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Thickness of retinal pigment epithelium–Bruch's membrane complex in adult Chinese using optical coherence tomography

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PURPOSE: To study thickness of RPE–BM complex in adult Chinese subjects and its correlation with systemic and ocular biometric parameters.
DESIGN: Population-based longitudinal study. Cross-sectional study.
PARTICIPANTS: The population-based Beijing Eye Study 2011 included 3468 individuals with a mean age of 64.6 ± 9.8 years (range: 50–93 years).
METHODS: A detailed ophthalmic examination was performed including spectral-domain optical coherence tomography (SD OCT) for measurement of the thickness of RPE–BM complex. Use Heidelberg software "Heidelberg Eye Explorer" for segmentation and measurements.
MAIN OUTCOME MEASURE: Thickness of RPE–BM complex.
RESULTS: In total, 3276 people (6530 eyes) were included in the study. In total, 1844 (56.3%) subjects were female. The mean age was 64.3 ± 9.6 years (range: 50–93 years). The mean refractive error (spherical equivalent) was −0.18 ± 2.04 diopters (range: −22.0 to +7.50 diopters). Mean thickness of the RPE–BM complex at the foveal center was 25.09 ± 3.98 µm (range: 17–37 µm). In multiple regression analysis, subfoveal thickness of the RPE–BM complex was associated with age ($p = 0.039$; beta: 0.22; B: 0.10 (95% CI: 0.01, 0.20)) and hypertension history ($p = 0.038$; beta: 0.23; B: 1.96 (95% CI: 0.12, 3.81)).
CONCLUSION: Mean subfoveal thickness of the RPE–BM complex was 25.09 ± 3.98 µm in elderly subjects with a mean age of 64.3 years increased with age and hypertension history. The increase in the thickness of RPE–BM complex may play a role in the pathophysiologic features of various age-related ocular conditions.

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The retinal pigment epithelium (RPE) comprises a monolayer of polarized pigmented epithelial cells. At its apical surface of the RPE faces the photoreceptor outer segments making a complex of close structural interactions. With its basolateral surface, the RPE faces Bruch's membrane, which separates the RPE from fenestrated endothelium of the choriocapillaris. The Bruch's membrane is a thin (2–4 um) connective tissue strategically located between the metabolically active RPE and its source of nutrition, the choriocapillaris. The RPE–Bruch's membrane complex performs a variety of vectorial transport functions (water, ions, metabolites, nutrients and waste products) that regulate the composition of the subretinal space and support the functions of photoreceptors and other cells in the neural retina; and also plays a key role in retinal physiology by forming the outer blood-retinal barrier that prevents nonspecific diffusion and transport of material from the choroid [1–3].

It was the landmark study by Staurenghi et al. [4] developed a consensus nomenclature for the classification of retinal and choroidal layers with spectral-domain optical coherence tomography (SD OCT), which were representative of the RPE–Bruch's membrane complex of foveal microstructures in greater detail. Destructions of the microstructures can be indicated in different retinal diseases, including retinal detachment, age-related macular degeneration, foveomacular vitelliform dystrophy, central serous chorioretinopathy, and acute, posterior multifocal placoid pigment epitheliopathy [5–7]. The primary aim of our research is to study thickness of RPE–Bruch's membrane complex in adult Chinese subjects by SD OCT and its correlation with systemic and ocular biometric parameters with a relatively large study population.

METHODS

The Beijing Eye Study 2011 is a population-based cross-sectional study in Northern China. The Medical Ethics Committee of the Beijing Tongren Hospital approved the study protocol and all participants gave informed written consent, according to the Declaration of Helsinki. It was carried out in five communities in the urban district of Haidian in the North of Central Beijing and in three communities in the village area of Yufa of the Daxing District south of Beijing. The only eligibility criterion for inclusion into the study was an age of 50+ years. In 2011, the eight communities had a total population of 4403 individuals aged 50 years or older. In total, 3468 individuals (1963 (56.6%) women) participated in the eye examination, corresponding to an overall response rate of 78.8%. The study was divided

