) was used for measurement of mfERG based on the International Society for Clinical Electrophysiology of Vision (ISCEV). The stimuli consisted of 61 scaled hexagons generated on a high-resolution color monitor. The viewing distance was set at 33 cm, which corresponded to a stimulated field of ±30° horizontally and ±24° vertically. The 1024 × 768 resolution corresponds to 3.6 arc minutes at the default viewing distance. A high-frame frequency of 120 Hz was chosen with the purpose of being outside the frequency of recorded signals and to provide higher temporal resolution. According to the eccentricities, the amplitudes and latencies were evaluated in five-ring retinal regions. The location and focus of the stimulation image were controlled with an infrared fundus video system and monitored on the computer screen. Corneal contact lens ERG-Jet electrodes were used for active electrode recording mfERG. The neutral and reference electrodes were large size and disposable mounted on fronto-central and external canthus, respectively. The pupil was dilated with 1% tropicamide and the cornea was anesthetized with 0.5% tetracaine ophthalmic drop. The fellow eye was occluded by a pad and eye position was monitored on the computer screen. Subjects were asked to fixate on the central cross. Patients with low visual acuity were asked to fixate steadily to the center of the screen. The recording process took approximately 6 minutes while cross fixation lines were applied on the screen. The recording procedure was repeated if there were spurious potentials from eye blinks or if ocular movements were recorded.

We measured components of the first order kernel of N1, N2, and P1 in five concentric rings centered on the fovea (i.e., 0°-2°, 2°-5°, 5°-10°, 10°-15°, and >15°) in both study groups. N1 amplitude was measured from the baseline trough to the N1 trough, P1 amplitude was measured from the N1 trough to the P1 peak, and N2 amplitude was measured from the P1 peak to N2 trough. Latencies of N1, N2, and P1 were measured form the time of presenting the stimuli.

Optical Coherence Tomography

OCT imaging was performed using a spectral domain device (Spectralis HRA-OCT, version 5.3.3.0; Heidelberg Engineering, Heidelberg, Germany). The average retinal thickness in the central ring was calculated using the retinal mapping software. Patients were asked to gaze at the fixation light during the test, and foveal fixation was controlled by observing the retina through the infrared monitoring camera.

In the first step, we compared mfERG amplitudes (response density) and latencies of N1 and P1, between control and diabetic eyes in the five-ring retinal regions. In the next step, correlation analysis was performed among BCVA, central macular thickness (CMT), central macular volume (CMV), and mfERG amplitude and latency measurements in the central ring.

Statistical Analysis

Data was analyzed using SPSS 16.0 software. We used the Kolmogorov-Smirnov test and box plots for checking normality of data. Independent *t*-test was used to compare the data obtained from mfERG results between test and control eyes. Correlation and regression analysis was performed among VA, CMT, CMV, mfERG amplitude, and latency of N1, N2, and P1 waves. Pearson's coefficient was used to evaluate correlations and data were modeled through linear regression analyses using BCVA as a dependent variable. *P* values less than 0.05 were considered as statistically significant.

RESULTS

Mean age of the patients was 60 ± 1.62 years, ranging from 42 to 76 years. Mean BCVA was 0.48 ± 0.32 LogMAR. Mean CMT was 392 ± 25 micrometers (μm) ranging from 233 to 718 μm and the mean total macular volume was 10.12 ± 1.38 μm^3.

There were significant differences in all mfERG parameters in five-ring regions of the retina between the diabetic and control groups. Comparisons of N1 amplitude, P1 amplitude, N1 implicit time, and P1 implicit time, between diabetic patients and controls, are shown in Tables 1-4. These findings show that amplitude of N1 and P1 were significantly decreased and their latency were significantly increased in patients with DME. In addition, we observed that N1 and P1 amplitudes were decreased gradually from ring 1 to ring 5. This trend was not observed for latency of N1 and P1. Figure 1 shows the trace array in a control subject and a patient with CSME.

