

Prognostic Value of Multifocal Electroretinography and Optical Coherence Tomography in Eyes Undergoing Panretinal Photocoagulation for Diabetic Retinopathy

Ying Zhu,^{1,2} Ting Zhang,¹ Ke-yan Wang,¹ and Ge-zhi Xu¹⁻³

¹Department of Ophthalmology, Eye and ENT Hospital of Fudan University, Shanghai, People's Republic of China

²Shanghai Key Laboratory of Visual Impairment and Restoration, Fudan University, Shanghai, People's Republic of China

³Institute of Brain Science, Fudan University, Shanghai, People's Republic of China

Correspondence: Ke-yan Wang, Department of Ophthalmology, Eye and ENT Hospital of Fudan University, 83 Fen Yang Road, Shanghai, 200031, People's Republic of China; drwangky@gmail.com.

YZ and TZ contributed equally to the work presented here and therefore should be regarded as equivalent authors.

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PURPOSE. To investigate the prognostic utility on visual acuity of multifocal electroretinography (mfERG) and optical coherence tomography (OCT) in diabetic eyes receiving panretinal photocoagulation (PRP).

METHODS. Patients with severe nonproliferative diabetic retinopathy (NPDR) or early proliferative diabetic retinopathy (PDR) who needed PRP were included in this study. The mfERG and OCT data were recorded before PRP, and the final best-corrected visual acuity (BCVA) was recorded at 6 months after PRP. The correlation between pre-PRP data and post-PRP BCVA was analyzed using Pearson's correlation analysis and multivariate linear regression analysis.

RESULTS. Among the 42 eyes included, 31 eyes (73.8%) had improvement or remained stable in visual acuity, and 11 eyes (26.2%) had deterioration in BCVA. The final BCVA was significantly correlated with the amplitude and latency of mfERG in all nine sectors, and the amplitude had a stronger correlation than latency. The foveal ellipsoid zone of the photoreceptors and external limiting membrane (ELM) status, as well as the retinal thickness in most sectors, were also correlated with the final BCVA. In a multivariate linear regression model, age, pre-PRP BCVA, amplitude of mfERG in the central sector, and foveal ellipsoid zone status were significantly correlated with the final BCVA. The retinal thickness was correlated with the amplitude or latency of mfERG in some sectors, and the correlation was tighter in temporal and inferior sectors.

CONCLUSIONS. A lower amplitude of mfERG and disrupted foveal ellipsoid zone status were significantly correlated with a worse visual prognosis in diabetic eyes after PRP.

Keywords: multifocal electroretinography, optical coherence tomography, panretinal photocoagulation, diabetic retinopathy

Designed to provide a topographic measure of retinal electrophysiological activity, a multifocal electroretinogram (mfERG) is able to record local ERG responses simultaneously from different regions in the central 40° to 50° of the retina (20°-25° radius from the fixation point).¹ Unlike pattern ERG or focal ERG, which focuses on the foveal region, mfERG could also provide information about nonfoveal lesions.² Since its introduction, mfERG has been found to be useful in the assessment of localized retinal dysfunction caused by various acquired or hereditary retinal disorders.³ A few studies have investigated the mfERG response in diabetic eyes⁴⁻⁸ and found that implicit time measures were more sensitive than amplitude changes in detecting retinal dysfunction. Based on the observation that the implicit time was significantly prolonged in diabetic patients without retinopathy and in diabetic eyes the delays became longer with increasing local retinopathy grade,⁷ Bearnse et al.⁹ formulated a model based on the mfERG response to predict the development of diabetic retinopathy (DR).