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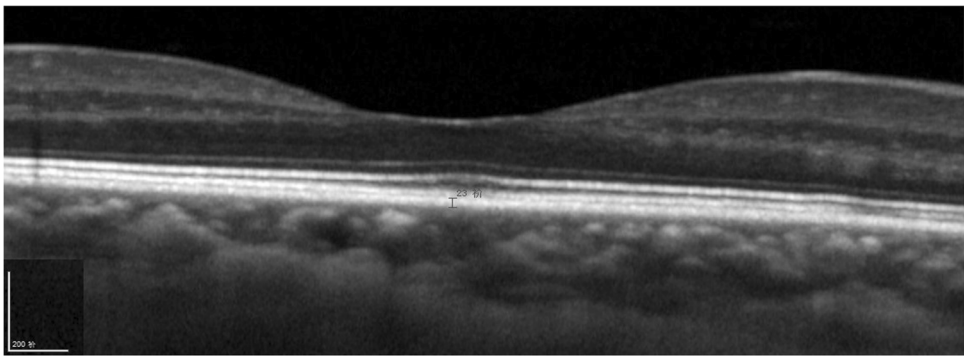

Fig. 1 Optical coherence tomogram of the RPE–BM complex. The inner and outer borders of the RPE–BM complex were manually segmented. The red line showed the subfoveal thickness of RPE–BM complex.

into a rural part (1633 (47.1%) subjects; 943 (57.7%) women) and an urban part (1835 (52.9%) subjects; 1020 (55.6%) women). The mean age was 64.6 ± 9.8 years (median, 64 years; range, 50–93 years).

All examinations were carried out in the communities. Trained research technicians asked the study participants questions providing information on demographic variables, socioeconomic background, and known major systemic diseases. Fasting blood samples were taken for measurement of blood lipids, glucose and glycosylated hemoglobin HbA1c. Blood pressure was measured. Body height and weight and the circumference of the waist and hip were recorded. The ophthalmic examination included measurement of presenting visual acuity (VA), best corrected VA (assessed by automatic refractometry Auto Refractometer AR-610, Nidek Co., Ltd, Tokyo, Japan), intraocular pressure, and slit lamp examination. Subjective refractometry was additionally measured if uncorrected VA was lower than 1.0. The anterior corneal curvature, central corneal thickness, anterior chamber depth, lens thickness and axial length of the right eyes were measured by optical low-coherence reflectometry (Lensstar 900® Optical Biometer, Haag-Streit, 3098 Koeniz, Switzerland). The corneal diameter and pupil diameter were measured by slit lamp adapted optical coherence tomography (OCT) (Heidelberg Engineering Co., Dossenheim, Germany). The pupil was dilated using tropicamide once or twice, until the pupil diameter was at least 6 mm. The optic nerve head, peripapillary area, and macula were scanned by two spectral-domain OCTs to measure ocular perfusion pressure, subfoveal choroidal thickness, subfoveal retinal thickness (iVue SD OCT; Optovue Inc. Fremont, CA, USA; Spectralis, Heidelberg Engineering, Heidelberg, Germany). Previous studies have found that the symmetry of the left and right eyes in this study population was good [8, 9].

To test interobserver variability, all images were reviewed by two examiners independently over the course of 2 months to determine the RPE–BM complex subfoveal thickness. A smaller study sample of 21 eyes from 21 healthy patients from the Tongren Eye Center was included in the study to investigate intraobserver repeatability. These patients were scanned ten times, with a 1-min pause between each scan [10]. Within 2 weeks, the same observer measured the thickness of the RPE–BM complex at the foveal center. The intra-class correlation coefficient (ICC), the coefficient of variation, and the intra-session within-subject standard deviation were calculated.

The inner and outer borders of the RPE–BM complex were manually segmented (Fig. 1). Each image was measured at five locations: in the fovea, and in the outer extreme section superior to the fovea, inferior to the fovea, temporal of the fovea and 2 mm nasal to the fovea in direction to the optic disc.

