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ORIGINAL RESEARCH ARTICLE

Structural and functional assessment after intravitreal injection of ranibizumab in diabetic macular edema

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Abstract

Purpose To evaluate structure and function improvement in central retina by optical coherence tomography (OCT) and multifocal electroretinography (mf-ERG) in diabetic macular edema (DME) patients after intravitreal injection of ranibizumab (IVR) treatment.

Methods Twenty-seven eyes in 27 patients with DME received three consecutive monthly injections of IVR (0.05 ml, 10 mg/ml) and as needed thereafter. The clinical parameters of best-corrected visual acuity (BCVA), central foveal thickness (CFT) and mf-ERG were monitored for 6 months before and after IVR. The findings at baseline, 1, 3 and 6 months were analyzed. Correlation and regression analyses were performed on BCVA, CFT, mf-ERG amplitude and implicit time of the N1 and P1 waves.

Results IVR significantly improved visual acuity from the beginning of the treatment ($P < 0.05$). There were significant decreases in the CFT compared with the baseline after IVR ($P < 0.05$). The mean amplitude of P1 and N1 in the central ring at all examinations increased significantly compared with the baseline ($P < 0.05$). The mean P1 and N1 implicit times in the central ring were shortened, but not significantly ($P > 0.05$). There were significant correlations of BCVA with CFT, P1 and N1 amplitudes in the central retina ($P < 0.05$).

Conclusion In addition to the improvement in BCVA and the reduction in CFT, IVR improved macular retinal function, as assessed by mf-ERG, in diabetic eyes. The combination of OCT and mf-ERG for macular evaluation may better assess DME.

Keywords Ranibizumab · Diabetic macular edema · Mf-ERG · OCT

Introduction

Diabetic retinopathy (DR) is one of the leading reasons of blindness throughout the world, and diabetic macular edema (DME) is a major complication of DR which lead to visual acuity loses/lost [1]. The Early Treatment Diabetic Retinopathy Study (ETDRS) pointed out that laser treatment was a significant therapy in clinically significant macular edema (CSME), and it has been identified as the gold standard for the treatment of DME [2]. However, it carries risks in many cases, and efficient laser treatment may still not prevent the progression of diffuse macula edema in the long term.

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Vascular endothelial growth factor (VEGF) is considered to be the main stimulus generation of diabetic macular edema, and pharmacologic therapies that inhibit VEGF may directly target the main cause of the pathology [3]. Ranibizumab is a human anti-VEGF monoclonal antibody, which can be used in combination with all VEGF-A active isomers. A small phase I clinical trial of the intravitreal injection of ranibizumab for treatment of DME showed that the patients' condition improved, and there were no ocular or systemic adverse reactions reported at the end of the treatment [4]. READ-2 [5] showed that BCVA was significantly better in a group given ranibizumab therapy alone than in a group given single laser therapy alone, or a group given combination therapy. IVR can effectively alleviate macular edema and increase BCVA in DME. However, most of the current studies have focused on the relationship between visual acuity and central retina structure, and the direct effects of IVR on the function of the central retina are not fully understood.

High-resolution optical coherence tomography (OCT) can be used to identify the changes in central retina microstructure. Previously, retinal morphological changes in DME could only be observed as a whole by time domain OCT scans. The current spectral domain optical coherence tomography (OCT) can give accurate analysis and provide precise data for the central retinal thickness. Advances in OCT technology have the ability to provide enhancement tools for clinicians to explain the cause of poor visual acuity (VA) in the treatment of DME. It determines the changes in the structure of the central retina, which may be related to subjective visual performance measurements, such as vision and visual field [6]. With the development of mf-ERG [7], we can use it to study central retina area more accurately, so as to objectively assess the macular dysfunction degree. It is an important objective test identifying functional changes in the retina in early phases of DR [8]. This objective measurement is introduced because mf-ERG records local responses from the central retina.