According to the results of the Early Treatment Diabetic Retinopathy Study (ETDRS), panretinal photocoagulation (PRP) could be beneficial for severe nonproliferative diabetic

retinopathy (NPDR) and early proliferative diabetic retinopathy (PDR).¹⁰ Panretinal photocoagulation stopped the progression of DR by improving the oxygen supply and subsequently decreasing the production of VEGF, which is responsible for neovascularization. The improved oxygen supply after PRP could be explained in two ways: first, the choriocapillaris is now physically closer to the inner retina, and second, the highly metabolically active photoreceptors are no longer present to absorb oxygen from the choriocapillaris in the area of the laser burns.¹¹ However, the patient response to PRP varies, largely dependent on the pretreatment visual acuity.^{12,13} As a vital functional indicator of retinal health, apart from predicting the development of disease, mfERG also may be able to reveal the recovery potential of a retina after PRP. Besides, ellipsoid zone of the photoreceptors (previously termed as photoreceptor inner and outer segment junction¹⁴) and external limiting membrane (ELM) statuses measured by optical coherence tomography (OCT) are gaining popularity in determining the prognosis of a variety of diseases.¹⁵⁻¹⁹ However, the prognostic value of ellipsoid zone and ELM statuses in diabetic eyes receiving PRP was not reported so far.

In this study, we investigated the prognostic value of the pretreatment mfERG response and OCT images with respect to visual acuity after PRP, as well as the correlation between retinal function and morphology.

METHODS

Subjects

This prospective interventional case series recruited patients with severe NPDR or early PDR who needed PRP from August 2012 to April 2013. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of Eye and ENT Hospital of Fudan University. Informed consent was obtained from all subjects before participation. The staging of DR and decisions regarding treatment were made by a single retina specialist (KYW) according to the recommendations of the ETDRS.^{10,20,21} Patients who had received photocoagulation, intravitreal injections of anti-VEGF agents, or previous retinal surgery were excluded from the study. Patients with diabetic macular edema (DME) were excluded from the study if the DME involved the fovea. Patients with retinal diseases other than DR (including AMD, pathologic myopia, retinal artery occlusion, and retinal vein occlusion), glaucoma, or a history of ocular trauma or inflammation were excluded from the study. To acquire clear OCT imaging, patients with opaque media also were excluded.

Study Protocol

Only one eye from each participant was included in the study. If both eyes met the inclusion criteria, the eye with better visual acuity was included. A single retina specialist (KYW) performed PRP at 1-week intervals over a course of 3 to 4 weeks for each participant with the advanced patterned scanning laser system (Pascal; OptiMedica, Santa Clara, CA, USA).²² Briefly, photocoagulation was applied in a pattern array with a spot size of 200 μm and a pulse duration of 20 ms. A Volk SuperQuad 160 widefield contact lens (Image Mag 0.5x, Laser Spot 2.0x; Volk Optical, Mentor, OH, USA) was used to focus the laser beam on each retina, magnifying the 200- μm -diameter laser spot to approximately 400 μm on the retinal plane. To achieve threshold laser photocoagulation, a mild gray-white burn (between grade 3 and grade 3+) was adopted according to the ETDRS guidelines. Different retinal areas were treated in the following order: inferior, nasal, superior, temporal. On average, a total of 2000 to 2500 laser spots were applied by the end of PRP. Demographic information collected from the patients included age, sex, duration of diabetes mellitus (DM), HbA1c level, presence of hypertension, and refractive error. The best-corrected visual acuity (BCVA) was measured using ETDRS charts. Slit-lamp biomicroscopy using a Volk Digital Wide Field (field of view 103°/124°; Volk Optical) noncontact lens and BCVA measurement were performed at baseline and 6 months after completion of PRP. Multifocal ERG and OCT were performed before PRP.

Optical Coherence Tomography Scan

Spectral-domain (SD)-OCT images were acquired by Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). A raster imaging protocol consisting of 31 horizontal scans was adopted, which covered a 30° × 25° area centered on the fovea.²³ The scans were each 8.4 mm in length and spaced 240 μm apart from each other. All scans were obtained for analysis after 25 frames were averaged using built-in automatic averaging software (TruTrack; Heidelberg Engineering). Auto-

generated macular thickness maps were generated by the device with the application of an ETDRS macular grid.²⁴

Analysis by OCT

The status of the foveal ellipsoid zone and ELM were examined for each eye. For the ellipsoid zone appearance, all eyes were categorized into three groups: intact, disrupted, and indeterminate. The intact group included eyes with a regular continuation of the hyperreflective line corresponding to the ellipsoid zone. The disrupted group included eyes characterized by hyporeflective discontinuities in the ellipsoid zone line. The indeterminate group included eyes with an unclearly delineated ellipsoid zone due to severe macular edema or poor image quality. The evaluation of ELM status was similar to that of the ellipsoid zone and all eyes were categorized into the three groups accordingly.

