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Assessment of Macular Function by Multifocal Electroretinography and Optical Coherence Tomography before and after Panretinal Photocoagulation in Diabetic Retinopathy

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We evaluated macular function before and after panretinal photocoagulation (PRP) in diabetic retinopathy using a multifocal electroretinogram (mfERG) and optical coherence tomogram (OCT). In mfERGs, the 1st positive wave (P1) minus the 1st negative wave (N1) amplitude (P1 – N1 amplitude), the P1 peak latency and the response density were measured in 7, 19, 37 and 103 hexagonal areas or elements (Areas 1, 2, 3 and 4) within a central radius of 5, 7, 10 and 20 degrees, respectively. The mean retinal thickness was estimated from 9 calculation points at the foveal region within 5 degrees; the central and each of the other 4 points at a distance of 250 μm and 500 μm from the central portion on horizontal and vertical sections on OCT. The P1 peak latencies from the 4 areas were remarkably prolonged in 14 eyes of 9 patients with preproliferative or early proliferative diabetic retinopathy showing no clinically significant macular edema before PRP as compared with those in 15 normal control eyes, without a tendency of recovery throughout the course after PRP except for area 1. The P1-N1 amplitudes and the mean response density levels from the 4 areas were remarkably decreased in the diabetic eyes before PRP as compared with those in the control eyes, followed by a maximum decrease in both parameters at 3 months after PRP. However, remarkable recoveries were detected in both decreased parameters from the 4 areas at 6 months after PRP. The mean foveal retinal thickness on OCT was remarkably increased in the diabetic eyes before PRP as compared with the thickness in 16 normal control eyes. Most remarkably, a transient increase in thickness was detected in diabetic eyes 1 month after PRP, followed by a tendency of recovery 3 to 6 months after PRP. These results indicate that mfERG and OCT examinations are useful in the assessment of macular function before and after PRP in diabetic retinopathy, especially within 5 degrees of the central portion, and that the effects of PRP on macular function in this entity seem to be reversible at the foveal region, although we need to do further investigation in relation to the outcome of visual acuity.

Key words: diabetic retinopathy; macular function; multifocal electroretinogram; optical coherence tomogram; panretinal photocoagulation

List of Abbreviations, p. 72.

Panretinal photocoagulation (PRP) is a beneficial procedure for the treatment of preproliferative or early proliferative diabetic retinopathy (Diabetic Retinopathy Study Research Group, 1981; Early Treatment Diabetic Retinopathy Study Research Group, 1991), even though vitrectomy has been performed in many patients with severe and complicated diabetic lesions (Lewis et al., 1992; Massin et al., 2003). On that occasion, the assessment of macular function is very important for predicting the patients' quality of vision after PRP. Several reports showed various changes in retinal sensitivity after PRP in this entity, using mostly the Goldmann kinetic perimeter (Frank, 1975), the computed static perimeter (Chee and Flanagan, 1993; Yoon et al., 1996) and the electroretinogram (ERG) (Frank, 1975; Bresnick and Palta, 1987).

Using an optical coherence tomogram (OCT), Hee and his co-workers (1995, 1998) and Kang and others (2004) quantified foveal retinal thickness correlated with visual acuity in patients with clinically significant diabetic macular edema. Recently, Palmowski and others (1997) and Fortune and others (1999) revealed local retinal dysfunction in the macular area in diabetic patients, with and without retinopathy, using a multifocal electroretinogram (mfERG) (Sutter and Tran, 1992). In general, morphological changes in the retina are assessed by OCT examination because optical coherence tomography offers high-resolution, cross-sectional images of the retina and quantitative measurement of retinal thickness (Hee et al., 1995, 1998; Kang et al., 2004), while topical functional changes in the retinal layer are assessed with mfERG examination, using a multifocal technique (Sutter and Tran, 1992; Palmowski et al., 1997; Fortune et al., 1999).

These tests allow a relatively fast, objective evaluation of retinal function in their images and patterns in contrast to subjective perimetric examinations such as the Goldmann kinetic perimeter (Frank, 1975) and the computed static perimeter (Chee and Flanagan, 1993; Yoon et al., 1996). However, little attention has been paid to the assessment of macular function by mfERG and OCT examinations before and after PRP in diabetic patients with retinopathy. We therefore evaluated macular function before and after PRP in diabetic retinopathy by multifocal electroretinography and optical coherence tomography in this survey.

