• Clinical Research •

Correlation between optical coherence tomography, multifocal electroretinogram findings and visual acuity in diabetic macular edema

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Abstract

● **AIM:** To analyze the correlation between macular morphology and function in eyes with diabetic macular edema (DME).

● **METHODS:** Fifty-five eyes with different visual acuity (VA) of 32 patients who suffered from DME were analyzed using multifocal electroretinography (mfERG) and optical coherence tomography (OCT). The parameters of mfERG including implicit times and response amplitude were compared to those of 50 normal eyes of 36 age-matched subjects. Correlation analysis was performed between VA, the parameters of mfERG including implicit times and response amplitude, and the central macular thickness (CMT).

● **RESULTS:** The amplitude of N1 and P1 were significantly decreased and their latency were significantly increased in five ring regions of the retina in patients with DME. There was statistically significant correlation between logMAR BCVA and P1 amplitude densities in rings 1-4 (r=-0.306, -0.536, -0.470, -0.362; P=0.023, <0.01, <0.01, 0.007 respectively), N1 amplitude in ring 2 and ring 3 (r=-0.035, -0.286; P=0.019, 0.034 respectively). There was poor correlation between the CMT and best-corrected visual acuity (BCVA; r=0.288, P=0.033), but there was no significant correlation between CMT and amplitude or implicit time of N1 and P1 (P>0.05) in the central macular ring. Multiple stepwise regression analysis showed that P1 amplitude density in ring 2 was the only contributor to the VA.

● **CONCLUSION:** It seems to be more appropriate of combining use of mfERG with OCT for the evaluation of macular function in eyes with DME.

● **KEYWORDS:** diabetic macular edema; optical coherence tomography; multifocal electroretinography; best-corrected visual acuity

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INTRODUCTION

Diabetic retinopathy (DR) and diabetic macular edema (DME) are the major complications in diabetes that can lead to visual impairment and blindness affecting more than 20 million people worldwide[1]. Although some studies have showed that timely treatment of DR and DME can significantly reduce the risk of visual complications, it was alarmed that visual impairment caused by DR and DME increased 64% over the last two decades globally[2].

As a noninvasive technique, optical coherence tomography (OCT) can provide information regarding the morphology of the retina, especially of the macular area *in vivo*. Some studies support the idea that OCT determines structural changes in the macula that are correlated with subjective visual function in patients with DME[3]. Additionally, it has been assessed that multifocal electroretinography (mfERG) is also an objective, non-invasive method in detecting subclinical DR and assessig changes in the retinal function of diabetic patients[4-5]. Moreover, mfERG allows atopographic mapping of retinal dysfunction in DR[6]. Some reports have concerned the combined use of mfERG and OCT for studying the correlation between retinal morphology and function of the macula in patients with different eye diseases[7-13]. The purpose of our study was to investigate the usefulness of mfERG in the detection of changes of macular function, and to determine whether a significant correlation exists between the amplitude or implicit time of mfERG and the retinal thickness in the central area of the macula in patients with DME.

SUBJECTS AND METHODS

Ethical Approval The study was conducted in accordance

with the tenets of the Declaration of Helsinki, and was approved by the Institutional Review Board of Joint Shantou International Eye Center of Shantou University and the Chinese University of Hong Kong (JSIEC). Informed consent was obtained from each patient after they were provided with an explanation of the nature of the study.

Involvement or threatening of the center of the macula was termed clinically significant macular edema (CSME) by the Early Treatment Diabetic Retinopathy Study (ETDRS)[14-15]. The study was based on 55 eyes of 32 type 2 diabetes patients (11 males and 21 females) with CSME, examined in JSIEC from January 2018 to December 2019. Also, 50 normal eyes of 36 age-matched subjects (21 males and 15 females) of the same period served as control group. The exclusion criteria were as follows: 1) having any disease other than DR that could impact visual function; 2) having previously received laser or intravitreal treatment in the examined eye; 3) being unable to perform reliable mfERG and OCT tests.

Ophthalmic Examinations A comprehensive ophthalmic examination, including noncontact tonometry, best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, fundus photography, OCT recordings, and mfERG recordings were performed for each patient included in this study. In addition, fluorescein angiography and OCT were conducted to confirm the diagnosis of CSME.

Optical Coherence Tomography OCT examination was performed with the Topcon 3D OCT-2000 (Topcon Corporation, Tokyo, Japan). Macula was scanned using standard 6×6 mm^2 protocol, in which 3D acquisition consisted of 64 B-scan slices. Fundus photographs were obtained from each subject at the same time. The distance between inner surface of the retinal pigment epithelium and vitreoretinal interface at fovea was defined as the central macular thickness (CMT).