Aims of our study were firstly to assess the changes in the central foveal thickness by SD-OCT and function of central retina with mf-ERG before and after intravitreal injection of ranibizumab (IVR), and secondly to investigate the correlation of functional and anatomical parameters changes in patients with DME.

Materials and methods

All patients involved in this study signed the written consent form. Our research was conducted to adhere to the tenets of Helsinki Declaration and the requirements of the Human Research Ethics Committee of the Affiliated Hospital of Qingdao University.

Participants

Twenty-seven eyes in 27 patients with DME, who were consecutively treated with IVR, were involved in this prospective research. All the participants attended the outpatient review regularly in the Affiliated Hospital of Qingdao University. Inclusion criteria for this research [9] were: (1) the presence of CSME due to diabetic retinopathy on fundus examination; (2) confirmed the presence of DME by angiography; (3) patients with adult onset diabetes, who had been under the endocrinologist's care for no less than 3 months; (4) as measured with spectral OCT, CFT at least 250 μm; (5) BCVA from 20/200 to 20/40 using the Early Treatment Diabetic Retinopathy Study (ETDRS) standard charts; (6) no previous vitreoretinal surgeries or laser photocoagulation; (7) not receive cataract surgery within 6 months before the first IVR; (8) no therapy for DME within 4 months before the first IVR; and (9) no vitreoretinal traction revealed by OCT. We arranged all the examinations at 08:00 to 11:00 am.

At the first examination, we got the data of patients' blood pressure, duration of diabetes and glycosylated hemoglobin (HbA1c).We also measured fasting blood glucose at all examinations.

The injections

Under topical anesthesia with oxybuprocaine hydrochloride ophthalmic solution, a standard intravitreal injection protocol was used, following flushing of the conjunctival sac with 0.05% anerdian. According to same procedure, 0.5 mg (0.05 mL) ranibizumab (Lucentis®, Novartis Pharma Stein AG) was injected intravitreally. After treatment, 0.5% Levofloxacin drops were prescribed for one week. All patients received IVR monthly for 3 months. Indirect ophthalmoscopy and tonometry were performed after the procedure to detect any injection-related complications. After the first three injections, patients received

an additional injection if any of the following criteria were met: 1) a decrease in BCVA by $\geq$ 5 letters, 2) an increase in CFT by $\geq$ 100 μm or 3) a decrease in BCVA due to newly formed intraretinal cyst or subretinal fluid, in the opinion of the investigator.

Visual acuity

The ETRDS charts were used to assess the best-corrected visual acuity (BCVA). All visual acuity results were transformed to the common logarithm of the minimum resolution angle (Log MAR).

Optical coherence tomography

A Spectralis™ OCT (Heidelberg Engineering, Dossenheim, Germany) was used to examine the central foveal thickness. All pupils were fully dilated with 0.5% phenylephrine and 5% tropicamide, and the OCT scan length was unified at 6 mm, using the size of the edematous area to adjust the scan length. The scanning depth was 4 mm, and the resolution was 5 μm. The distance from the inner boundary layer to the inner side of the pigment epithelium layer was measured. The survey was completed by two experienced technicians and repeated three times.

mf-ERG

UTAS-E4000 System (LKC Technologies, Gaithersburg, MD, USA) was used for the measurement of multifocal ERG. The recording parameters were consistent with guidelines and standards of International Society for Clinical Electrophysiology of Vision (ISCEV) [10]. The distance of examination was set at 30 cm, and the pupils of patients were dilated (>6 mm) with 0.5% tropicamide and 5% phenylephrine. A golden grounding electrode was pasted on the forehead. Under local anesthesia, activity of retina was recorded using a golden bipolar contact lens, which was attached to the cornea. Recording electrode's infrared light and a fundus camera were used to control the fixation, with the hexagonal elements' visualization over the retina. The stimulus region can be divided into 61 hexagon patterns. The first and second rings hexagon pattern of the standard MF-ERG were collectively referred to as the central ring [11, 12] (Fig. 1). The analysis included the response amplitude and implicit time of the P1-wave and N1-wave, which correspond to the central ring.