Subjects and Methods

Nine patients (14 eyes) with preproliferative or early proliferative diabetic retinopathy showing no clinically significant macular edema were referred to us for this study. Their ages ranged from 51 to 77 years averaging 61.2 ± 8.6 years (SD). The mean corrected visual acuity of the 14 diabetic eyes before PRP was 0.87 ± 0.37 (SD), followed by 0.80 ± 0.37, 0.76 ± 0.33 and 0.84 ± 0.38 at 1, 3 and 6 months after PRP, respectively. They were examined using a VERIS Science System for the mfERG (Mayo Corp., Nagoya, Japan) and a Humphrey OCT scanner (Carl Zeiss Co., Ltd., Tokyo, Japan) before PRP and at 1, 3 and 6 months after the procedure, as described later.

Fourteen healthy volunteers (15 normal eyes) aged 51.1 ± 13.1 years (SD) on the average served as controls for the VERIS study, and 12 healthy volunteers (16 normal eyes) aged 66.1 ± 12.5 years (SD) on an average served as controls for the OCT study in the present estimation. These healthy volunteers were randomly divided into either study group.

The diabetic patients were randomly chosen for the present survey over the past 4 years (August 1996 to September 2000) at the Department of Ophthalmology, Tottori University Hospital. The tenets of the Declaration of Helsinki were followed. Upon giving informed consent, all subjects including volunteers participated in the present study. Error of refraction did not exceed ± 3 diopters in the diabetics or normal controls. Eyes with clouding of the media or subjected to previous surgery were excluded from the analysis.

Abbreviations: ERG, electroretinogram; ETDRS, Early Treatment Diabetic Retinopathy Study; mfERG, multifocal electroretinogram; N1, 1st negative wave; OCT, optical coherence tomogram; P1, 1st positive wave; PRP, panretinal photocoagulation

PRP procedure

Treatment with PRP on the diabetic patients was performed according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol (Diabetic Retinopathy Study Research Group, 1981; Early Treatment Diabetic Retinopathy Study Research Group, 1991). All patients underwent PRP in 2 sittings 1 week apart, lower hemifield followed by upper hemifield. Photocoagulation covered the entire mid periphery beyond the equator, and posteriorly to the area bordered by the temporal vascular arcades, nasal disc border and 2-disc diameter temporal to the fovea. All eyes were treated with either a green argon laser (Coherent Inc., Palo Alto, CA) or a dye laser (Biophysic Medical Ins., Clermont-Ferrand, Cedex, France). Approximately 1,000 to 2,000 burns of a 200 to 500 μm spot size were made 1 to 2 burn spaces apart through a 3-mirror universal lens (Ocular Instruments Inc., Bellevne, WA) or a double aspheric lens Trans Equator or Quadr Aspheric (Volk Optical Inc., Mentor, OH).

mfERG examination

The VERIS Science System, which is a visual evoked response imaging system originally developed by Sutter and Tran (1992), was used for the mfERG recording. The mfERG stimulus matrix consisted of 103 concentrically scaled hexagons, which covered the fundus area within a central radius of 20 degrees (Fig. 1). Alternated color changes were set in each hexagon between black and white in binary m-sequences at a rate of 75 Hz. Luminance levels ranged from 5 to 200 cd/m^2. A Burian-Allen bipolar contact lens electrode was used for signal derivation. A grounding electrode was attached to either earlobe, a routine procedure. The pupil of one eye was fully dilated with 2.5% phenylephrine hydrochloride, and the other eye was occluded. The net recording time for each eye was 4 min. The entire procedure was divided into eight 30-s segments. The signals were amplified using the VERIS Science System with bandpass filters (10–300 Hz).

