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ORIGINAL RESEARCH ARTICLE

Photoreceptor dysfunction in early and intermediate age-related macular degeneration assessed with mfERG and spectral domain OCT

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Abstract
Purpose To evaluate the changes of the photoreceptor layer (PRL) thickness with spectral domain optical coherence tomography (SD-OCT) and the retinal function by mfERG, as well as the correlation of morphology and function parameters in subjects with early and intermediate age-related macular degeneration (AMD).
Methods Subjects with clinical diagnosis of early or intermediate AMD and age-matched healthy subjects were recruited prospectively in this study. Color fundus photography, SD-OCT, and mfERG were conducted. Retinal photoreceptor thickness was measured, and first-order kernel responses were recorded. The differences between AMD group and control group were compared, and the correlations between macular photoreceptor thickness and the mfERG were analyzed.
Results PRL thickness (μm) in four areas including foveola and 0.5, 1.5, and 3 mm away from foveola was 192.48 ± 17.37, 163.73 ± 12.95, 130.93 ± 9.20, and 108.78 ± 7.81, respectively, in normal eyes, whereas in AMD group, they were 158.61 ± 45.25, 138.91 ± 20.92, 118.91 ± 12.85, and 95.00 ± 9.64, respectively ($P < 0.001$). The mean amplitude response densities of AMD patients decreased significantly compared to the control group in ring 1–6 ($P < 0.001$). The mean mfERG N1 and P1 latency of AMD patients prolonged compared to the control group, except the ring 1 ($P = 0.588$ and $P = 0.084$). The macular PRL thickness was significantly associated with the mfERGN1 and P1 amplitude density in ring 1–4 ($r = 0.338$–0.533, $P < 0.01$).
Conclusions PRL thickness decreases are in accordance with the deterioration of retinal electrophysiological activity. The retinal PRL thickness is important parameter to assess of early and intermediate AMD severity.

Keywords Age-related macular degeneration · Drusen · Photoreceptor · Multifocal electroretinography · Optical coherence tomography

Introduction

Age-related macular degeneration (AMD), especially neovascular AMD, is the leading cause of blindness in people aged over 60 years in developed countries. Neovascular AMD accounts for about 75 % of the patients with severe vision loss in AMD [1]. Although vascular endothelial growth factor inhibitors and photodynamic therapy can reduce vision loss effectively,

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there are increasing problems such as endophthalmitis, retinal pigment epithelium (RPE) tear, and high cost of treatment coming with frequently repeated treatment [2–4]. Therefore, several studies have transferred the emphasis of treatment from therapy to early detection and prevention [5, 6]. The early stage of AMD is characterized by the presence of drusen, which leads to choroidal neovascularization (CNV) in 24 % of cases with large, soft drusen over a period from 3 to 5 years [7]. However, research and evaluation of novel interventions for early and intermediate AMD currently are hampered by the lack of measurable parameters. Such parameters are required to provide an objective, quantified assessment of disease severity and serve as valuable clinical reference.

The microstructural changes of the macular can be identified by means of high-resolution OCT. Previously, the time domain OCT could only be used to observe the retinal morphological changes as a whole in early AMD. The present SD-OCT can provide precise analysis of retina layer by layer and give accurate retinal thickness data, especially the photoreceptor layer (PRL) thickness of early AMD. Moreover, although the early damage of retinal function can be evaluated objectively by multifocal electroretinography (mfERG) in early AMD, the corresponding retinal morphological changes have not been reported [8, 9]. It has been documented that the combined use of OCT and mfERG could provide novel parameters for early macular diseases such as diabetic retinopathy, and hydroxychloroquine retinopathy as well as glaucoma [10–12]. The purpose of our study was to evaluate the changes of the PRL thickness with SD-OCT and retinal function by mfERG and to discover the correlation of morphological and functional parameters in subjects with early and intermediate AMD.