All patients underwent ophthalmic examinations one day before IVR, one week after IVR and then monthly. The same equipment and methods were used for each examination. At every visit, all patients underwent ophthalmic examinations, including BCVA, OCT, mf-ERG and intraocular pressure. The last examination was performed at the third months after the third injection.

Statistical analysis

We used Shapiro–Wilk test to assess the normality of the analyzed parameters' distribution. Repeated-measures analysis of variance and paired t test were used to estimate the differences among injections. BCVA was the dependent variable, and we assessed the correlation among data using the Pearson coefficient. All data were analyzed with SPSS 22.0 software. *P* value less than 0.05 was considered as significant.

Results

No patients withdrew from this study. The duration of diabetes mellitus ranged from 5 to 16 years (average 9.2 years). At baseline, the mean HbA1c ± SD was 8.27% ± 1.36. The systolic blood pressure and

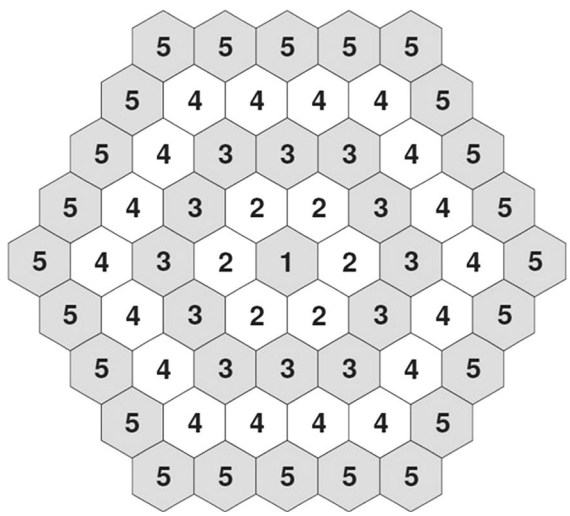

Fig. 1 Mf-ERG ring topography showing the 5 concentric rings consist of 61 hexagon patterns used in the analyses, rings 1 and 2 were summed: central ring

diastolic blood pressure were 136.5 ± 10.8 and 83.3 ± 9.7 mmHg, respectively. There was no significant change in fasting blood glucose in all examinations ($P > 0.05$).

The mean number of injections recorded at the 6-month follow-up examination was 3.58. Nineteen patients needed 3 injections, five patients needed 4, and three patients were given 5 injections. No serious ocular adverse effects or complications were seen in any of the eyes. All intraocular pressures were in the normal range. All data for BCVA, CFT and mf-ERG of test groups are summarized in Table 1.

After 6 months of treatment, the VA of 22 eyes was obviously improved; improvement was not seen in 5 eyes, but none showed deterioration. The mean BCVA at baseline was 0.80 ± 0.27, which improved to 0.36 ± 0.14 at 1 month, 0.34 ± 0.13 at 3 months and 0.38 ± 0.13 at 6 months ($P = 0.000$ for each). No significant differences were found among the three records after IVR ($P = 0.750$, 0.658, 0.447, respectively).

After three ranibizumab injections, all measurements of the central foveal thickness (CFT) were decreased. We could find significant decreases in the average CFT from baseline (375.16 ± 66.23 μm) to 266.89 ± 37.55 μm at 1 month, 261.58 ± 37.55 μm at 3 months, and 270.05 ± 48.87 μm at 6 months (for each, $P = 0.000$). However, no significant differences were found among the three postoperative records ($P = 0.375$, 0.706, 0.609, respectively; Fig. 2).