As demonstrated in Fig. 2, in the response arrays of the mfERG consisting of the mean focal flash response (Fig. 2a), the 1st positive wave of each mean focal flash response (P1) minus the 1st negative wave of each response (N1) amplitude (P1 – N1 amplitude) in μV and the P1 peak latency in ms were measured as mfERG parameters in 7, 19, 37 and 103 hexagonal areas or elements (Areas 1, 2, 3 and 4; 4 mfERG areas) within a central radius of 5, 7, 10 and 20 degrees, respectively (Fig. 1). Three-dimensional topography revealed the re-

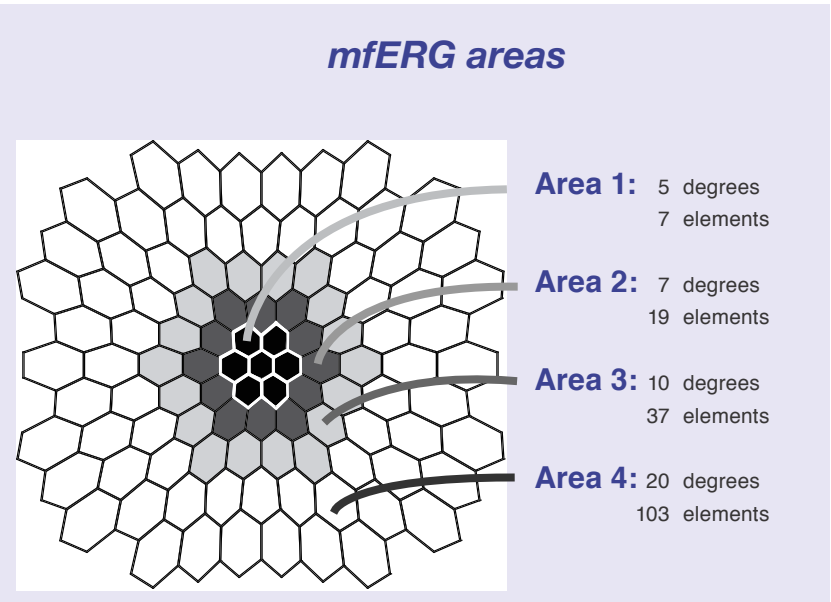


Fig. 1. The multifocal electroretinogram (mfERG) stimulus matrix consisting of 103 concentrically scaled hexagons. The matrix was divided into 7, 19, 37 and 103 hexagonal areas or elements (Areas 1, 2, 3 and 4; 4 mfERG areas) within a central radius of 5, 7, 10 and 20 degrees, respectively.

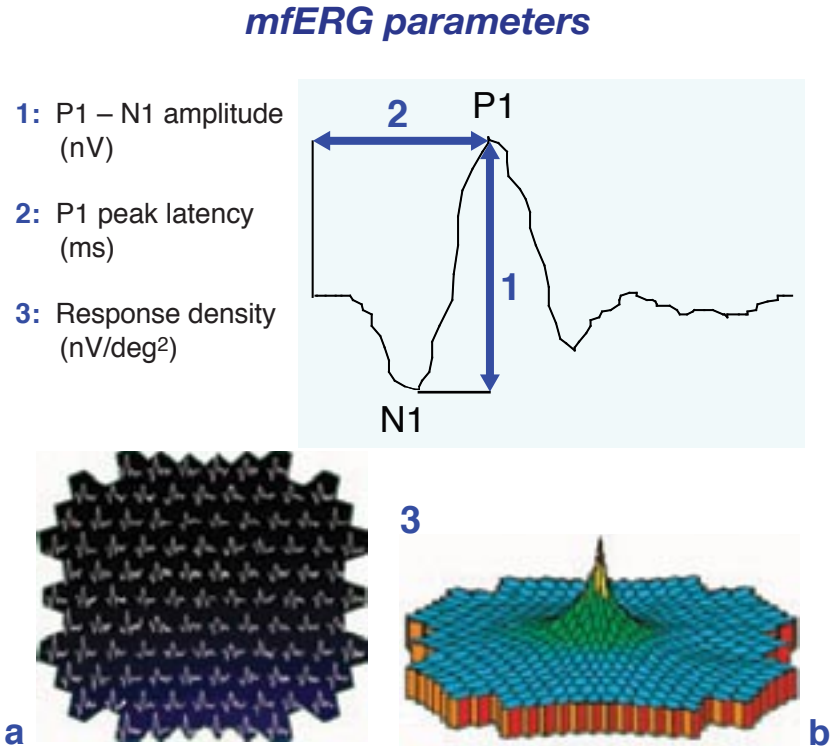


Fig. 2. Multifocal electroretinogram (mfERG) parameters calculated in this survey. The P1 and N1 indicate the 1st positive and negative wave of each mean focal flash response in the response arrays of the mfERG (**a**), respectively. The 3-dimensional topograph (**b**) represents the response density in each hexagonal area (amplitude per retinal area: nV/deg^2). The mfERG parameters, that is, the P1 – N1 amplitude, the P1 peak latency and the response density are demonstrated as 1, 2 and 3 in this figure, respectively.