Methods

Our study was approved by the Human Ethics Committee of Zhongshan Ophthalmic Center, and informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Participants

Forty-five eyes of 45 patients with early or intermediate AMD (grade 2–8 on the AREDS 9-step severity scale [13], age range 50–85 years, median 67 years) and 30 eyes of 30 healthy subjects (age range 50–80 years, median 65 years) examined at the Zhongshan Ophthalmic Center, Sun Yat-sen University were included. Eligibility criteria were: Presence of at least twenty or more drusen with a minimum size of 63 μm, within 3000 μm from the foveola and in the absence of signs of any other retinopathy or advanced AMD in the study eye. Exclusion criteria were: Bilateral late-stage AMD, including central geographic atrophy and CNV, significant corneal or media opacity, diabetics, uncontrolled hypertension (systolic >150 mmHg and diastolic >90 mmHg), amblyopia, glaucoma or high intraocular pressure, neurologic or systemic disease that could compromise vision, medications that are known to affect retinal function (e.g., hydroxychloroquine), physical and/or mental impairment or inability to sign a consent form. None of them had history of high myopia, ocular trauma, or ocular surgery except for cataract surgery more than 3 months. The best-corrected visual acuity (BCVA) was taken in both eyes of each patient. When both eyes met the eligibility criteria, the eye with the better visual acuity was chosen as the study eye. The study eyes with BCVA lower than 0.1(Snellen vision) were excluded. Color fundus photography, SD-OCT, and mfERG were performed in the study eye.

Optical coherence tomography (OCT)

Retinal imaging was captured using the Spectralis™ OCT (Heidelberg Engineering, Dossenheim, Germany), which installs a super luminescence diode with a center wavelength of 870 nm as a light source. Single 9-mm line scan along the horizontal and vertical meridian crossing the foveola was used. Scan speed was 40,000 A-scans per second, and axial resolution achieves approximately 5 μm in tissue. Eye motion artifacts were eliminated by in-system eye tracking, and 100 SD-OCT images were acquired and averaged to reduce speckle noise.

All participants were examined by the same examiner. SD-OCT images were scanned when pupil size was larger than 7 mm dilated with 0.5 % tropicamide and 5 % phenylephrine. PRL thickness is defined as the distance between the outer border of outer plexiform layer and the inner border of RPE [14, 15]. At the foveola, the thickness of PRL was the mean thickness of the horizontal and vertical PRL. At 0.5, 1.5, 3 mm away from the foveola, the thickness of PRL was the average

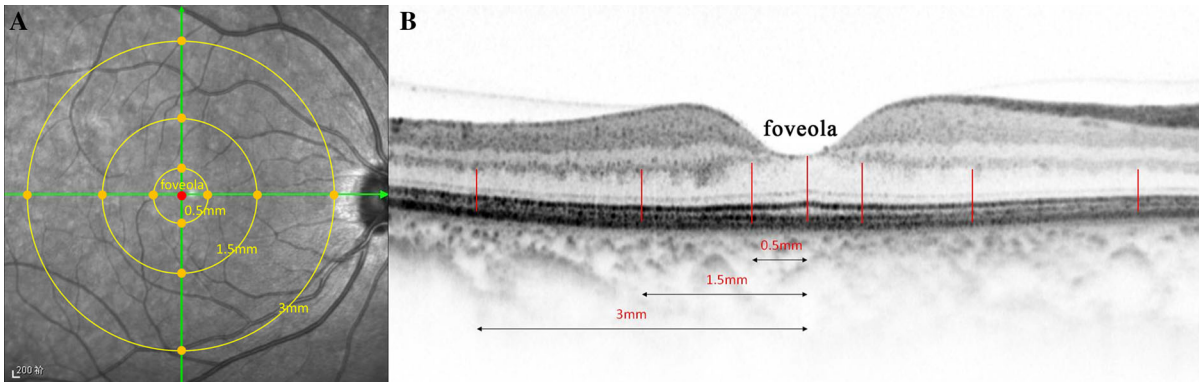

Fig. 1 Retinal photoreceptor thickness measured by SD-OCT. **a** The PRL thickness measuring points include foveola and the superior, inferior, nasal and temporal of ring 0.5 mm, ring 1.5 mm, ring 3 mm away from the foveola were demonstrated. **b** The measurement of PRL height was marked with *red line* between the outer plexiform layers and inner border of RPE

thickness of the superior, inferior, nasal and temporal PRL (Fig. 1). Each OCT figure was reviewed by at least two of the readers, and the thickness of PRL was recorded. In a few cases, there was disagreement in measurement, and the determination was referred to author XL, the senior author.