Recording by mfERG

Multifocal ERGs were recorded using a visual evoked response imaging system (VERIS 4.3; Electro-Diagnostic Imaging, San Mateo, CA, USA). Stimulation and recording of the mfERG responses were performed using the m-sequence technique according to the International Society for Clinical Electrophysiology of Vision guidelines.²⁵ Briefly, after dilation of the pupil and topical anesthesia, a Burian Allen bipolar contact lens electrode (Hansen Ophthalmic, Solon City, IA, USA) was applied to the cornea and a ground electrode was attached to the forehead. The fixation was controlled using a fundus camera and illumination with infrared light from the recording electrode, with visualization of the hexagonal elements over the retina. The stimulus array was centered on the fovea and consisted of 103 hexagonal elements covering a visual field of 30°, displayed at a 75-Hz frame rate. The sizes of the hexagons were scaled with eccentricity to elicit approximately equal amplitude responses at all locations. The luminance of each hexagon was independently alternated between black (<2 cd/m²) and white (200 cd/m²), according to a pseudorandom binary m-sequence. Each recording was taken in 16 segments of approximately 15 seconds each. The fellow eye was covered with an eye patch.

Analysis by mfERG

Only the first-order response of the mfERG was analyzed.¹ The first negative deflection (N1) and the first positive peak (P1) of the local mfERG response waveforms were identified. The P1 amplitude was measured from the trough of N1 to the peak of P1. The P1 latency was measured from the onset of the stimulus flash to the P1 peak. By superimposing the OCT pattern over the mfERG hexagonal pattern, hexagons corresponding to the OCT pattern were identified (Fig. 1). For each area of the nine sectors, the responses from the corresponding hexagons were summed for the analysis.

Statistical Analysis

All statistical analyses were performed using SPSS software version 16.0 (SPSS, Inc., Chicago, IL, USA). One-way ANOVA was used to determine whether the final BCVA and mfERG values were significantly dependent on ellipsoid zone or ELM status. The correlations between the final BCVA and retinal thickness, amplitude, or latency of mfERG responses before PRP were analyzed using Pearson's correlation test. Multiple linear regression was used to evaluate the influence of each potential factor (including the central foveal thickness,