sponse density in each hexagonal area in amplitude per retinal area (nV per degree squared: nV/deg^2) in the topograph (Fig. 2b). The response density was also adopted as one of the mfERG parameters (Fig. 2) and measured in the 4 mfERG areas in this survey. The recording procedure was repeated at the time when spurious potentials from eye blinks on ocular movement were involved.

OCT examination

Optical coherence tomography was used for measurement of retinal thickness in μm. The optical coherence tomography system was interfaced using fiber optics to a conventional slit-lamp biomicroscope and a fixed +78-diopter condensing lens for retinal examination. An infrared-sensitive video camera provided a view of the scanning probe beam on the fundus so that the location of each scan on the retina could be monitored. A computer-controlled light placed in the visual field fixated the eye being scanned. Fine positioning for the OCT examination on the retina was accomplished by keyboard control for scan length, angular orientation and position relative to the patient's fixation point.

The mean retinal thickness was estimated from 9 calculation points at the foveal region within 5 degrees in the thickness estimation in the averaged OCT scans by our computer program, that is, the central and each of the other 4 points at a distance of 250 μm and 500 μm from the central portion on horizontal and vertical sections in linear pattern on OCT (Fig. 3). Retinal thickness was measured at the distance between the strongest 2 edges in each tomogram, which most likely corre-

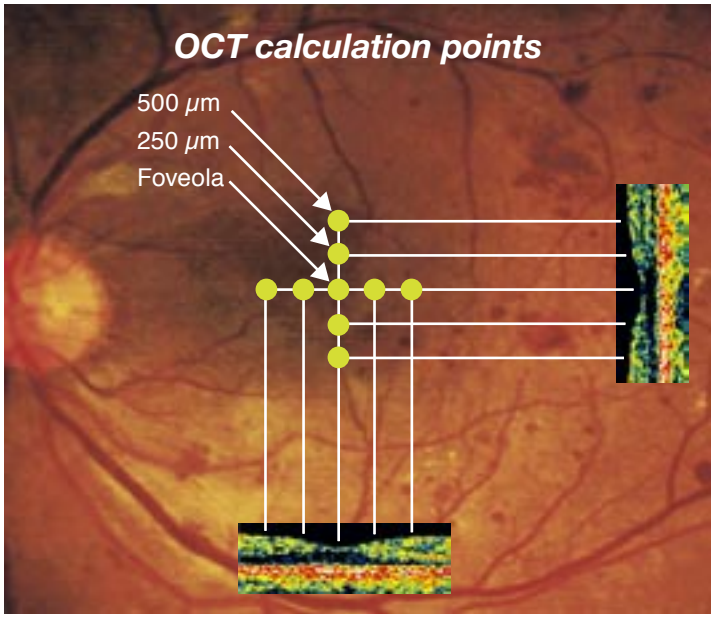


Fig. 3. Calculation points on optical coherence tomogram (OCT). The mean retinal thickness was estimated from 9 calculation points at the foveal region within 5 degrees; the central and each of the other 4 points at a distance of 250 μm and 500 μm from the central portion on the horizontal and vertical sections on OCT. Horizontal and vertical cross-sectional tomographic images are inserted in this figure.

sponded to the vitreoretinal interface and the retinal pigment epithelium, respectively.

We not only used the retinal thickness program, but also hard copies of each OCT image for checking errors, because the layer of cystoid macular edema was sometimes detected as the edge of the retinal pigment epithelium and the detached vitreoretinal membrane was also detected as the edge of the vitreoretinal interface. In OCT measurement, the subject's pupil was fully dilated with 2.5% phenylephrine hydrochloride.

Statistical analysis

All values obtained in the mfERG and OCT examinations were expressed as mean ± SEM. Statistical analysis was performed with Mann-Whitney's *U* test. A *P* value of < 0.05 was considered statistically significant.