Multifocal electroretinography (mfERG)

The VERIS Science^{TM} 4.0 (Electro-Diagnostic Imaging, Redwood City, CA, USA) was used for the multifocal ERG measurement. The stimulus matrix with 103 hexagon elements was displayed on a high-resolution screen with 75 Hz frame rate at a viewing distance of 37 cm. Each hexagon was independently alternated between black and white according to a pseudorandom binary m-sequence. The maximum luminance and minimum luminance were 200 and 4 cd/m^2. The lower cutouts and higher cutouts of the amplifier were 3 and 100 Hz, respectively. The signal was amplified 100,000 times. Sampling frequency was 1200 Hz (0.833 ms).

All mfERG examinations were carried out by the same examiner at least 120 min after the SD-OCT scan. Biomicroscopy, fundus imaging, or other examinations that would affect the cornea or retina could not be done between OCT and mfERG examinations. The pupil was dilated one or more times again to make sure it was still dilated enough during the mfERG examination. Retinal activity was recorded with the Burian–Allen bipolar contact lens that was placed on the cornea after anesthetized with 1 % proxymetacaine (Alcaine). The Ag–Agcl ground electrode was placed on the earlobe. Patients' fixations were monitored using a fundus camera.

The first-order kernel responses were recorded according to the International Society for Clinical Electrophysiology of Vision guidelines. The latencies and average response densities of the six concentric rings were measured. The rings of 1–6 correspond to the foveola of 4°, 7°, 12°, 16°, and 22°, respectively according to the eccentricity. By superimposing the OCT pattern (Ø 6 mm) on over the hexagonal pattern from the mfERG registration, hexagons corresponding to the OCT pattern were identified. One millimeter of the OCT radial line corresponds to 4° of the mfERG rings. As the tested rings of foveola, 0.5, 1.5, and 3 mm away from the foveola in OCT were corresponding to ring 1–4 of mfERG, the correlation between the functional changes to the morphological change of the macula using mfERG and SD-OCT in each ring of the macular area was analyzed.

Statistical analysis

Values were given as mean and standard deviation. Chi-square test was used for calculation of categorical data. *T* test was used for comparing the differences of age and retinal photoreceptor thickness between normal eyes and eyes with AMD. Mann–Whitney tests were used for comparing the amplitude density and latency in different areas between the groups. Spearman's test was used for analyzing the correlations of macular photoreceptor thickness and the mfERG data. For all tests, a P value <0.05 was considered to be statistically significant.

Results

Patient characteristics

The age, gender, mean BCVA, and the rate of OD/OS between the AMD patients and the controls were compared, and no statistical differences were found ($P > 0.05$, Table 1). The BCVA for all subjects was presented as logarithm of the minimum angle of resolution (logMAR).

Retinal photoreceptor thickness

In AMD group, the PRL (μm) was significantly thinner compared to the control group in foveola and at the distance of 0.5, 1.5, and 3 mm away from the foveola (Table 2).

First-order kernel responses

The mean N1 and P1 retinal response of AMD and control groups is listed in Table 3. The average amplitude response densities (nV/deg^2) of N1 and P1 in AMD group were significantly lower than control group in all six rings recorded. The delay of latency (ms) was also found in the AMD group compared with the controls except for the similar N1, P1 latency of the first ring between the two groups (Table 3).

Table 1 Demographic characteristics of AMD and control group

	AMD	Control
No. of subjects	45	30
Age (years)	67.31 ± 8.59	64.80 ± 8.60
Gender (M/F)	26/19	17/13
BCVA (logMAR)	0.09 ± 0.29	0.21 ± 0.27
OD/OS	18/27	15/15

AMD age-related macular degeneration, *M/F* no. of male/no. of female, *BCVA* best-corrected visual acuity, *logMAR* logarithm of the minimum angle of resolution

Table 2 Retinal photoreceptor thickness of AMD and control group

	AMD	Control	*P* value
Foveola	158.61 ± 45.25	192.48 ± 17.37	<0.0001
0.5 mm	138.91 ± 20.92	163.73 ± 12.95	<0.0001
1.5 mm	118.91 ± 12.85	130.93 ± 9.20	<0.0001
3 mm	95.00 ± 9.64	108.78 ± 7.81	<0.0001

Correlation of macular photoreceptor thickness and the first-order kernel responses

To measure correlation of macular morphological and functional parameters, we performed a Spearman's correlation analysis of OCT and multifocal ERG parameters in rings 1–4 (Table 4; Figs. 2, 3). There were statistically significant correlations between N1, P1 retinal response average amplitude densities and retinal photoreceptor thickness in each ring. No significant correlation was found between N1, P1 latency and retinal photoreceptor thickness, except for the modest significant correlation of ring 3 and ring 4 (Fig. 4).