Statistical analysis was performed by using a commercially available statistical software package (SPSS for Windows, version 25.0, SPSS, Chicago, IL, USA). The thickness of RPE–BM complex were described by the mean values (presented as mean ± standard deviation). Categorical variables were assessed individually with the chi-square test, and the Fisher exact test was used for samples with an expectancy of less than 5. Continued data were analyzed using an independent sampled *t*-test. The paired *t*-test was used to analyze differences in thickness by location in the macula. Simple liner regression was calculated for variations in the thickness of RPE–BM complex and the interdigitation band relative to systemic and ocular risk factors. Multiple linear regression was used to evaluate the explanatory variables with regard to the dependent variable. Only the right eye of each study participant was assessed in liner regression analysis. The average thickness of RPE–BM complex measures acquired from both visits was compared using paired *t*-tests in the interobserver research. Ten OCT images from the 21 volunteers were used to assess intraobserver repeatability. The intra-session within-subject standard deviation (Sw), the coefficient of variation (COV, 100% × Sw/overall mean), and the ICC were all calculated (ICC). An ICC > 0.80 was used to denote almost perfect reliability, and 95% confidence intervals (CI) were reported. All *p* values were two-sided and were considered statistically significant when the values were less than 0.05.

RESULTS

Out of the 3468 subjects included in the study, OCT images with sufficient quality for examination were available for 6530 eyes of 3276 (94.5%) participants (1844 (56.3%) women). The mean age was 64.3 ± 9.6 years (median: 63 years; range: 50–93 years), the mean refractive error (spherical equivalent) was −0.18 ± 2.04 diopters (median: 0.25 diopters; range: −22.0 to +7.50 diopters). For 192 (5.5%) subjects, OCT images could not be examined either because images were not taken or because available images could not be assessed owing to lens opacities or vitreous clouding. The group of subjects without OCT examinations as compared with the group of subjects with OCT examinations was significantly older (70.1 ± 11.2 years versus 64.3 ± 9.6 years; $p < 0.001$; 95% CI: 4.15, 7.39) but did not vary significantly in gender ($p = 0.12$) and refractive error ($p = 0.29$).

Grader 1 and grader 2 measured mean subfoveal thickness of RPE–BM complex of 25.09 ± 3.98 µm and 25.07 ± 3.97 µm, respectively, with a mean difference of 0.02 ± 0.24 µm (95% CI: 0.01, 0.03). The correlation coefficient of the connection between the measures taken by the two examiners separately was $r = 0.998$ (Fig. 2). The images of 21 healthy volunteers (11 (52%) women) with no known eye illness were re-examined to determine intraobserver repeatability. The average age was 63.1 ± 10.6 years (median: 61 years; range: 50–83 years). The uncorrected VA was at or above 1.0. The intraobserver variability was found to have an ICC of 1.00 ($p < 0.001$). The mean COV was 3.42 ± 1.10%.

The mean thickness of the RPE–BM complex at the foveal center was significantly ($p < 0.001$) thicker (25.09 ± 3.98 µm; range: 17–37 µm) than that at 2.0 mm distant from nasally (23.65 ± 3.64 µm; range: 13–36 µm) and superiorly (23.34 ± 3.29 µm; range: 15–33 µm), where it was significantly ($p < 0.001$) thicker than inferiorly (22.48 ± 3.29 µm; range: 14–34 µm) and temporally (22.44 ± 3.47 µm; range: 15–32 µm).

In univariate analysis, the foveal thickness of the RPE–BM complex was significantly associated with age ($p = 0.001$), hypertension history ($p = 0.001$), lower best corrected VA ($p = 0.025$); and marginal related ($0.05 < p < 0.10$) to creatinine ($p = 0.058$), shallower anterior chamber depth ($p = 0.057$), lens thickness ($p = 0.093$), and flatter corneal curvature ($p = 0.076$) (Table 1). It was not significantly (all $p > 0.05$) associated with the systemic