Results

The P1 peak latencies obtained from the 4 mfERG areas were significantly prolonged in the 14 eyes of the 9 patients with preproliferative or early proliferative diabetic retinopathy who showed no clinically significant macular edema before PRP as compared with those in 15 normal control eyes of 14 healthy volunteers at level of 1%, with no tendency for recovery throughout the course after PRP except for area 1 (within a central radius of 5 degrees) (Fig. 4).

The P1 – N1 amplitudes obtained from the 4 mfERG areas were significantly decreased in the 14 diabetic eyes before PRP as compared with those in the 15 control eyes at the 1% or 5% level, followed by a maximum decrease in the parameter 3 months after PRP. However, significant recoveries were detected in the decreased P1 – N1 amplitudes from the 4 areas at 6 months after PRP at the 1% or 5% level (Fig. 5).

The mean response density levels obtained from the 4 mfERG areas also showed almost the

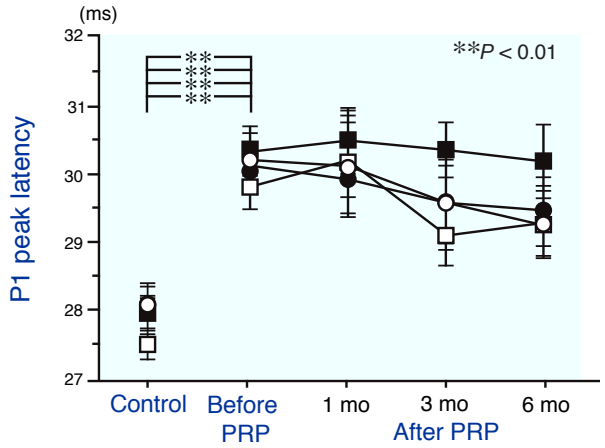


Fig. 4. Changes in the P1 peak latencies of the mfERG obtained from 4 mfERG areas in 14 diabetic eyes before and after PRP. The diabetic eyes were derived from 9 patients with preproliferative or early proliferative diabetic retinopathy showing no clinically significant macular edema in this series. All values were expressed as mean ± SEM. Each bar indicates SEM. ** indicates $P < 0.01$ by Mann-Whitney's U test. PRP, panretinal photocoagulation; mo, month(s). Control: 15 normal control eyes of 14 healthy volunteers.

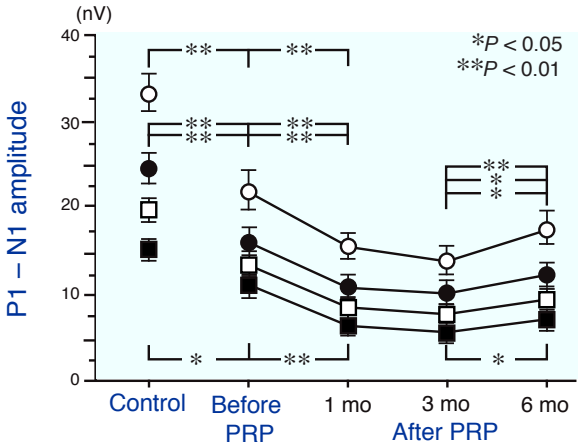
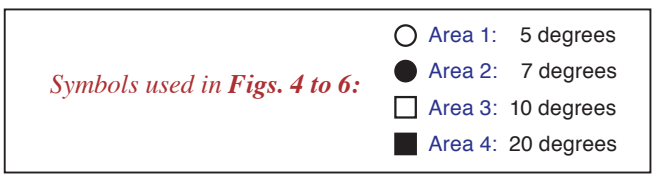


Fig. 5. Changes in the P1 – N1 amplitudes of the mfERG obtained from 4 mfERG areas in 14 diabetic eyes before and after PRP. All values were expressed as mean ± SEM. Each bar indicates SEM. * indicates $P < 0.05$, and ** indicates $P < 0.01$ by Mann-Whitney's U test. PRP, panretinal photocoagulation; mo, month(s). Control: 15 normal control eyes of 14 healthy volunteers.