Based on regression analysis, the association between BCVA as a dependent variable and central P1 amplitude was significant ($P = 0.001$); there was also a significant association between BCVA and central N2 amplitude ($P = 0.001$). The association between BCVA and other mfERG parameters in the central macular area was not significant, but there was a borderline association between BCVA and CMT ($P = 0.045$). Also, there was a significant inverse association between BCVA and central N1 latency ($P = 0.012$). Based on the Pearson correlation, the correlation among BCVA (LogMAR), P1, and N2 was stronger than others ($r = -0.646$ and $r = -0.487$). Table 5 shows the statistical analysis for central macular measurements.

There was no statistically significant correlation between CMT and mfERG parameters (amplitude and latency) in the central macular ring; similarly, the correlation between CMV and mfERG was not significant ($P > 0.05$).

Other investigations into the spread of individual values showed that in ring 1 measurements in CSME participants, most of the foveal retinal thickness and mfERG amplitude values confirmed that both methods are associated with the level of VA. Nevertheless, some individual values deviated from the expected range. In 7 eyes with reduced BCVA, retinal thickness was in the normal range, whereas mfERG parameters were abnormal. Conversely, in 3 eyes,

Table 1. N1 amplitude of mfERG (nv/deg²) in five-ring retinal regions in control and test groups

Rings	Control group		Test group		*P**
	Range	Mean±SD	Range	Mean±SD	
1	−94.90-(−20.50)	−53.91±15.53	−60.80-11.60	−28.70±16.00	<0.0001
2	−60.50-(−13.00)	−35.64±13.07	−48.00-(−3.70)	−19.83±8.86	<0.0001
3	−46.90-28.40	−23.95±13.76	−29.60-(−4.20)	−17.78±5.32	0.028
4	−35.00-(−7.60)	−18.17±6.61	−24.30-(−1.30)	−14.16±4.32	0.008
5	−31.70-(−6.30)	−13.93±5.46	−22.00-(−1.50)	−11.14±−3.63	0.025

Independent *t*-test. *$P<0.05$ were considered significant. SD, standard deviation; mfERG, multifocal electroretinogram

Table 2. N1 implicit time of mfERG (ms) in five-ring retinal regions in control and test groups

Rings	Control group		Test group		*P**
	Range	Mean±SD	Range	Mean±SD	
1	24.00-30.60	27.29±1.70	18.30-39.20	30.07±4.90	0.005
2	22.40-28.70	26.60±1.13	23.10-34.60	30.54±2.51	<0.0001
3	22.60-27.20	25.83±0.87	27.30-39.10	31.09±2.74	<0.0001
4	22.50-27.90	25.51±1.40	28.00-35.00	30.48±2.11	<0.0001
5	22.00-27.90	25.36±1.80	27.20-43.10	31.03±3.06	<0.0001

Independent *t*-test. *$P<0.05$ were considered significant. SD, standard deviation; mfERG, multifocal electroretinogram

Table 3. P1 amplitude of mfERG (nv/deg²) in five-ring retinal regions in control and test groups

Rings	Control group		Test group		*P**
	Range	Mean±SD	Range	Mean±SD	
1	50.10-150.00	89.36±25.71	7.40-94.00	40.25±20.85	<0.0001
2	47.80-99.00	72.35±16.91	13.20-56.40	37.62±11.81	<0.0001
3	30.00-83.60	51.61±13.77	8.30-57.50	32.15±9.98	<0.0001
4	22.10-62.40	40.29±9.94	4.80-48.30	29.15±7.89	<0.0001
5	17.40-54.30	29.96±9.21	4.00-47.70	25.00±8.12	0.033

Independent *t*-test. *$P<0.05$ were considered significant. SD, standard deviation; mfERG, multifocal electroretinogram

Table 4. P1 implicit time of mfERG (ms) in five-ring retinal regions in control and test groups

Rings	Control group		Test group		*P**
	Range	Mean±SD	Range	Mean±SD	
1	44.40-50.90	47.08±1.68	41.60-74.60	50.61±5.72	0.002
2	41.70-56.00	45.70±2.58	45.60-56.40	49.76±2.64	<0.0001
3	40.00-46.00	43.79±1.46	45.20-55.90	49.47±2.80	<0.0001
4	40.60-48.50	43.69±1.50	45.50-58.50	49.44±3.17	<0.0001
5	40.30-45.40	43.16±1.33	44.80-62.40	49.47±3.59	<0.0001