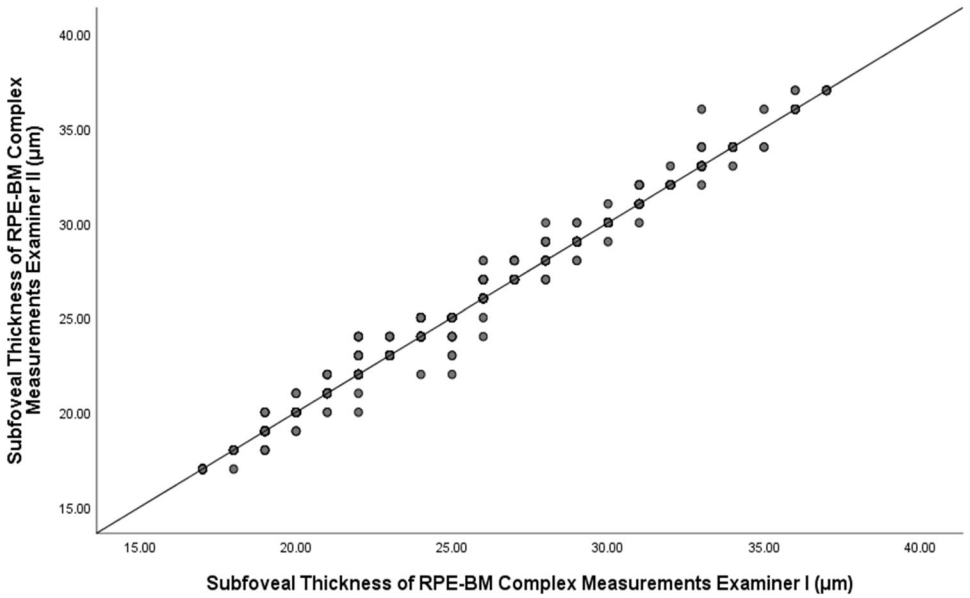

Fig. 2 The correlation between the subfoveal thickness of RPE-BM complex. Scatterplot showing the correlation between the subfoveal thickness of RPE–BM complex measurements performed on optical coherence tomograms by two examiners independently of each other.

parameters of gender, body height, weight, rural region of habitation, level of education, systolic blood and diastolic pressure, serum concentrations of glucose, high-density lipoproteins, low-density lipoproteins, cholesterol and triglycerides, presence of diabetes mellitus, smoking and alcohol consumption, aspirin intake and frequency of reported snoring, history of hyperlipidemia; with the ocular parameters of axial length, refractive error, subfoveal retinal thickness, ocular perfusion pressure, corneal thickness and diameter, and pupil diameter (Table 1).

Then, we performed a multiple linear regression analysis, and the results showed that age ($p = 0.039$; beta: 0.22; *B*: 0.10 (95% CI: 0.01, 0.20)) and hypertension history ($p = 0.038$; beta: 0.23; *B*: 1.96 (95% CI: 0.12, 3.81)) was also significantly related to the subfoveal thickness of RPE–BM complex. Other factors were not significantly (p all >0.05) correlated with it, including best corrected VA ($p = 0.710$), creatinine ($p = 0.881$), anterior chamber depth ($p = 0.838$), lens thickness ($p = 0.893$), and corneal curvature ($p = 0.994$).

DISCUSSION

In our population-based study on a relatively large study population, we found that mean thickness of the RPE–BM complex at the foveal center was 25.09 µm, ranging from 17 to 37 µm. In multiple regression analysis, subfoveal thickness of the RPE–BM complex was associated with age ($p = 0.039$; beta: 0.22) and hypertension history ($p = 0.038$; beta: 0.23). In multivariate analysis, subfoveal thickness of the RPE–BM complex was not significantly associated with blood pressure, ocular perfusion pressure, intraocular pressure, cigarette smoking, alcohol consumption, serum concentrations of lipids, creatinine and glucose, diabetes mellitus, best corrected VA, anterior chamber depth, lens thickness, and corneal curvature. Under routine examination conditions, RPE–BM complex measurements by EDI-OCT showed a high intraobserver reproducibility and interobserver reproducibility.