The amplitude of P1 at baseline was 20.39 ± 3.96 nV/deg^2 in the central ring. After 6-months of follow-up, the increases in the average P1 amplitude of the central ring at all examinations when compared with baseline were significant ($P = 0.008$, 0.001, 0.000, respectively). Similar to the P1 results, examination of N1 amplitude at the 6-month follow-up visit showed a tendency for a good response to intravitreal ranibizumab treatment in the central ring. Compared with the baseline (11.38 ± 2.98), the difference was significant (for each, $P = 0.000$; Fig. 3).

After 6 months, although numerically decreased, the P1 and N1 implicit time in the central ring did not significantly change after three ranibizumab injections when compared with baseline (for P1, $P = 0.406$, 0.250, 0.115; for N1, $P = 0.364$, 0.105, 0.077).

All changes in the mean BCVA, CFT, P1/N1 amplitude and implicit time are shown in relation to the time after IVR in Fig. 4.

At baseline, the association between BCVA as a dependent variable and the P1 amplitude of the central ring was significant ($P = 0.008$); there was also a significant association between BCVA and central N1 amplitude ($P = 0.013$). The association between BCVA and P1/N1 implicit time in the central retina was not significant ($P = 0.766$, 0.512, respectively), but the association between BCVA and CFT was significant ($P = 0.041$) at baseline (Table 2, Fig. 5).

At 6 months, the association between BCVA and the central ring P1 amplitude was also significant ($P = 0.006$); there was also a significant association between BCVA and central N1 amplitude ($P = 0.012$). The association between BCVA and P1/N1 implicit time in the central retina was also not significant ($P = 0.479$, 0.408, respectively), but the association between BCVA and CFT was significant ($P = 0.036$) at 6 months (Table 2; Fig. 5).

Discussion

DME is a complicated process associated with many factors; the pathogenesis is thought to be due to altered permeability of the blood–retinal barrier, which results in fluid accumulation at the macula [2]. The previous treatment standard of DME was laser photocoagulation, but there are different degrees of complication, including lack of an obvious increase in visual acuity

Table 1 Mean BCVA, CFT and mf-ERG (central ring) data

	Baseline	1 month	3 months	6 months
BCVA (Log MAR)	0.80 ± 0.27	0.36 ± 0.14	0.34 ± 0.13	0.38 ± 0.13
CFT (μm)	373.25 ± 59.39	277.26 ± 39.89	266.89 ± 29.77	272.85 ± 36.18
P1 amplitude (nv/deg^2)	20.39 ± 3.96	23.14 ± 3.63	23.98 ± 3.87	24.51 ± 3.43
N1 amplitude (nv/deg^2)	11.38 ± 2.98	14.27 ± 3.02	14.71 ± 2.71	15.29 ± 2.79
P1 implicit time (ms)	41.60 ± 3.84	40.74 ± 3.84	40.41 ± 3.82	39.97 ± 3.69
N1 implicit time (ms)	24.96 ± 1.54	24.57 ± 1.76	24.27 ± 1.40	24.21 ± 1.42