Independent *t*-test. *$P<0.05$ were considered significant. SD, standard deviation; mfERG, multifocal electroretinogram

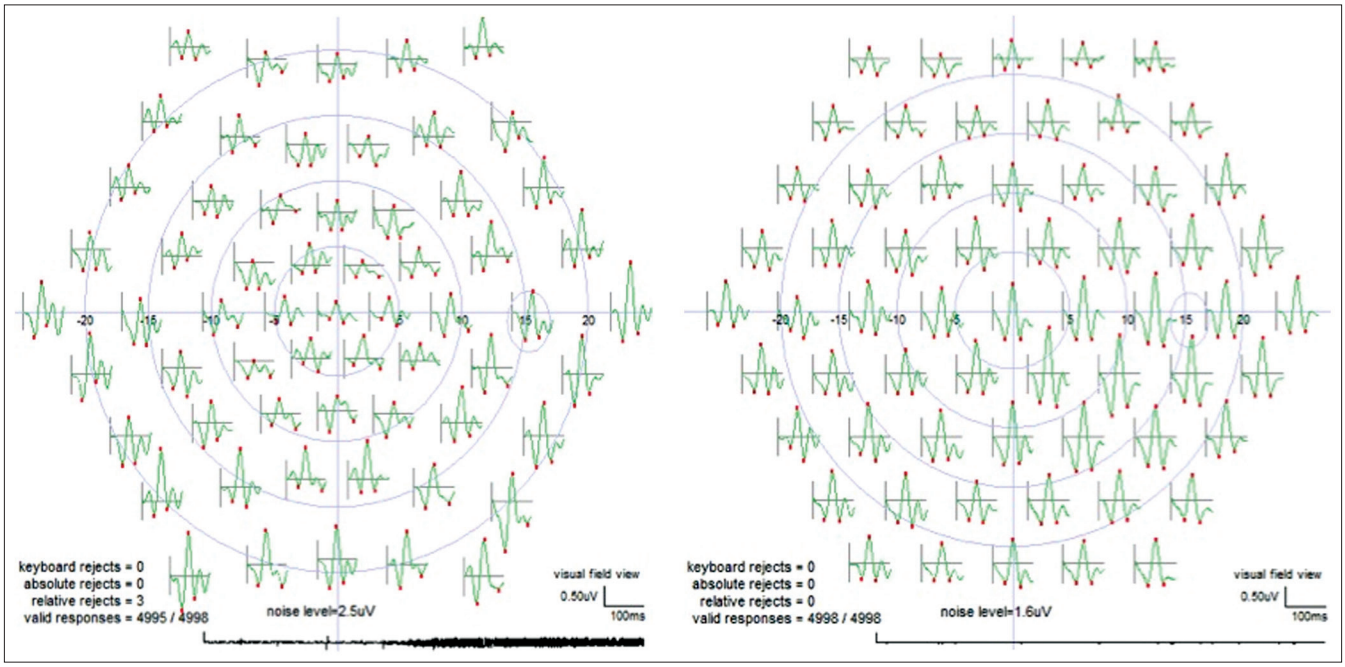

Figure 1. Trace array in a control subject (left) and a patient with diabetic macular edema (right).

despite high retinal thickness, respective VA was normal with near-normal mfERG parameters. Graphically, the relationships between VA and foveal thickness, and VA and mfERG P1 amplitude in ring 1 are depicted in Figures 2 and 3, respectively.

DISCUSSION

Our goals in this study were to compare functional retinal changes between diabetic patients with CSME and controls using mfERG, and to correlate possible functional changes with structural measures and visual acuity in these patients. mfERG findings demonstrated that retinal function was significantly worse in diabetic eyes with CSME than normal eyes. The present study showed that N1 and P1 amplitudes were significantly decreased and their latencies were significantly increased, respectively, in eyes with CSME. These results support findings reported by Weiner et al that mfERG parameters were observed to be abnormal in patients with CSME.[10] In addition, we observed N1 and P1 amplitudes were decreased gradually from ring 1 to ring 5.

mfERG has been developed for recording local electrophysiological responses of different retinal regions. The responses are biphasic waves including a negative trough (N1) followed by a positive peak (P1). Typically, there is a second negative wave titled N2.[11] It is believed that N1 is generated by photoreceptors and P1 is generated by Müller and bipolar cells.[12,13] In the present study, we focused on N1 and P1 and their characteristics including amplitude and latency.