Multifocal Electroretinography Measurements MfERG was performed according to the guidelines of the International Society for Clinical Electrophysiology of Vision[16] using RETI Scan multifocal system (Roland Consult, Brandenburg, Germany). The viewing distance was 26 cm with a viewing angle of approximately 30°. The stimulus consisted of 61 hexagons. 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 frontocentral and external canthus, respectively. Pupils were dilated with 0.5% tropicamide for all of the measurements. Measurements were performed after near addition to the other refractive error corrections. P wave amplitude and P wave implicit times were taken into consideration during evaluation. P wave amplitude was measured as the highest positive wavelength and P implicit time was measured as time interval between negative and positive peak points. P wave amplitude values and P wave implicit times were analyzed in rings.

The mfERG stimuli location and anatomic areas corresponded roughly as follows: ring 1 to the fovea (0-2°), ring 2 to the parafovea (2°-7°), ring 3 to the perifovea (7°-13°), ring 4 to the near periphery (13°-22°), and ring 5 to the central part of the middle periphery (22°-30.5°).

In the first step, we compared mfERG amplitudes and latencies of N1 and P1, between control and DME eyes in the five-ring retinal regions. In the next step, correlation analysis was performed among BCVA, CMT, and mfERG amplitude and latency measurements.

Statistical Analysis Statistical analysis was performed using SPSS13.0 (IBM, Armonk, New York, USA). Comparison of data was performed using independent-samples *t* test. Pearson correlation analyses were performed for correlation analysis. Multivariate stepwise linear regression analyses by stepwise selection approaches were performed to investigate the relationship between the VA and other values. *P* values less than 0.05 were considered as statistically significant.

RESULTS

Mean age of the DME patients was 60.09±7.76y, ranging from 46 to 76y. Mean BCVA was 0.52±0.34 logMAR. Mean CMT was 269±157 μm ranging from 133 to 849 μm.

The mean age of controls was 56.03±9.64y, ranging from 28 to 73y, which was not statistically significant compared with the patient eyes (t=1.901, P=0.062).

Comparisons of P1, N1 amplitude, P1, and N1 implicit time, between diabetic patients and controls, are shown in Table 1. There were significant differences in all mfERG parameters in five ring regions of the retina between the DME and control groups.

Correlation analysis among logMAR BCVA, CMT and mfERG values are shown in Table 2. Statistical analysis showed that there was statistically significant correlation between logMAR BCVA and P1 amplitude densities in rings 1-4 (r=-0.306, -0.536, -0.470, -0.362; P=0.023, <0.01, <0.01, 0.007, respectively), N1 amplitude in rings 2 and 3 (r=-0.035, -0.286; P=0.019, 0.034; Table 2, Figure 1).

There was poor correlation between the CMT and BCVA (r=0.288, P=0.033; Figure 2), but there was no statistically significant correlation between CMT and mfERG parameters (amplitude and latency) in the central macular ring (Table 3).

The contribution of CMT and mfERG values in defining for logMAR BCVA was tested through multiple linear stepwise regression analysis. Parameters (including CMT, P1 amplitude densities in rings 1-4, N1 amplitude in rings 2 and 3) that had statistically significant correlation with logMAR BCVA were considered for the model as potential predictors. Multiple linear regression equation: Y=0.986-0.011X1, X1=P1 amplitude densities in ring 2, R=0.536.

Table 1 Comparisons of P1, N1 amplitude, P1 and N1 implicit time, between DME patients and controls mean±SD

Group	P1 amplitude (nV/deg^2)	N1 amplitude (μV)	P1 implicit time (ms)	N1 implicit time (ms)
Ring 1				
DME	68.44±31.74	0.41±0.33	40.28±5.29	19.66±5.72
Control	130.55±32.05	0.60±0.23	34.95±2.11	16.51±2.25
t	-9.970	-3.385	6.896	3.768
P	<0.01	0.001	<0.01	<0.01
Ring 2				
DME	42.86±17.02	0.30±0.12	38.39±3.66	20.01±3.66
Control	76.01±18.38	0.52±0.15	32.68±1.54	15.46±2.10
t	-9.595	-8.370	10.565	7.885
P	<0.01	<0.01	<0.01	<0.01
Ring 3				
DME	31.15±11.00	0.30±0.11	37.80±2.84	19.41±2.85
Control	45.87±11.79	0.45±0.11	31.90±1.15	15.01±2.09
t	-6.622	-6.787	14.219	8.952
P	<0.01	<0.01	<0.01	<0.01
Ring 4				
DME	23.20±7.95	0.32±0.10	38.95±3.26	20.43±2.72
Control	32.42±8.44	0.47±0.13	32.80±1.38	15.17±1.81
t	-5.764	-6.595	12.788	11.766
P	<0.01	<0.01	<0.01	<0.01
Ring 5				
DME	17.23±6.10	0.36±0.11	39.55±3.36	21.47±2.57
Control	22.89±6.00	0.49±0.13	33.48±1.61	16.69±1.63
t	-4.782	-5.844	11.957	11.501
P	<0.01	<0.01	<0.01	<0.01