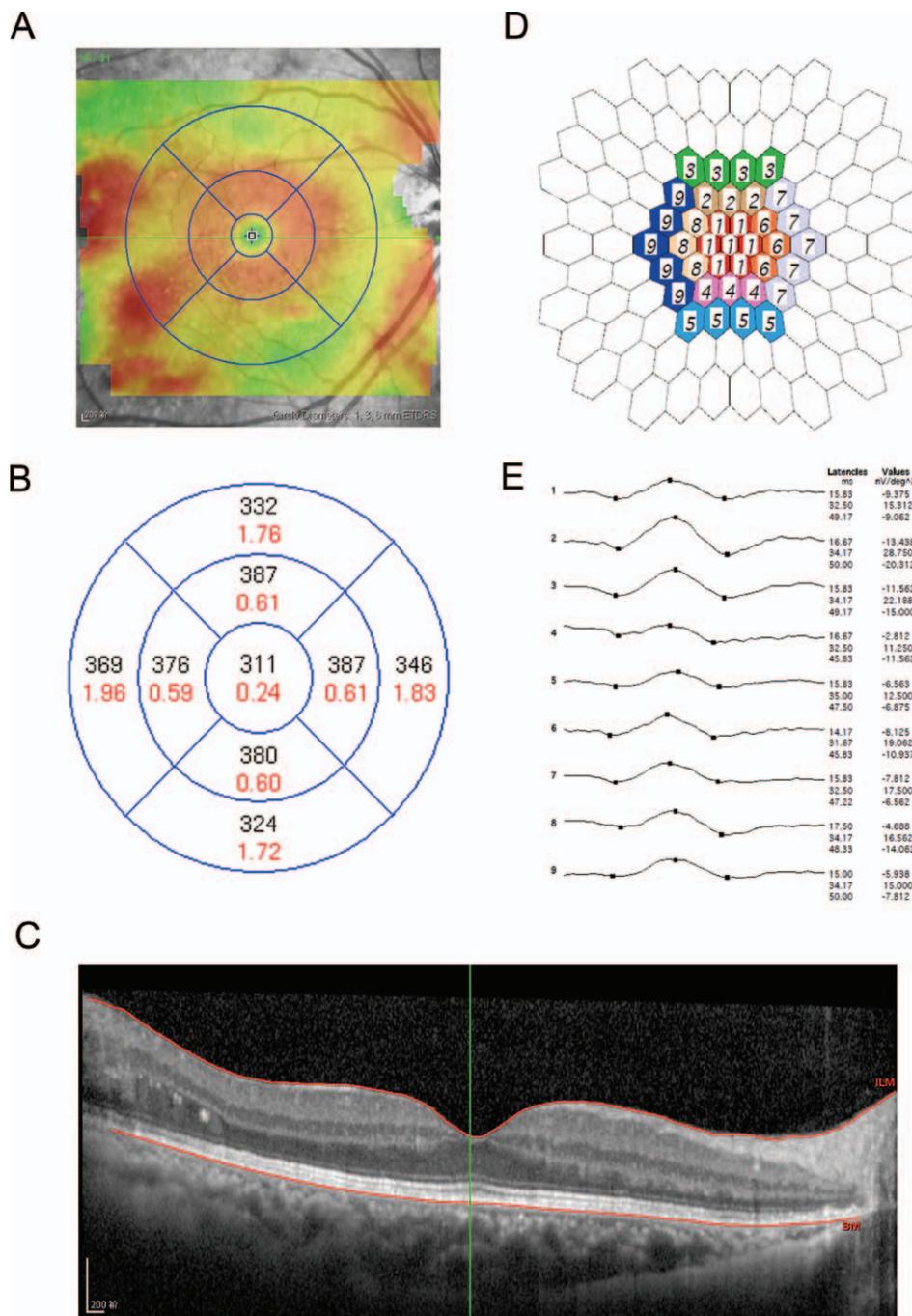


FIGURE 1. Representative OCT scans (A–C) and mfERG images (D, E) from a 60-year-old man who had type 2 diabetes mellitus for 20 years. With the use of 1-3-6-mm ETDRS macular grid (A), the mean retinal thicknesses of the corresponding sectors were automatically calculated by the built-in software (B). The foveal OCT scan was analyzed with caution to determine the status of the ellipsoid zone of the photoreceptors and the ELM (C). By superimposing the OCT pattern over the mfERG hexagonal pattern, hexagons corresponding to the OCT pattern were identified (D). For each sector represented by a different number, the responses from the corresponding hexagons were summed for analysis of amplitude and latency (E).

amplitude, latency, initial BCVA, age, and duration of DM) on final BCVA.

A *P* value less than 0.05 was considered statistically significant.

RESULTS

A total of 42 patients with DR who needed PRP were recruited into this study, including 18 males and 24 females. Patient age

ranged from 31 to 78 years, with a mean of 53.4 ± 10.0 years. All patients were diagnosed with type 2 diabetes, and the duration of diabetes ranged from 2 to 20 years, with a mean of 10.0 ± 4.9 years. The mean HbA1c level was $8.0\% \pm 1.5\%$. A total of 16 (38.1%) of the 42 patients suffered from hypertension and were taking oral medications. The refractive error mean was -0.56 ± 1.60 diopter. The demographics of the participants are listed in Table 1.