Previous histopathological observations in eyes with DME have indicated that retinal swelling initiates intracytoplasmic swelling of Müller cells, and that the outer plexiform layer or Henle's fiber layer is markedly swollen in diabetic eyes. Persistent retinal edema is reported to result in necrosis of Müller and adjacent neural cells, leading to formation of cystoid cavities.[14] Hence, it may be implied that duration of macular edema may significantly influence both anatomical and functional results.[15]

Some previous studies have suggested that for measuring retinal function in diabetic patients, temporal characteristic (latency) of mfERG waves is more important than amplitudes.[16] The researchers believed that patients with diabetes mellitus show temporal changes indicating delayed neural transmission due to local impairment of blood glucose metabolism.[16] Greenstein et al reported decreased amplitude and significantly increased latency in patients with CSME.[17] In contrast, recent studies emphasize the importance of both mfERG characteristics (latency and amplitude) in identifying retinal effects in DM.[18] It seems that mfERG characteristics could be used to examine outer retinal function and monitor impairment of the photoreceptors.[19] In the present study, we observed significantly reduced amplitudes of mfERG components (N1 and P1) and delayed latencies in patients with DME indicating functional impairments in the outer retina.

Based on the International Society for Clinical Electrophysiology of Vision (ISCEV), mfERG responses show greater amplitudes in the fovea having the greatest number of cone photoreceptors and bipolar cells.[11] Our results are in line with this definition. In other words, we observed that the average amplitude of mfERG responses decreased gradually from the first ring to the last ones (fifth ring) parallel with the sparser population of cone and bipolar cells in the peripheral region of the macula than the foveal center. Such a trend was not observed for latency of N1 and P1.

We also showed a significant correlation between BCVA as a dependent variable, with P1 and N2 amplitudes in the central macular area, but there was only borderline significance between BCVA and CMT. The significant correlation between the mfERG amplitude and BCVA has also been reported in previous studies regarding maculopathies, such as Best macular dystrophy,[20] Stargardt disease, and retinal vein occlusion.[21,22]

We also observed that there was no significant correlation between P1 and N2 latencies with BCVA. This

Table 5. Regression analysis between best corrected visual acuity as a dependent variable with CMT, CMV, and mfERG parameters for central ring

	Mean±SD	*P*
CMT	392±134.8	0.045
N1 amplitude	28.14±12.42	0.823
N1 latency	30.10±4.46	0.012
N2 amplitude	35.40±15.18	0.001
N2 latency	74.40±9.15	0.579
P1 amplitude	38.75±14.66	0.001
P1 latency	49.75±4.45	0.050
CMV	0.30±0.11	0.047

SD, standard deviation; mfERG, multifocal electroretinogram; CMT, central macular thickness; CMV, central macular volume

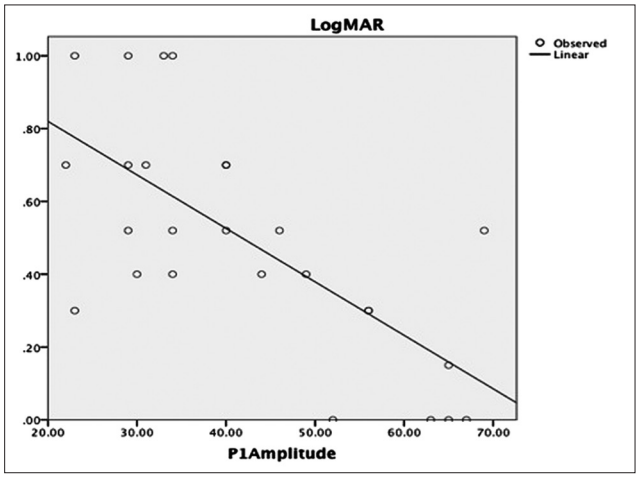

Figure 2. Scatter plot for the association between P1 amplitude (ring 1) and visual acuity.