Table 2 Correlation analysis among logMAR BCVA, CMT and mfERG values

Rings	BCVA	*r*	*P*
CMT		0.288	0.033
Ring 1	P1 amplitude	-0.306	0.023
	N1 amplitude	-0.132	0.336
	P1 implicit time	0.263	0.052
	N1 implicit	0.086	0.534
Ring 2	P1 amplitude	-0.536	<0.01
	N1 amplitude	-0.315	0.019
	P1 implicit time	0.226	0.097
	N1 implicit	0.142	0.301
Ring 3	P1 amplitude	-0.470	<0.01
	N1 amplitude	-0.286	0.034
	P1 implicit time	0.231	0.090
	N1 implicit	0.103	0.454
Ring4	P1 amplitude	-0.362	0.007
	N1 amplitude	-0.214	0.117
	P1 implicit time	0.211	0.122
	N1 implicit	0.172	0.209
Ring 5	P1 amplitude	-0.260	0.055
	N1 amplitude	-0.125	0.362
	P1 implicit time	0.158	0.250
	N1 implicit	0.086	0.535

CMT: Central macular thickness.

Table 3 Correlation analysis between CMT and mfERG values in the first ring

mfERG parameters	*r*	*P*
P1 amplitude	-0.259	0.056
N1 amplitude	0.061	0.658
P1 implicit time	0.172	0.208
N1 implicit	0.073	0.595

CMT: Central macular thickness; mfERG: Multifocal electroretinography.

DISCUSSION

The mfERG can examine retinal responses from many localised regions and can provide a functional assessment, solving the limitation of full-field ERGs in detecting localised lesions, as well as the limited test field of focal ERGs[17-18]. Some researches have studied the feature of mfERG at different stages of DR[19-20], our purpose was to analyze the correlation between macular morphology and function in eyes with DME. Previous studies[8-9,19] have revealed that the values of mfERG in DME were reduced in the central retina. Consistent with previous reserches, our study showed that the amplitude of N1 and P1 were significantly decreased and their latency were significantly increased in five ring regions of the retina in patients with CSME. The changes in the values of mfERG shows that visual function impairment of DME occurred in areas not only at fovea but also beyond fovea, which was consistent with extensive macular edema to perifovea in OCT figures. The P1 wave forms of mfERG are considered