Discussion

Drusen are deposits between the RPE and the layer of Bruch's membrane and are a risk factor for the initial of pathologic stage of AMD. There have been several postmortem studies of retina over drusen. Some of them identified the relationship between structural and functional photoreceptor changes and underlying drusen [16–18]. It is hypothesized that drusen patients have a progressive loss of vision and progression of disease due to accumulation of photoreceptor cell apoptosis.

The results of this study validate this speculation using the high-speed high-resolution SD-OCT to measure the retinal layers in living eyes with AMD, with a precision adequate to measure focal abnormalities over drusen. In the current study, early and intermediate stage AMD eyes showed significant decrease in PRL thickness at the foveola, 0.5, 1.5 and 3 mm away from foveola compared to age-matched control eyes. Our findings are consistent with those by Curcio et al. [16] who observed the histopathology of 13 AMD eyes (from 7 donors) and found the phenomenon of retinal photoreceptor loss is the beginning of a continuum that includes AMD progression.

MfERG was developed by Sutter and Tran, which enables topographic mapping of retinal function in central 40°–50°. It can provide valuable objective assessment of visual function, especially in the

Table 3 First-order kernel responses by rings between AMD and control group

	AMD	Control	*P* value
Ring 1 (foveola)			
Amplitude density N1	29.48 ± 8.53	40.81 ± 4.75	<0.001
Amplitude density P1	67.91 ± 18.19	98.46 ± 6.68	<0.001
Latency N1	17.84 ± 1.94	17.51 ± 0.72	0.588
Latency P1	32.94 ± 2.25	32.13 ± 0.82	0.084
Ring 2			
Amplitude density N1	17.86 ± 3.92	26.05 ± 2.69	<0.001
Amplitude density P1	41.56 ± 10.18	62.38 ± 4.99	<0.001
Latency N1	17.60 ± 1.21	17.11 ± 0.39	0.018
Latency P1	32.99 ± 2.08	31.58 ± 0.67	<0.001
Ring 3			
Amplitude density N1	12.53 ± 3.16	17.02 ± 1.47	<0.001
Amplitude density P1	28.28 ± 6.82	40.50 ± 3.64	<0.001
Latency N1	17.30 ± 1.29	16.40 ± 0.44	0.001
Latency P1	32.12 ± 2.92	30.86 ± 0.94	0.018
Ring 4			
Amplitude density N1	9.22 ± 2.45	12.55 ± 1.21	<0.001
Amplitude density P1	21.00 ± 5.23	30.57 ± 3.12	<0.001
Latency N1	17.36 ± 1.90	16.47 ± 0.50	0.028
Latency P1	32.61 ± 3.22	30.90 ± 1.29	0.025
Ring 5			
Amplitude density N1	16.88 ± 4.25	24.69 ± 2.12	<0.001
Amplitude density P1	7.49 ± 2.28	10.08 ± 0.68	<0.001
Latency N1	17.89 ± 2.01	16.83 ± 0.57	0.005
Latency P1	33.18 ± 2.47	31.47 ± 1.19	0.001
Ring 6			
Amplitude density N1	6.60 ± 1.72	9.03 ± 0.88	<0.001
Amplitude density P1	15.12 ± 3.71	22.11 ± 1.62	<0.001
Latency N1	18.38 ± 1.75	17.25 ± 0.54	<0.001
Latency P1	33.94 ± 2.41	31.51 ± 1.09	<0.001

Table 4 Correlations of retinal photoreceptor thickness and first-order kernel responses

	N1-I		P1-I		N1-A		P1-A	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Foveola	0.040	0.731	−0.201	0.084	0.338	0.003	0.460	<0.001
Ring 0.5 mm	−0.194	0.095	−0.350	0.002	0.530	<0.001	0.533	<0.001
Ring 1.5 mm	−0.371	0.001	−0.388	0.001	0.385	0.001	0.398	<0.001
Ring 3 mm	−0.281	0.015	−0.269	0.019	0.350	0.002	0.481	<0.001