The results of the mean subfoveal thickness of the RPE–BM complex as measured in our study were similar to those reported previously. In the study by Karampelas et al. [11] on 25 healthy and young volunteers with a mean age of 69.0 years, the subfoveal thickness of the RPE–BM complex was 22.7 µm. But if one takes into account the age difference between both study populations, with a mean increase in SFCT of ~0.1 µm per year of age, the measurements in the study by Karampelas et al. are lower than the results of the present study.

Likewise, the study by Xu et al. [12] on 525 Chinese subjects with a mean age of 44.8 years showed a mean subfoveal thickness of the RPE–BM complex of 17.5 µm, which becomes comparable to our results if the age difference is taken into account. Other reasons for differences between various studies in the subfoveal thickness of the RPE–BM complex measurements could be differences in the distribution of age in the study populations and ethnic differences in the anatomy of the globes.

In present study, the mean thickness of the RPE–BM complex was thickest (25.09 µm) in the foveal center, followed by the nasal (23.65 µm) and superior (23.34 µm) regions, and finally the inferior (22.48 µm) and temporal (22.44 µm) sector. A similar distribution of sectors was found in previous studies in which the foveal center was thickest followed by pericentral quadrant (1–3 mm from the fovea) with the consistent rules [11, 12]. The reasons for the differences between the four sectors in the thickness of the RPE–BM complex have remained unclear, however, regional variations in the blood supply from the choroid and effects of the gravity could have played a role.

The two parameters with the highest influence on thickness of the RPE–BM complex in multivariate analysis were age (beta = 0.22) and hypertension history (beta = 0.23). The association between the thickness of the RPE–BM and age was also reported by Demirkaya et al. [13], who found the foveal RPE thickness ($R = 0.467$, $p < 0.001$) increased significantly with increasing age. In our study, the study population was more than 50 years of age, and showed a significant association in the thickness of the RPE–BM complex, with a increasing in the thickness of 2.2 µm (95% CI: 0.01, 0.20) per decades of age. The differences of the thickness of the individual RPE–BM layers with age observed in the present study are mostly in concordance with previous studies [11–14], and confirmed in a histomorphometric studies, which demonstrated that several structural changes occur as the RPE ages, including loss of melanin granules, increase in the density of residual bodies and accumulation of lipofuscin, accumulation of basal deposits on or within Bruch's membrane, formation of drusen, and thickening of Bruch's membrane [15, 16]. The reason for the relations between thickness of the RPE–BM and hypertension history was

Table 1. Univariate associations between foveal thickness of the RPE–BM complex and ocular and general parameters.