The mean BCVA increased slightly but not significantly from 62.6 ± 15.0 letters to 64.0 ± 17.8 letters at 6 months after PRP.

TABLE 1. Participant Demographics

Age, y	53.4 ± 10.0
Male/female, n	18/24
Duration of DM, y	10.0 ± 4.9
HbA1c, %	8.0 ± 1.5
Hypertension, n (%)	16 (38.1)
Refractive error, diopter	-0.56 ± 1.60

Data presented as mean ± SD.

Among the 42 eyes included, 31 eyes (73.8%) showed improvement or remained stable in visual acuity, and 11 eyes (26.2%) showed deterioration in BCVA. Fourteen eyes (33.3%) had extrafoveal DME; however, there was no statistically significant difference in BCVA between patients with extrafoveal DME and patients without.

Pearson's correlation analysis was conducted to investigate the correlation between final BCVA and the amplitude or latency of mfERG in all nine sectors. In the central sector corresponding to the fovea, the Pearson's correlation coefficient was 0.585 ($P < 0.001$) between the final BCVA and amplitude and -0.429 ($P < 0.001$) between the final BCVA and latency. A statistically significant correlation between final BCVA and amplitude or latency also was detected in the other eight sectors (Table 2). Generally, good visual prognosis was associated with a larger amplitude or a shorter latency. In most sectors, the ρ^2 of latency was larger than that of amplitude, which indicated a stronger correlation between latency and final BCVA.

The prognostic value of retinal structure, which was represented by retinal thickness, was analyzed by Pearson's correlation analysis. A statistically significant correlation between the final BCVA and retinal thickness was detected in all sectors except the inner nasal sector (Table 2).

The impact of the ellipsoid zone status or the ELM status on visual prognosis was analyzed with ANOVA (Fig. 2). Based on the ellipsoid zone status before PRP, 27 eyes had intact ellipsoid zone, 14 eyes had disrupted ellipsoid zone, and 1 eye had an indeterminate status. The mean post-PRP BCVA was 69.5 ± 17.0 letters in the intact group and 54.1 ± 15.0 in the disrupted group ($P = 0.006$). The mean P1 amplitude of the central sector was 23.4 ± 12.7 nV/deg² in the intact group and 10.6 ± 5.9 nV/deg² in the disrupted group ($P = 0.001$). The mean P1 latency of the central sector was 34.2 ± 2.4 ms in the intact group and 35.7 ± 4.8 in the disrupted group ($P = 0.182$). Based on the ELM status before PRP, 30 eyes had intact ELM, 11 eyes had disrupted ELM, and 1 eye had an indeterminate ELM status. The mean post-PRP BCVA was 69.6 ± 16.0 letters in the intact group and 49.9 ± 12.9 in the disrupted group ($P = 0.001$). The mean P1 amplitude of the central sector was 21.6

± 13.1 nV/deg² in the intact group and 11.7 ± 6.1 nV/deg² in the disrupted group ($P = 0.017$). The mean P1 latency of the central sector was 33.6 ± 2.2 ms in the intact group and 37.3 ± 4.6 ms in the disrupted group ($P = 0.001$).

A multiple linear regression model also was built to explore the role of retinal function and structure in the prognosis (Table 3). It turned out that the amplitude of mfERG ($P = 0.001$), foveal ellipsoid zone status ($P = 0.013$), pre-PRP BCVA ($P < 0.001$), and age ($P = 0.004$) were correlated with the final BCVA.