N1-I N1 latency (ms), *P1-I* P1 latency (ms), *N1-A* N1 amplitude density (nV/deg^2), *P1-A* P1 amplitude density (nV/deg^2)

regional disorders affecting the outer retinal layers [19, 20]. It has been used to evaluate retinal function in patients with AMD or with other macular diseases and has been proved to be an objective measurement to observe the functional changes of retina. Study of Gerth et al. [21] confirmed that mfERG was more

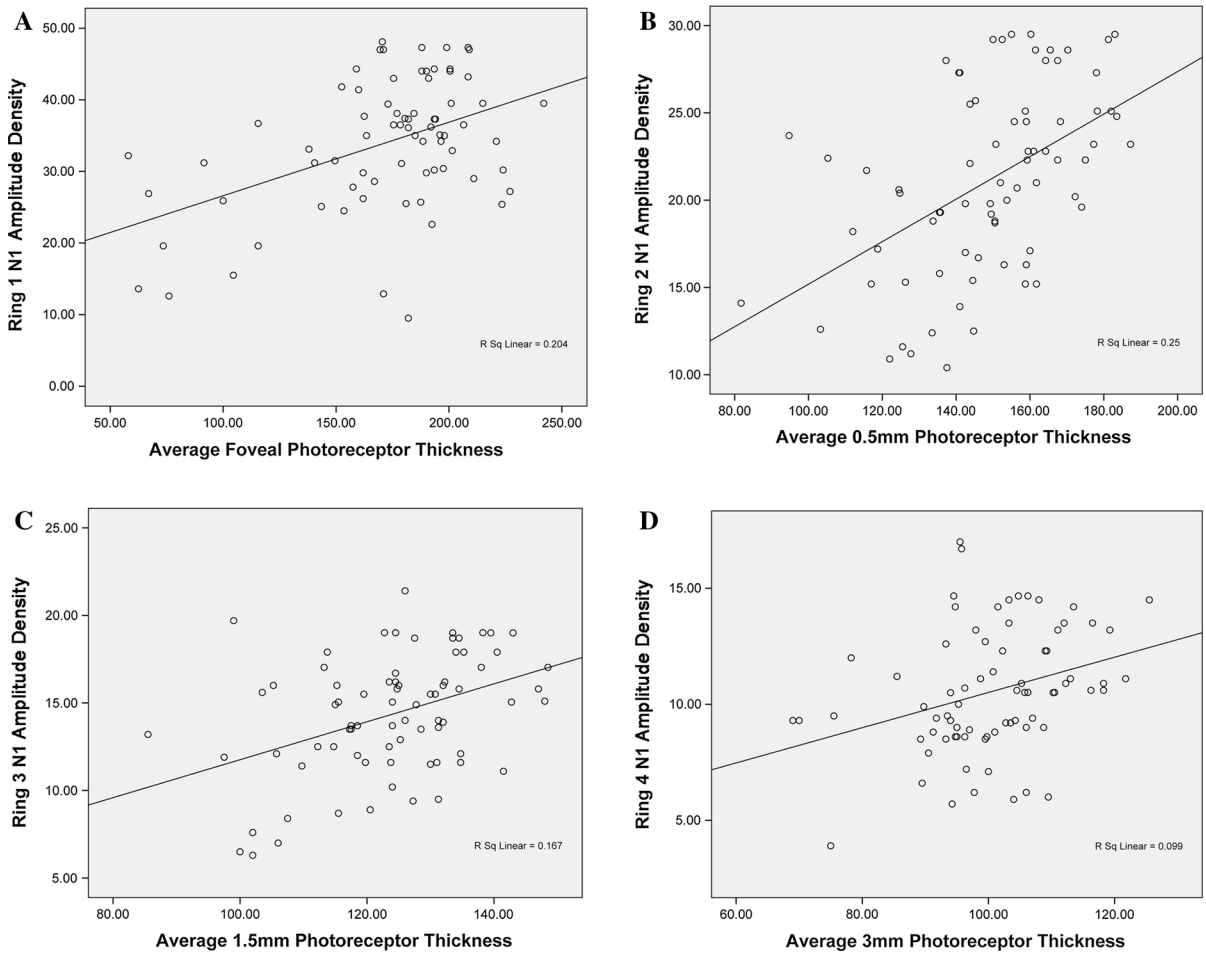

Fig. 2 *Graphs* showing the correlations between retinal photoreceptor thickness and N1 average amplitude densities in rings 1–4. **a**, **b** Demonstrate that foveola and 0.5 mm from the foveola retinal photoreceptor thickness were associated with N1 average amplitude densities ($r = 0.338$ and 0.530; $P = 0.003$ and <0.001). **c**, **d** Show that 1.5 mm and 3 mm from the foveola retinal photoreceptor thickness were associated with N1 average amplitude densities ($r = 0.385$ and 0.350; $P = 0.001$ and 0.002)

sensitive in evaluation of early AMD compared with visual acuity and fundus photograph after 28- to 41-month follow-up. To objectively assess the influence of drusen on retinal function, we compared the differences of rings 1–6 in the mfERG between AMD group and the control. As far as we know, only a few studies have used mfERG to evaluate central retinal function in early AMD patients. Li et al. [22] reported that foveal amplitude density of 15 early AMD eyes was significantly suppressed, and their foveal average latency was significantly prolonged when compared with the 20 age-matched normal eyes. Similar changes in amplitude density and latency were also observed in the asymptomatic fellow eyes. Our study objectively demonstrates the dysfunction of mfERG in cases of drusen maculopathy, including decreased amplitude density and prolonged latency in six concentric rings centered on the foveola when compared to controls, which is in agreement with Li et al. [22].

In the present study, we found that the retinal photoreceptor thickness on high-resolution SD-OCT was significantly associated with the mfERGN1 and P1 amplitude density in all subjects after controlling for age and gender. This novel finding suggested that the retinal photoreceptor thickness is an important parameter to assess the severity of early and intermediate AMD. As AMD progresses, the foveal retinal photoreceptor thickness becomes increasingly thinner