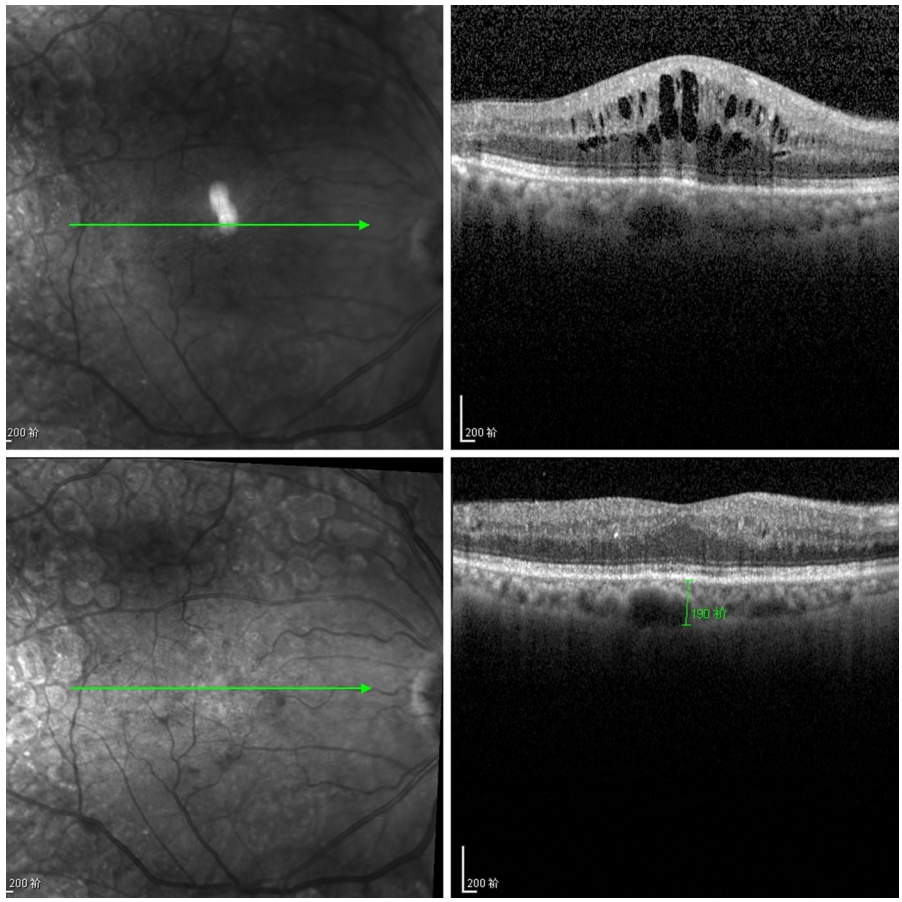

Fig. 2 Representative images obtained from OCT before (*up*) and after (*down*) IVR