The association between retinal structure and retinal function was analyzed by Pearson's correlation analysis (Table 4). The amplitude of the mfERG response had a statistically significant correlation with retinal thickness in the central ($\rho = -0.305$, $P = 0.049$), inner temporal ($\rho = -0.366$, $P = 0.017$), outer temporal ($\rho = -0.390$, $P = 0.011$), and outer superior ($\rho = -0.387$, $P = 0.011$) sectors. The latency of the mfERG response was significantly correlated with retinal thickness in the inner inferior ($\rho = 0.330$, $P = 0.033$), outer inferior ($\rho = 0.376$, $P = 0.014$), outer nasal ($\rho = 0.366$, $P = 0.017$), outer temporal ($\rho = 0.319$, $P = 0.039$), and outer superior ($\rho = 0.370$, $P = 0.016$) sectors. Briefly, a thicker retinal thickness was associated with a smaller amplitude or a longer latency, and the correlation was tighter in the temporal and inferior sectors, especially in the outer ring.

DISCUSSION

The present study is the first to demonstrate the prognostic utility on visual acuity of an mfERG in eyes requiring panretinal photocoagulation, as well as to investigate the correlation between mfERG values and OCT features. We found that functional parameters assessed by mfERG and structural parameters assessed by OCT were correlated with the final visual prognosis, and these two assessments correlated well with each other. In all nine sectors, both the amplitude and latency of mfERG were correlated with the final BCVA after PRP. Of the various OCT parameters, foveal ellipsoid zone status and ELM status were tightly correlated with visual prognosis, and retinal thickness in most sectors also was correlated with the final BCVA.

As a viable tool to evaluate retinal function, mfERG was found to be valuable in predicting the development of DR^{9,26} and diabetic edema.²⁷ In the present study, we demonstrated the prognostic value of mfERG in patients with DR who underwent PRP. Both the amplitude and latency of mfERG were correlated with final BCVA after PRP, and amplitude remained a key contributor in a multiple linear regression analysis. Unlike previous studies,^{9,27,28} amplitude seemed to be more sensitive than latency in our study. There may be two

TABLE 2. Correlations Between Final BCVA and Amplitude, Latency of mfERG, or Retinal Thickness Before PRP in Different Sectors

	Amplitude		Latency		Retinal Thickness	
	ρ	P Value	ρ	P Value	ρ	P Value
Central	0.585	<0.001	-0.429	0.005	-0.395	0.010
Inner superior	0.414	0.006	-0.525	<0.001	-0.360	0.019
Inner nasal	0.551	<0.001	-0.448	0.003	-0.241	0.125
Inner inferior	0.311	0.045	-0.571	<0.001	-0.357	0.020
Inner temporal	0.403	0.008	-0.573	<0.001	-0.339	0.028
Outer superior	0.368	0.017	-0.652	<0.001	-0.311	0.045
Outer nasal	0.479	0.001	-0.511	0.001	-0.410	0.007
Outer inferior	0.416	0.006	-0.653	<0.001	-0.413	0.007
Outer temporal	0.538	<0.001	-0.569	<0.001	-0.337	0.029

ρ (rho) indicates Pearson's correlation coefficient.