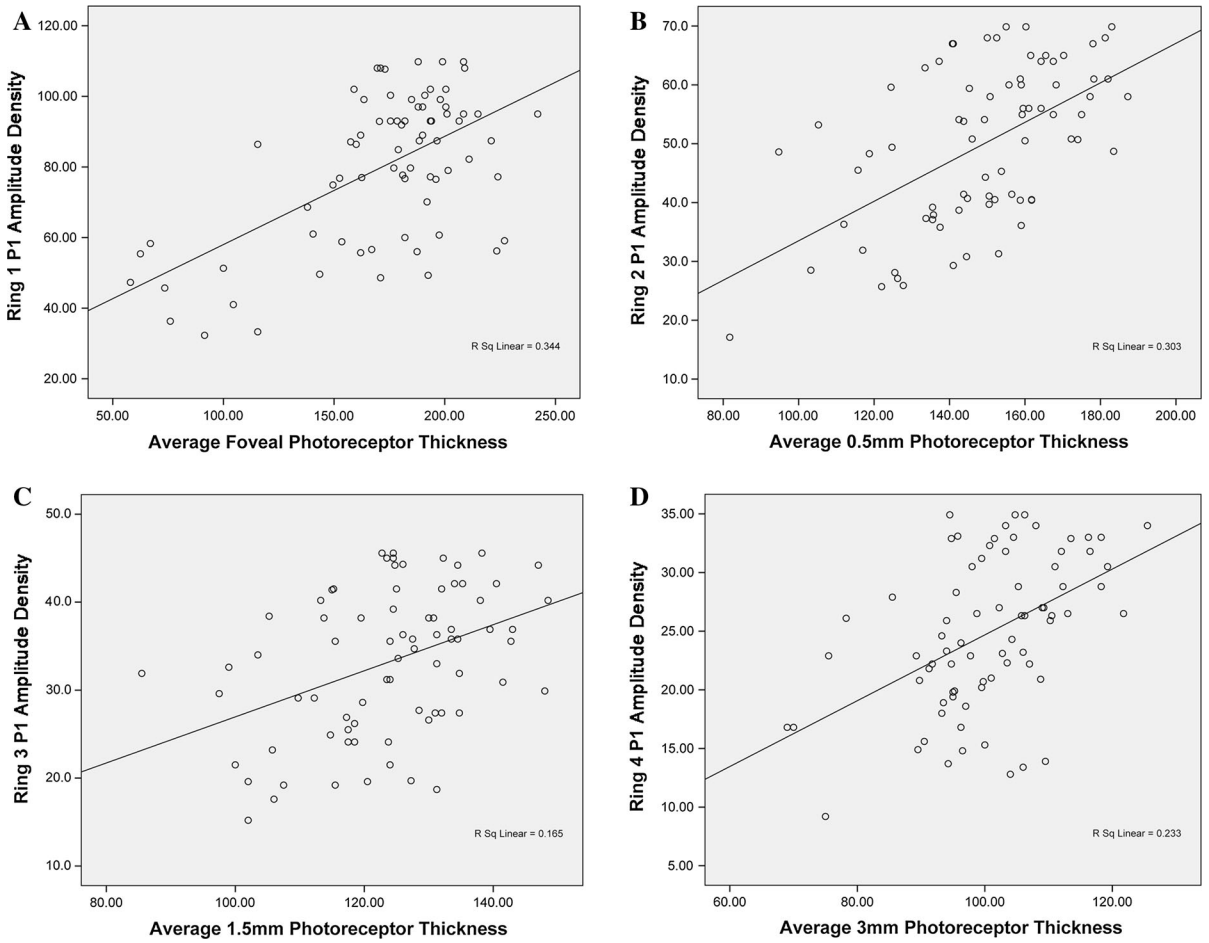

Fig. 3 *Graphs* showing the correlations between retinal photoreceptor thickness and P1 average amplitude densities in rings 1–4. **a**, **b** Demonstrate that foveal and 0.5 mm from the foveola retinal photoreceptor thickness were associated with P1 average amplitude densities ($r = 0.460$ and 0.533; $P < 0.001$). **c**, **d** Show that 1.5 mm and 3 mm from the foveola retinal photoreceptor thickness were associated with P1 average amplitude densities ($r = 0.398$ and 0.481; $P < 0.001$)

and the retinal photoreceptor cell function deteriorates gradually. Even though previous studies have shown evidence of functional changes in the retina with large drusen by mfERG, morphological changes, such as color stereo fundus photography, red-free fundus photography, or fluorescein angiography, could not predict functional changes [23]. Our findings may suggest that the morphological evaluation by SD-OCT can reflect the functional changes of macular degeneration more precisely than color stereo fundus photography, red-free fundus photography, and fluorescein angiography. The correlations were not so high in this study. It is probably because PRL and mfERG do not reflect exactly the same layer. PRL represents photoreceptor layer, while mfERG response represents ON and OFF-bipolar cell contributions plus smaller contributions from inner retina and photoreceptors [24]. So the mfERG presents function of photoreceptors indirectly. But because PRL and mfERG were sensitive parameters in early detection destructions of macula, they were still widely used in macular assessment and were found to be correlated with each other [25].

To the best of our knowledge, only one study has correlated the functional changes to the morphological status by means of mfERG and time domain OCT in early or intermediate AMD patients [26]. They found no significant correlation between retinal thickness and macular function (mfERG). It is possible that SD-OCT, which enables the detailed