Parameter	Unstandardized coefficients (*B*)	95% Confidence interval	Standardized coefficients (beta)	*p* value
Systemic parameters				
Age (years)	0.11	0.05, 0.18	0.26	0.001
Gender	−0.52	−1.72, 0.69	−0.07	0.401
Body height (cm)	−0.04	−0.12, 0.03	−0.08	0.278
Body weight (kg)	−0.03	−0.08, 0.02	−0.09	0.238
Rural/urban region	0.37	−0.84, 1.59	0.05	0.544
Level of education	0.06	−0.65, 0.77	0.01	0.866
Systolic blood pressure (mmHg)	0.02	−0.02, 0.05	0.08	0.294
Diastolic blood pressure (mmHg)	0.02	−0.03, 0.07	0.07	0.391
High-density lipoproteins(mmol/l)	0.52	−1.13, 2.17	0.06	0.532
Low-density lipoproteins(mmol/l)	−0.21	−1.00, 0.59	0.00	0.607
Cholesterol (mmol/l)	0.08	−0.66, 0.81	0.02	0.835
creatinine (mmol/l)	0.05	0.00, 0.11	0.19	0.058
Triglycerides (mmol/l)	−0.05	−0.26, 0.15	−0.04	0.618
Glucose (mmol/l)	−0.02	−0.62, 0.59	−0.01	0.954
Diabetes mellitus	0.26	−1.89, 2.41	0.02	0.814
Smoking	−0.46	−1.21, 0.92	−0.09	0.230
Alcohol consumption	0.00	−0.32, 0.32	0.00	0.998
Aspirin intake	1.06	−0.24, 2.4	0.13	0.110
Snoring	−0.68	−1.58, 0.22	−0.12	0.138
Hypertension history	2.06	0.85, 3.27	0.26	0.001
Hyperlipidemia history	−0.07	−0.24, 0.01	−0.06	0.415
Ocular parameters				
Refractive error (D)	0.11	−0.21, 0.44	0.05	0.488
Best Corr. visual acuity (logMAR)	−3.58	−6.71, −0.45	−0.17	0.025
Axial length (mm)	−0.39	−0.98, 0.20	−0.10	0.197
Center corneal thickness (μm)	0.01	−0.01, 0.03	0.12	0.182
Anterior chamber depth (mm)	−1.65	−3.35, 0.05	−0.15	0.057
Lens thickness (mm)	1.64	−0.27, 3.55	0.14	0.093
Corneal curvature (mm)	−2.10	−4.41, 0.22	−0.14	0.076
Corneal diameter (mm)	−0.51	−1.18, 0.16	−0.12	0.135
Pupil diameter (mm)	0.02	−0.79, 0.83	0.00	0.967
Ocular perfusion pressure (mmHg)	−0.06	−0.27, 0.14	−0.05	0.543
Subfoveal choroidal thickness (μm)	0.00	−0.01, 0.07	0.01	0.899
Subfoveal retinal thickness(μm)	−0.02	−0.06, 0.02	−0.07	0.348

p values were <0.05.

not clear. While ischemic status in hypertension may influence the metabolism of RPE cells and excessive metabolic strain that accumulates over the years.

Potential limitations of our study should be mentioned. First, the present epidemiologic research with a relatively large sample size, the rate of nonparticipation should be a major concern. The Beijing Eye Study 2011 had a reasonable response rate of 78.8%, however, differences between participants and non-participants could have led to a selection artifact. Second, as in any population-based study, our investigation included all eligible and participating subjects from the study region; thus, patients with diseases, such as disorders of the optic nerve and macula, and these diseases may have affected the thickness of RPE–BM complex and interdigitation band. Third, Manual measurement may have errors, but currently there is a lack of stable automatic measurement software for RPE layer in clinical practice. The consistency of measurement results with other study with software [12], proves that the manual measurement used in this study has good clinical application value. Last, the re-examinations in our study were performed at the same time of the day, so that the potentially physiological variations in thickness of RPE–BM complex have to be added to the variations due to the measurement technique, if re-examinations are performed at different times of the day. Future studies may develop and evaluate the consistency of automatic measurement software and manual measurement technology, then address whether related diseases were associated with abnormalities of RPE–BM complex.

In conclusion, the mean subfoveal thickness of the RPE–BM complex was 25.09 ± 3.98 μm in elderly subjects with a mean age of 64.3 years increased with age and hypertension history.

SUMMARY

What was known before

- The RPE–Bruch's membrane complex performs a variety of vectorial transport functions that regulate the composition of the subretinal space and support the functions of photoreceptors and other cells in the neural retina.
- It plays a key role in retinal physiology by forming the outer blood-retinal barrier that prevents nonspecific diffusion and transport of material from the choroid.

What this study adds

- Mean subfoveal thickness of the RPE–Bruch's membrane complex was 25.09 ± 3.98 μm in elderly subjects.
- It increased with age and hypertension history.
- The increase in the thickness of RPE–Bruch's membrane complex may play a role in the pathophysiologic features of various age-related ocular conditions.

DATA AVAILABILITY

The raw data supporting the conclusions of this article will be made available by the correspondence authors to any qualified researcher with appropriate request.

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AUTHOR CONTRIBUTIONS

Design of the study: LS and WBW; development of the algorithm: LS; gathering the data: LS, QLZ, CZ, LD, WDZ, RHZ, and HTW; performing the data analysis: LS; drafting the first version of the manuscript: LS and CZ; revision and approval of the manuscript: all authors.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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