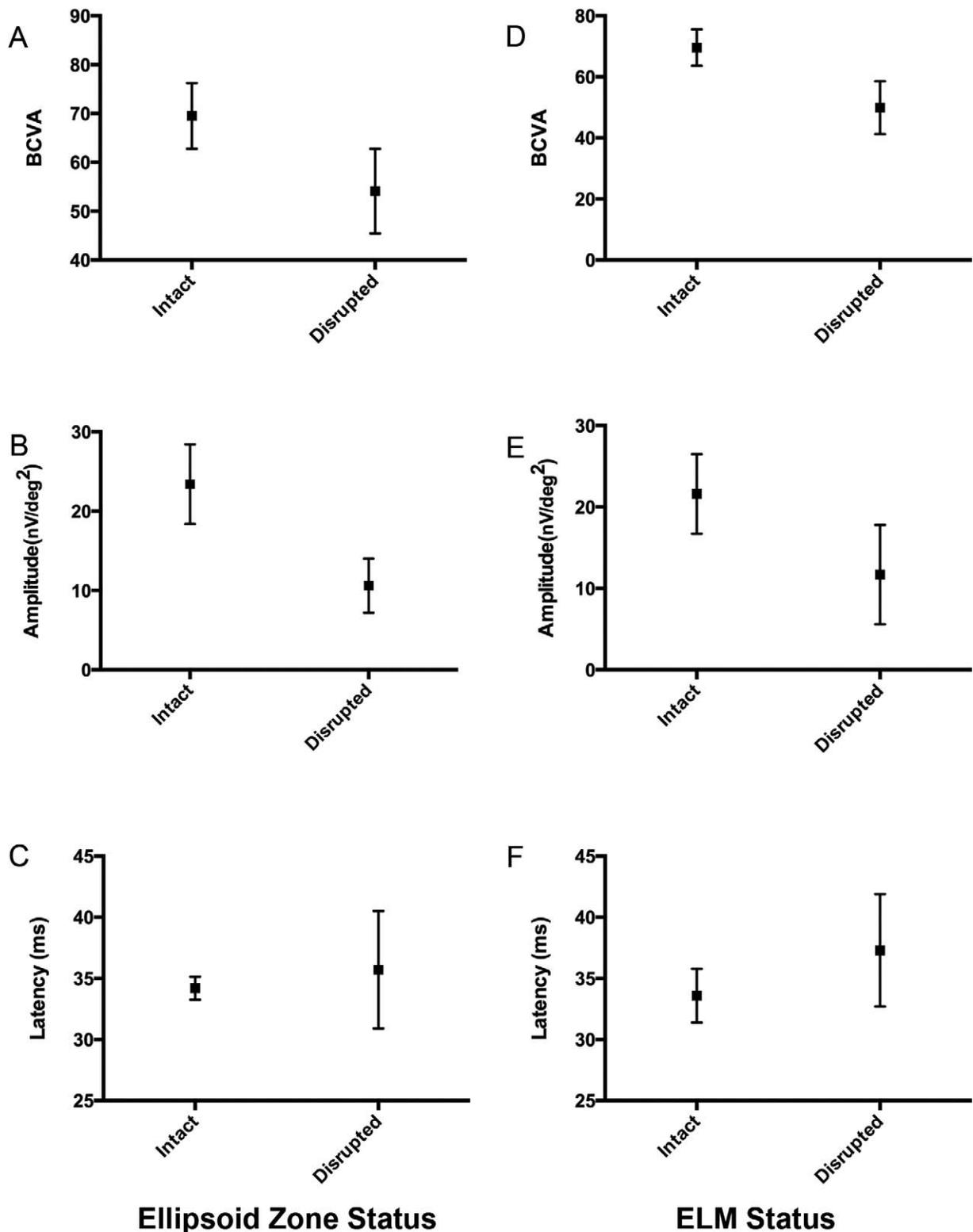


FIGURE 2. Final BCVA, amplitude, and latency of mfERG based on the foveal ellipsoid zone status (A–C) or the ELM status (D–F). In the group of intact ellipsoid zone, the post-PRP BCVA (A) was significantly better ($P=0.006$) and the mean P1 amplitude (B) was significantly larger ($P=0.001$). In the group with intact ELM, the patients had a better post-PRP BCVA (D) ($P=0.001$), a larger P1 amplitude (E) ($P=0.017$), and a shorter P1 latency (F) ($P=0.001$).

TABLE 3. Multiple Linear Regression Analysis for Final BCVA at 6 Months After PRP

	B	Standardized β	P Value
Amplitude	0.473	0.328	0.001
Latency	-0.099	-0.019	0.512
Central foveal thickness	-0.001	-0.009	0.926
Ellipsoid zone	9.013	0.246	0.013
ELM	-5.629	-0.145	0.211
BCVA before PRP	0.977	0.824	0.000
Age	0.504	0.283	0.004
Duration of DM	-0.398	-0.109	0.534

explanations for this finding. First, there were conflicting results regarding the change in mfERG parameters before and after laser treatment in diabetic patients.^{29,30} Lovestam-Adrian et al.²⁹ found that the amplitude decreased significantly and the latency remained unchanged after PRP, whereas Greenstein et al.³⁰ found that the latency rather than the amplitude changed significantly after focal laser treatment for DME. PRP, therefore, may have a closer relationship with amplitude than latency. Second, the patients included in our study were at a relatively late stage of DR, and most of them had severely impaired retinas; thus, some of the mfERG curves were low and flat and it was difficult to identify N1 and P1. The accuracy of latency was affected much more than that of amplitude because amplitude did not vary as much along the curve as did latency.