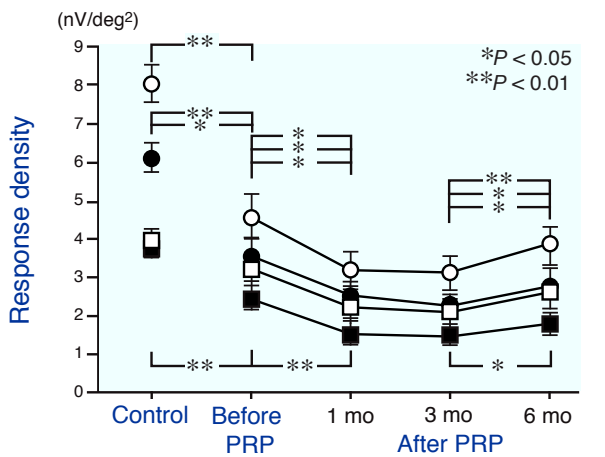


Fig. 6. Changes in the mean response density levels of the mfERG obtained from 4 mfERG areas in 14 diabetic eyes before and after PRP. All values were expressed as mean ± SEM. Each bar indicates SEM. * indicates $P < 0.05$, and ** indicates $P < 0.01$ by Mann-Whitney's U test. PRP, panretinal photocoagulation; mo, month(s). Control: 15 normal control eyes of 14 healthy volunteers.

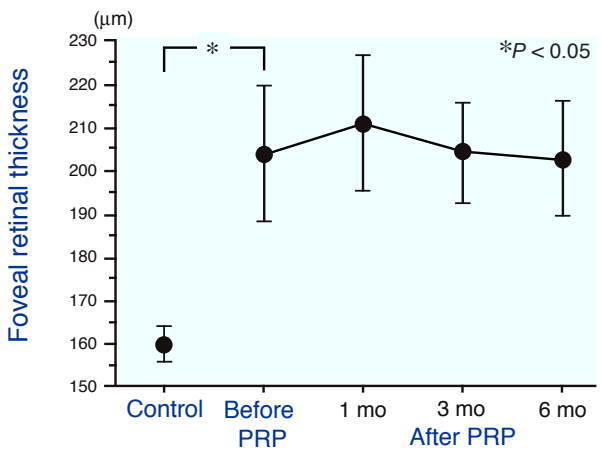


Fig. 7. Changes in the mean foveal retinal thickness within 5 degrees on OCT in 14 diabetic eyes before and after PRP. All values were expressed as mean ± SEM. Each bar indicates SEM. * indicates $P < 0.05$ by Mann-Whitney's U test. PRP, panretinal photocoagulation; mo, month(s). Control: 16 normal control eyes of 12 healthy volunteers.

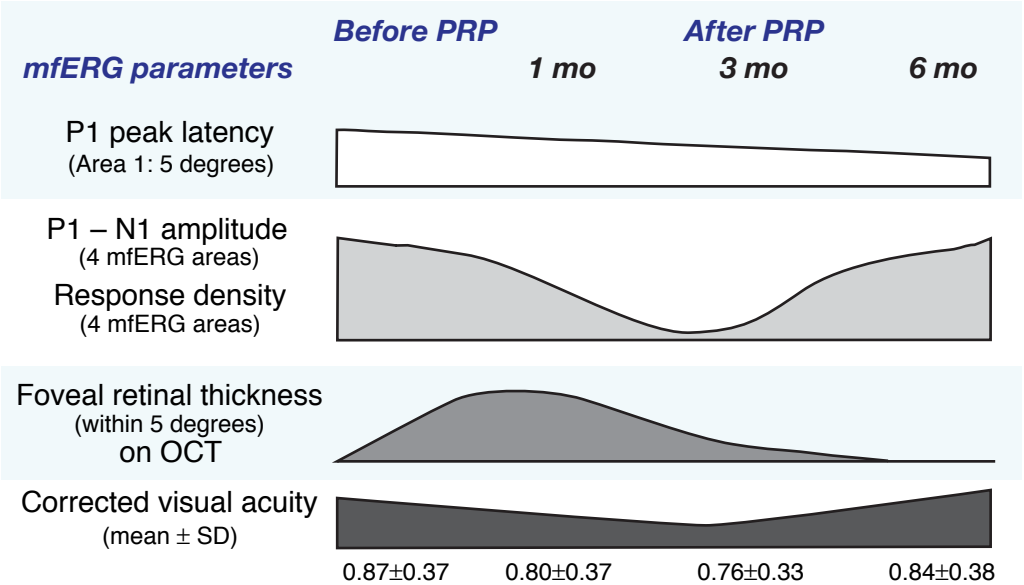


Fig. 8. Summarized data obtained in the present study before and after PRP in 14 diabetic eyes. In the mfERG parameters, the P1 peak latency from the area 1 (within a central radius of 5 degrees), the P1 – N1 amplitudes and the mean response density levels from the 4 mfERG areas are presented at 1, 3 and 6 months after PRP following each data before PRP in addition to the mean foveal retinal thickness within 5 degrees on OCT. The mean corrected visual acuity in the 14 diabetic eyes is also presented throughout the course. PRP, panretinal photocoagulation; mo, months(s).