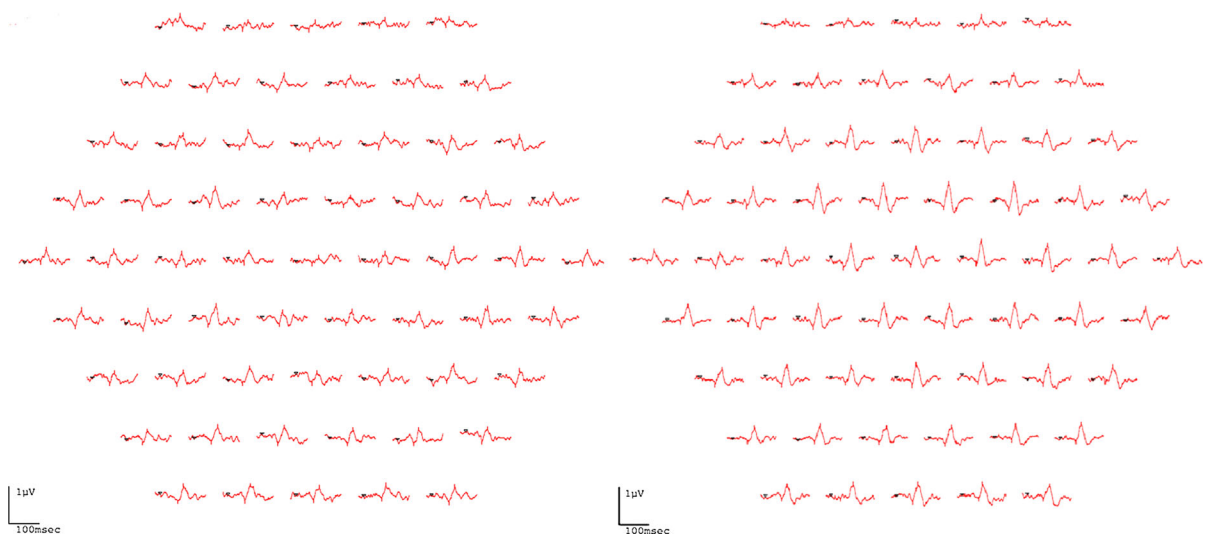

Fig. 3 Trace array before (*left*) and after (*right*) IVR

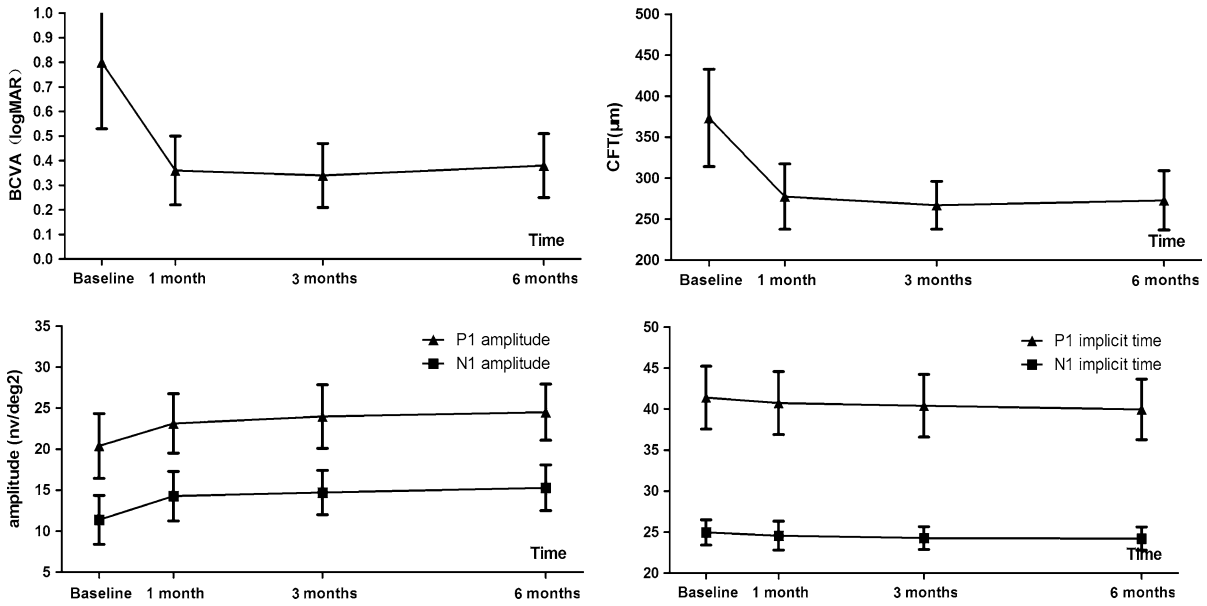

Fig. 4 Change in the mean BCVA, CFT, P1/N1 amplitude and implicit time over time after IVR

Table 2 Regression analysis between BCVA as a dependent variable with CFT and mf-ERG parameters for central ring at baseline and 6 months

	Mean ± SD		*P*	
	Baseline	6 months	Baseline	6 months
CFT(μm)	373.25 ± 59.39	272.85 ± 36.18	0.041	0.036
P1 amplitude (nv/deg^2)	20.39 ± 3.96	24.51 ± 3.43	0.008	0.006
N1 amplitude (nv/deg^2)	11.38 ± 2.98	15.29 ± 2.79	0.013	0.012
P1 implicit time (ms)	41.60 ± 3.84	39.97 ± 3.69	0.766	0.479
N1 implicit time (ms)	24.96 ± 1.54	24.21 ± 1.42	0.512	0.408

and intraocular pressure elevation. A quantity of randomized multicenter researches have proven that repeated IVR have superior outcomes on patients with DME when compared to laser treatment alone [13]. Compared with laser photocoagulation, anti-VEGF therapy can achieve better corrected visual acuity and less visual field defect; the lower incidence of center involving macular edema and vitreous hemorrhage reported in the anti-VEGF group than laser photocoagulation group [14]. Nguyen et al. [15] proposed that anti-VEGF treatment by IVR should be the first-line treatment for DME.