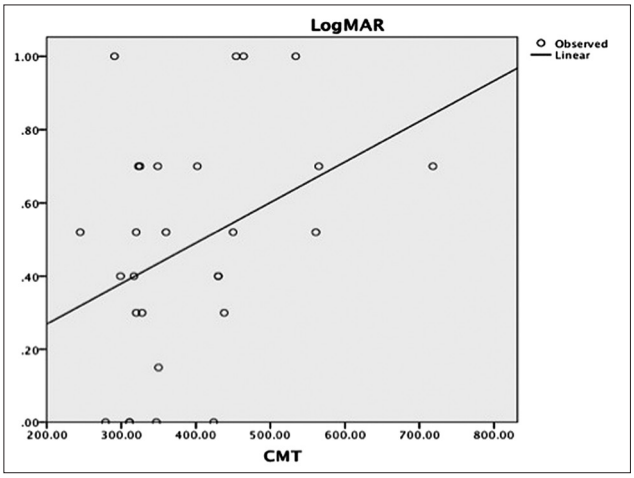

Figure 3. Scatter plot for central macular thickness and visual acuity.

result was in line with previous studies reporting that latencies were just moderately increased or even within normal values despite severe visual loss and reduced amplitudes, implying that reduced visual acuity is not necessarily associated with implicit time changes.[20,21]

As mentioned earlier, visual acuity was more correlated with P1 and N2 amplitudes than CMT and therefore BCVA was significantly associated with total mfERG amplitude (P1 plus N2) in the central macular area. In other words, in patients with near-normal total mfERG amplitude, visual acuity may remain intact although CMT may be increased due to DME. Some studies have reported similar results, indicating a modest correlation between OCT measured center point thickness and visual acuity, and modest correlation between changes in retinal thickening and visual acuity following focal laser treatment for DME.[23] In addition, in some clinical settings, macular thickness decreased without any improvement in vision showing a discrepancy between OCT findings and visual function.[24,25]

Browning et al mentioned, despite a modest correlation, there was substantial variation in visual acuity at any given retinal thickness. Many eyes with thickened macula had excellent visual acuity, and many eyes with normal CMT had decreased visual acuity. These results suggest that OCT measurement alone may not be a good surrogate for visual acuity as a primary outcome in studies on DME.[23]

We demonstrated that no significant correlations were present between CMT and mfERG parameters ($P > 0.05$). We did not expect these two tests, one functional and the other structural, to always be in agreement. However, it is clear that structural and functional tests will never be in complete agreement.[26] Dale et al revealed that for detection of retinal abnormalities, considerable disagreement exists between these two methods. mfERG tends to miss small local abnormalities that are detectable on OCT. On the other hand, OCT can appear normal in the face of clearly abnormal mfERG results. In some cases, functional damage may appear on mfERG before structural change is detected on OCT.[26]

In our study, some individual values deviated from the expected range; for example, in 7 eyes with reduced BCVA, retinal thickness was within normal range, whereas mfERG parameters were abnormal. Conversely, in 3 eyes, despite high retinal thickness, BCVA was normal with near normal mfERG parameters. Therefore, mfERG and OCT findings can complement each other to estimate visual acuity among CSME patients. From a practical point of view, OCT and mfERG tests together may provide a powerful way to identify the locus and severity of retinal damage.

It seems clear that mfERG has a potential role in demonstrating functional retinal impairment in patients with diabetes. Therefore, it may be suggested that early alterations in retinal function due to DR should be further studied. In addition, it is suggested that OCT and mfERG could be used together to better demonstrate possible anatomical and functional impairment in eyes with DME. Furthermore, we suggest caution in the exclusive use of structural data, such as that from OCT imaging, to reflect the retinal function or to assess feasibility or effects of treatment.

In summary, it may be concluded that patients with DME have significantly abnormal mfERG responses, i.e., decreased amplitudes and delayed latencies. In addition, visual acuity was correlated with mfERG waves, especially P1 and N2, more than CMT based on OCT. These findings indicate that functional changes in the retina of patients with diabetes mellitus assessed by mfERG can complement OCT findings.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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