same tendency as in the P1 – N1 amplitudes, as shown in Fig. 6. That is, the mean response density levels from the 4 areas were remarkably decreased in the 14 diabetic eyes before PRP as compared with those in the 15 control eyes at the 1% or 5% level, followed by a maximum decrease in the parameter at 3 months after PRP. However, remarkable recoveries were detected in the mean response density levels from the 4 areas at 6 months after PRP at the 1% or 5% level.

The mean foveal retinal thickness within 5 degrees on OCT was significantly increased in the 14 diabetic eyes before PRP as compared with the thickness in the 16 control eyes of the 12 healthy volunteers at the 5% level. Most remarkably, a transient increase in the thickness was detected in the diabetic eyes at 1 month after PRP, followed by a tendency for recovery at 3 to 6 months after PRP (Fig. 7).

Discussion

As summarized in Fig. 8, in the mfERG parameters, the P1 peak latency from the area 1 (within a central radius of 5 degrees) was markedly prolonged in the 14 diabetic eyes before PRP as compared with that in the 15 control eyes, but a tendency for recovery was detected throughout the course after the procedure (Fig. 4).

The P1 – N1 amplitudes and the mean response density levels from the 4 mfERG areas were remarkably decreased in the diabetic eyes before PRP as compared with those in the control eyes, followed by a maximum decrease in both parameters at 3 months after PRP. However, remarkable recoveries were detected in both decreased parameters from the 4 areas at 6 months after PRP (Figs. 5, 6 and 8).

The mean foveal retinal thickness within 5 degrees on OCT was remarkably increased in the diabetic eyes before PRP as compared with the

thickness in the 16 control eyes. Most remarkably, a transient increase in the thickness was detected in the diabetic eyes at 1 month after PRP, followed by a tendency of recovery at 3 to 6 months after the procedure (Figs. 7 and 8).

This time, statistical analysis was not undertaken on the correlation between the corrected visual acuity and each data from the mfERG or OCT examinations before and after PRP in each diabetic eye due to the relatively small number of samples. However, as demonstrated in Fig. 8, it is of note that the mean corrected visual acuity before PRP in the 14 diabetic eyes showed a gradual decrease at 1 month, followed by a maximum decrease at 3 months and a tendency of gradual recovery at 6 months after the procedure in each mean corrected visual acuity in those eyes, as in the changes in the P1 – N1 amplitudes and the mean response density levels of the mfERG obtained from the 4 mfERG areas in the 14 diabetic eyes before and after PRP.

The OCT findings showed no coincidental changes between mean foveal retinal thickness and mean corrected visual acuity in the 14 diabetic eyes throughout the course after PRP. However, tendency of recovery in mean foveal retinal thickness at 3 to 6 months after PRP may reflect a reversible foveal function resulting in a gradual recovery of the mean corrected visual acuity at 6 months after the procedure in diabetic eyes (Fig. 8), although we need to do further investigation on this point in more subject patients.

The mfERG derived from the fundus area, especially within 5 degrees of the central portion (Area 1) is supposed to reflect a cone-dominated response, which originates predominantly in the outer 70% of the retina, as in the full-field flash ERG (Hood et al., 1997; Palmowski et al., 1997; Fortune et al., 1999).

Optical coherence tomography provides noninvasively a cross- sectional tomographic image of the retina as described above and is more sensitive to small changes in retinal thickness than slit-lamp biomicroscopy (Hee et al., 1995, 1998; Kang et al., 2004).

Thus, the results obtained in the present survey indicate that the mfERG and OCT examinations are useful for assessment of macular function before and after PRP in diabetic retinopathy, especially within 5 degrees of central portion, and that the effects of PRP on the macular function in this entity seem to be reversible at the foveal region, although we need a further investigation in relation to the outcome of visual acuity.

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