In this study, we observed that IVR significantly improved BCVA from baseline, which was due to the reduction in macular edema (CFT). Our findings are in accordance with previous studies' results concerning the relationship between central retina thickness and visual acuity after IVR [5, 15]. At the same time, we also found that, in five eyes, macular thickness decreased significantly as observed by OCT but the visual acuity was not significantly improved; a decrease in macular thickness without any improvement in vision shows a discrepancy between OCT findings and visual function [16]. Browning et al. [17] mentioned that although correlation between BCVA and CFT, there was a great change in visual acuity at any given retinal thickness, and OCT measurement solely may not be a nice replacement for visual acuity as a main result in researches on DME. OCT can only record the degree of edema; the duration of edema and the damage to cells cannot be evaluated. In contrast, mf-ERG is a technique that through simultaneous stimulation of different regions of the retina [18], retinal function can be mapped in the posterior pole. It has been used for recording local electrophysiological responses of different retinal regions. Yamamoto et al.

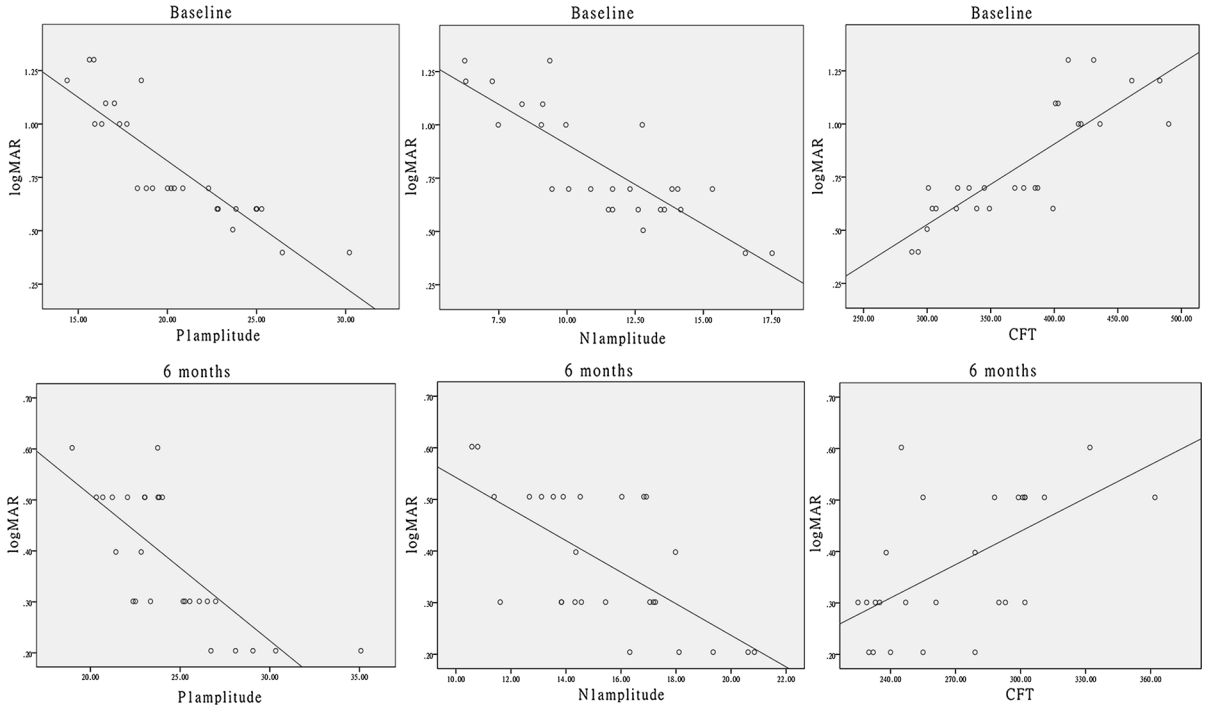

Fig. 5 Scatter plot for the association at baseline and 6 months

[19] showed that mf-ERG readings from the macular area were a good objective indicator of macular function in patients with DME and were strongly correlated with morphologic changes in the macula.