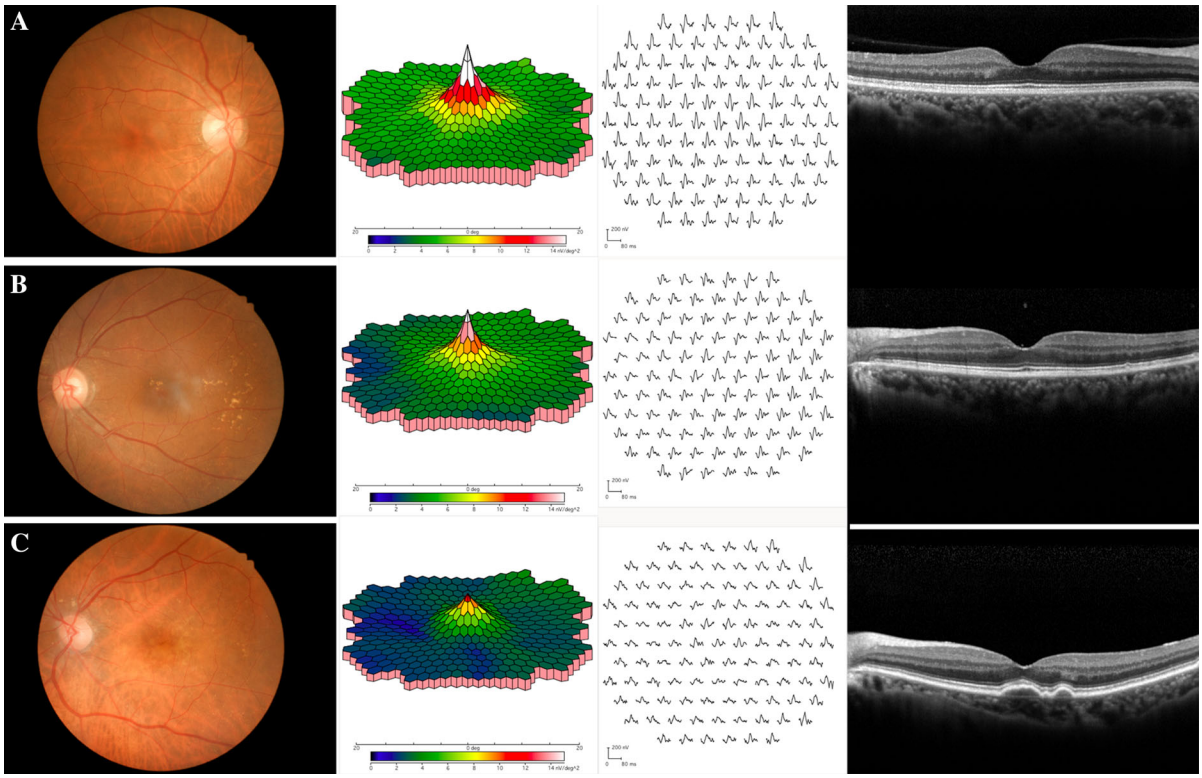

Fig. 4 Example of SD-OCT and mfERG images of normal subjects, early and intermediate drusen patients. The retinal photoreceptor thicknesses, three-dimensional *density plots* and trace arrays of the first-order kernel responses were shown. **a** A control subject with normal fundus showed normal retinal response amplitude density and average foveal retinal photoreceptor thickness of 200 μm. **b** An early drusen patient demonstrated few hard drusen within temporal macular. The peak amplitude density decreased slightly and the amplitude density of temporal trace arrays decreased obviously. The foveal retinal photoreceptor thickness decreased slightly with a value of 194 μm. **c** A medium drusen patient showed large soft foveal drusen. The peak amplitude and the amplitude density of central trace arrays decreased obviously. The average foveal retinal photoreceptor thickness decreased obviously with a value of 145.25 μm

analysis of the retinal photoreceptor thickness in vivo, yields better visualization of intraretinal layers and more accurate definition of outer boundary of retina than time domain OCT. As we all know that the decrease in retinal thickness may only be observed when the photoreceptor thickness decreased significantly in early and intermediate AMD [27]. Therefore, the retinal photoreceptor layer thinning may be an earlier clue of the retinal damage. Our study found the correlation of PRL thickness and retinal function, which means the thinning of PRL might be an indicator in early detection retinal function damage in AMD patients. The results of present study are encouraging in that, the retinal photoreceptor thickness could be a useful tool to precisely and effectively evaluate the severity of early and intermediate AMD.

In retinal morphology and function correlation analysis, we have only considered the four inner rings of the mfERG in order to correspond it to the OCT retinal photoreceptor thickness map. Since the summed response from the four defined rings on the mfERG recording corresponds well to the OCT mapping protocol [10], we are confident that our research method is suitable for this study.

The main limitations of our study include a selection bias at baseline. To ensure good fixation and imaging during the SD-OCT and mfERG recordings, our study excludes patients with severe refractive media opacity or with vision acuity lower than 0.1. Another limitation is as a cross-sectional observation; the study cannot predict progression of drusen and damage of visual function according to the parameters. Longitudinal studies are needed to confirm the use of

early detections in SD-OCT and mfERG in AMD prognosis.

In conclusion, the study observed the decrease in retinal photoreceptor thickness and first-order kernel response. The retinal photoreceptor thickness was significantly associated with the mfERG N1 and P1 amplitude density. The retinal photoreceptor apoptosis and decreases of electrophysiological activity were the early changes of AMD.

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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.

Ethical approval 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.

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

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