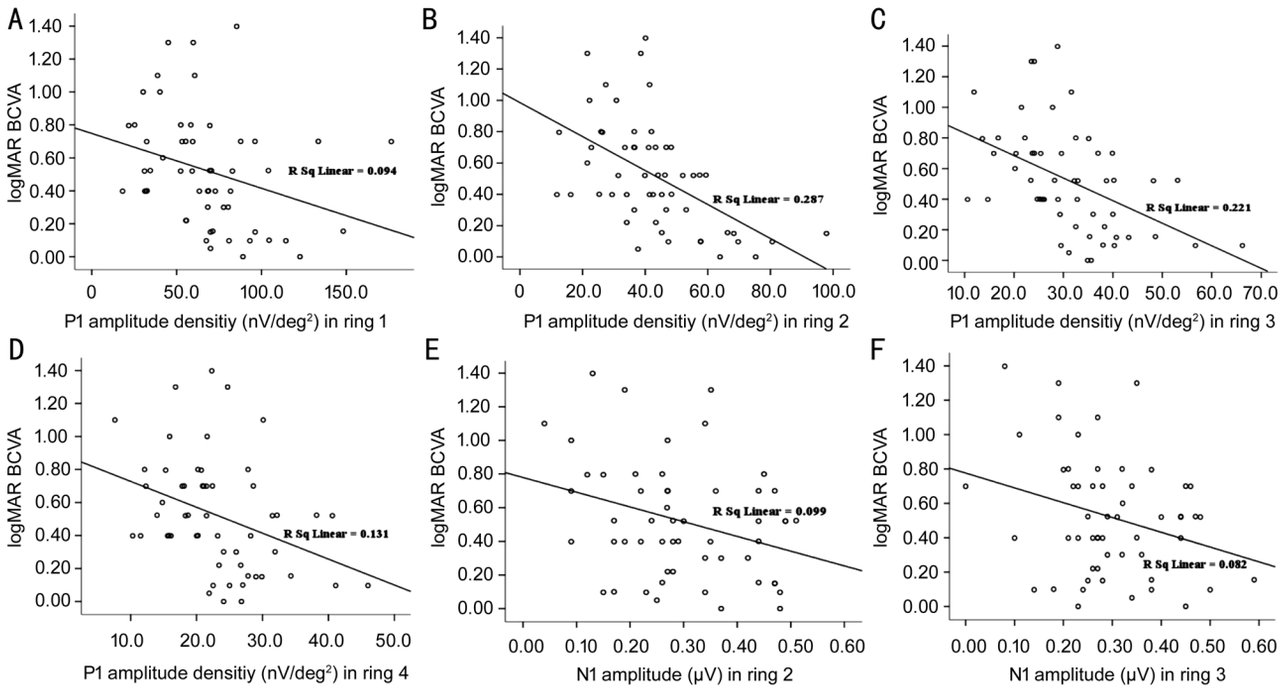

Figure 1 Correlation between logMAR BCVA and P1 amplitude densities in rings 1-4 (A-D), N1 amplitude in rings 2 and 3 (E, F).

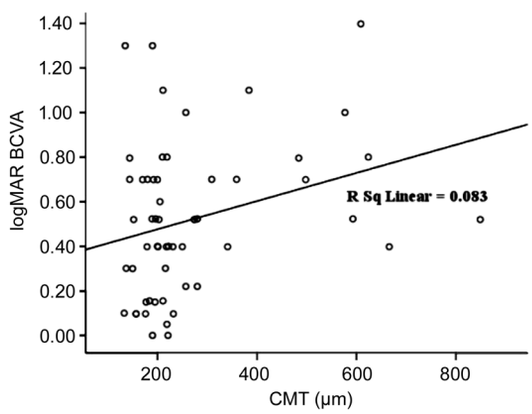

Figure 2 Correlation between of BCVA and CMT.

to originate from Müller and bipolar cells in the inner retinal layer, but those of N1 wave are believed to originate from photoreceptors in the outer retinal layer[21-23]. It seems that mfERG characteristics could be used to examine outer retinal function and monitor impairment of the photoreceptors[17].

In our study, significant correlations were found between logMAR BCVA and P1 amplitude densities in rings 1-4, N1 amplitude in rings 2 and 3 in eyes with CSME. This result is different from previous report[4,8]. Only the ring 1 and ring 2 responses of the N1 and P1 waves that could reflect fovea and parafovea function respectively were used for analysis in previous studies. In the present study, we focused on the correlations between BCVA and CMT, N1, P1 and their characteristics including amplitude and latency in all the five rings. Because in the clinical observation, we found a large area of the patients' retina was affected by DME.

The retinal thickening and edema are the major causes of vision losses in DME patients. In our study, multiple stepwise regression analysis indicated P1 amplitude density in ring 2 was the only factor that correlated with the VA. Although it remains unclear that how the cellulars were impaired underlying DME, we believed that the changes of P1 wave especially P1 amplitude density in ring 2 in this study may reflect the inner retina layer damages induced by CSME, which seemed to play an important role in vision loss.

Concerning the OCT findings, our results showed that there was no significant correlation between CMT and amplitude or implicit time of N1 and P1 (P>0.05) in the central macular ring, but there was poor correlation between the CMT and BCVA (r=0.288, P=0.033). Previous studies[17] have showed that the VA was negatively correlated with the CMT. Browning *et al*[24] mentioned, despite a modest correlation, there was substantial variation in VA at any given retinal thickness. Many eyes with normal CMT had decreased VA, and many eyes with thickened macula had excellent VA. These results suggest that OCT measurement alone may not be a good surrogate for VA as a primary outcome in studies on DME[24].

The current study is rare in that it correlates electrophysiology (mfERG), VA and OCT in DME patients and compares to age-similar controls in order to explore electrophysiology-function correlation. Understanding these relationships may provide insights for possible therapeutic interventions to improve vision in DME.

Many studies have indicated that the corresponding macular function of macular lesions changes, even if there is no significant change in histomorphology. This further demonstrates that the mfERG is sensitive to detecting lesions, especially at the macula. Thus, only a histological examination,

accompanied by functional inspection, can reflect fully the real status of the retinal condition in different stages.

There are two limitations in our study. A relative small sample size was included, which might influnce mfERG values and statistical analysis. Also, the mfERG abnormalities as described here needs further study.

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