Apart from retinal thickness, ellipsoid zone and ELM statuses are widely used in determining the prognosis of retinal diseases.¹⁵⁻¹⁹ Maheshwary et al.³¹ and Otani et al.³² demonstrated that the integrity of the ellipsoid zone was crucial to the BCVA of patients with DME. Murakami et al.³³ was the first to demonstrate the relevance of ELM as representative of visual function in DME. Shah et al.³⁴ proved that ELM and ellipsoid zone integrity correlated well with BCVA after pars plana vitrectomy for PDR. In patients with DME who were treated successfully with intravitreal triamcinolone injection, Shin et al.³⁵ found that ellipsoid zone and ELM status, rather than central macular thickness, were useful hallmarks for predicting the final BCVA. Our results echoed these findings. Both ellipsoid zone and ELM status were correlated with final BCVA after PRP, but not in the same manner. Only ellipsoid zone status remained statistically significant in the multiple linear regression model, whereas ELM status showed a better correlation with mfERG latency. Because ellipsoid zone and ELM reflect different parts of retina,^{15,36} the difference was plausible. Future studies are necessary to clarify the mechanism behind the difference.

The correlation of OCT and mfERG parameters in our study was statistically significant in most sectors, thus showing the link between retinal function and structure. Yamamoto et al.⁵ demonstrated that implicit times were directly correlated with foveal thickness in patients with DME. Apart from edema, other signs of DR (including dot hemorrhages, microaneurysms, hard exudates, and cotton wool spots) are all associated with abnormalities in mfERG.⁹ Although the exact mechanism remains unknown, hypoxia, perfusion defects, or changes in local metabolism may play a role in the process.^{26,37} All the signs of DR indicating disruption of the blood retinal barrier could cause thickening of retina. It is, therefore, not surprising that increased retinal thickness correlated with decreased retinal physiologic function by mfERG in most sectors. However, Dhamdhere et al.³⁸ investigated the association between local neuroretinal function and local retinal thickness, but the correlation was not significant. In the study by Dhamdhere et al.,³⁸ all included patients were diagnosed with

TABLE 4. Correlations Between Retinal Thickness and Amplitude or Latency of mfERG Response in Different Sectors

	Amplitude		Latency	
	ρ	P Value	ρ	P Value
Central	-0.305	0.049	0.119	0.451
Inner superior	-0.190	0.228	0.284	0.069
Inner nasal	-0.087	0.585	0.098	0.536
Inner inferior	-0.225	0.152	0.330	0.033
Inner temporal	-0.366	0.017	0.170	0.283
Outer superior	-0.387	0.011	0.370	0.016
Outer nasal	-0.112	0.479	0.366	0.017
Outer inferior	-0.298	0.055	0.376	0.014
Outer temporal	-0.390	0.011	0.319	0.039

diabetes but without DR, whereas the patients included in the present study were all diagnosed with relatively late-stage DR. The stage of disease played a key role here. In an early stage of diabetes, at least before the onset of DR, the OCT and mfERG results reflected different aspects of the disease. With disease progression, both the structure and function of the retina were severely affected, and the measurements of the two tests echoed each other.

The present study had several limitations. First, the number of participants included in the study was small. When it comes to correlation analysis, it is not easy for a small sample to detect reliable statistically significant results. Second, we primarily focused on visual acuity prognosis after PRP and failed to provide detailed information about other visual functions.

In conclusion, the present study investigated both the functional and structural parameters for the prognosis of diabetic eyes after PRP. The amplitude of mfERG and the foveal ellipsoid zone status were the most valuable indications.

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