Our study focused on P1 and N1 of the central ring, including amplitude and implicit times. The results have shown that, in addition to improvement in BCVA and reduction in CFT, intravitreal injections of ranibizumab improved macular function as assessed by mf-ERG in diabetic patients. The increases were significant in the average central ring response of P1 and N1 at all examinations, compared with baseline, after IVR.

Hood et al. [20] reported that P1 was generated by Müller and bipolar cells, and N1 was generated by photoreceptors, so a decrease in P1 amplitude mainly reflects functional damage to the inner retina, and a decrease in N1 amplitude shows that the function of the outer retina is compromised. This study found that the effect of DME on the mf-ERG central ring was mainly based on the P1 and N1 amplitude: the amplitude of P1 decreased significantly compared with that of N1. The results showed that DME causes damage to the inner and outer layers of the macular retina, but the inner damage was more obvious than that to the outer layer. Through the observations made during a short period of 6 months after IVR treatment, the central ring amplitude of P1 was most closely related to the BCVA and with the decrease in the CFT. This showed that IVR is not only able to reduce macular edema, but also can aid in the recovery of inner retina cell function.

Significant correlations between BCVA and mf-ERG amplitude have been reported in previous studies of maculopathies [21]. We also found a significant correlation of BCVA, as a dependent variable, with P1 and N1 amplitudes in the central ring at baseline and after 6 months of treatment. Previous studies reported [22] that implicit times were just increased reasonably or still within normal ranges, in spite of amplitudes diminished and severe visual loss, implying that the decrease in visual acuity is not necessarily related to the change in implicit time. Our results were consistent with this report, and the correlation of P1 and N1 implicit times with BCVA was not significant.

Holm et al. [12] found that BCVA and CFT were improved after IVR treatment, but there was no difference in mf-ERG results when compared with baseline; this may be related to the frequency of

intravitreal injection of ranibizumab. Most researchers believe that the injection project of 3 + PRN is the best scheme for IVR [23]. DME can be divided into three types by results of OCT [24]: diffuse retinal thickening (DRT), cystoid macular edema (CME) and serous retinal detachment (SRD). After patients with the three different OCT types of DME had received IVR, differences in macular edema and visual acuity were obvious, and the effect on DRT was the best [25]. Therefore, we believe that, although other the studies have used the same treatment process and injection frequency as ours, the mf-ERG results were obviously different, and this may be related to the different proportion of the different OCT types among the patients with DME. Therefore, use of OCT for DME typing before evaluating the mf-ERG findings may give more reliable results.

All patients had no complications during the follow-up period, and their fast blood glucose levels were stable. Although it is reported that fasting blood glucose levels may affect mf-ERG outcomes [26], no differences in fasting blood glucose were found between the examinations in our study.

In summary, improvements in visual acuity and mf-ERG parameters, and decreases in central foveal thickness, were all maintained for 6 months of follow-up in our patients with DME. Eyes with DME have significantly abnormal mf-ERG responses. Visual acuity was closely correlated with P1 and N1 amplitude in the central ring, based on mf-ERG, showing a greater correlation than with CFT based on OCT. It is important to improve our understanding of DME in order to produce more elaborate suggestions regarding when to begin therapy and when not. These findings indicate that functional changes in the retina of patients with diabetes mellitus assessed by mf-ERG can complement OCT findings. Long-term researches and bigger sample sizes are required for more substantial documentation.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Informed consent Informed consent was obtained from all individual participants included in the study.

Statement of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statement on the welfare of animals This article does not contain any studies with animals performed by any of the authors.

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