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Associations with Retinal Pigment Epithelium Thickness Measures in a Large Cohort

Results from the UK Biobank

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Purpose: To describe associations of ocular and systemic factors with retinal pigment epithelium (RPE)–Bruch's membrane (BM) complex thickness as measured by spectral-domain (SD) optical coherence tomography (OCT).

Design: Multisite community-based study. This research has been conducted using the UK Biobank Resource.

Participants: Sixty-seven thousand three hundred eighteen people 40 to 69 years old received questionnaires, physical examination, and eye examination, including macular SD OCT. Systematic selection process identified 34 652 eyes with high-quality SD OCT images from normal individuals for analysis.

Methods: We included people with no self-reported ocular disease, diabetes, or neurologic disorders; visual acuity of $\geq$20/25 or better; refraction between −6 diopters (D) to 6 D, and IOP of 6 to 21 mmHg. Only high-quality, well-centered SD OCT images with central, stable fixation were included. Descriptive statistics, *t* tests, and regression analyses were performed. Multivariate regression modeling was used to adjust for covariates and to identify relationships between RPE–BM thickness and ocular and systemic features.

Main Outcome Measures: Retinal pigment epithelium–BM thickness, as measured by SD OCT segmentation using Topcon Advanced Boundary Segmentation at 9 Early Treatment of Diabetic Retinopathy Study subfields.

Results: Mean RPE–BM thickness was 26.3 μm (standard deviation, 4.8 μm) at central subfield. Multivariate regression with age stratification showed that RPE thinning became apparent after age 45 years. Among those aged $\leq$45, RPE–BM was significantly thicker among those of black or mixed/other race (+3.61 μm and +1.77 μm vs. white, respectively; $P < 0.001$) and higher hyperopia (+0.4 μm/D; $P < 0.001$), but not for other variables considered. Among those age >45, RPE–BM was significantly thinner with older age (−0.10 μm/year; $P < 0.001$), Asian ethnicity (−0.45 μm vs. white; $P = 0.02$), taller height (−0.02 μm/cm; $P < 0.001$), higher IOP (−0.03 μm/mmHg; $P < 0.001$), and regular smoking (−0.27 μm vs. nonsmokers; $P = 0.02$). In contrast, RPE–BM was significantly thicker among black or mixed/other race (+3.29 μm and +0.81 μm vs. white, respectively; $P < 0.001$) and higher hyperopia (+0.28 μm/D; $P < 0.001$). There was no significant association with sex or Chinese ethnicity.

Conclusions: We describe novel findings of RPE–BM thickness in normal individuals, a structure that varies with age, ethnicity, refraction, IOP, and smoking. The significant association with IOP is especially interesting and may have relevance for the etiology of glaucoma, while the association between age and smoking may have relevance for the etiology of age-related macular degeneration. *Ophthalmology 2016;■:1–13 © 2016 by the American Academy of Ophthalmology*

*Supplemental material is available at www.aaojournal.org.

Optical coherence tomography (OCT) is an imaging method that allows unprecedented in vivo study of the macula.[1,2] Advances in both hardware and software now facilitate resolution and segmentation of optical reflectivity boundaries thought to represent retinal sublayers with resolution of 4 to 6 μm including, but not limited to, the retinal pigment epithelium (RPE).[3,4] The RPE plays an important role in metabolic activity in the retina and is critical in visual function.[5] Failure of RPE function is involved in blinding diseases such as age-related macular degeneration, the

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leading cause of blindness among white people 65 years of age and older.[6–10]

Despite its importance, little is known about the normal distribution of RPE thickness in the nondiseased state. Postmortem histologic studies suggest increases in RPE autofluorescence and Bruch's membrane (BM) thickness with age.[11–13] A small histologic study of 18 maculae showed mean RPE thickness of 14.1 μm and mean BM thickness of 4.7 μm at the foveal center.[14] Histologic studies are limited in that they are postmortem or use enucleated eyes and can be affected easily by artifact during handling of tissue. In vivo investigations have been made with spectral-domain (SD) optical coherence tomography (OCT), but sample sizes remain small. A study of 25 healthy individuals showed mean RPE–BM complex thickness of 22.7 μm at the central subfield and also suggested that the thickness increases with age.[15] Recently, a database of SD OCT images was created, but includes images from only 115 healthy people and 269 with macular degeneration.[16]

The UK Biobank is a community-based cohort study in the United Kingdom and includes SD OCT image acquisitions from 67 321 participants in addition to systemic biomarkers and laboratory testing. To our knowledge, this is the largest study of retinal imaging yet undertaken. Our aim was to determine the distribution of the RPE among individuals who report no ocular disease and to examine variation with age, gender, race, refraction (between 6 and −6 diopters [D]), intraocular pressure (IOP; 6–21 mmHg), smoking status, blood pressure (BP), and body mass index (BMI).

Methods

The UK Biobank is a 22-site community-based cohort study of 502 656 noninstitutionalized civilian United Kingdom residents 40 to 69 years of age who were registered with the National Health Service. Health questionnaire and biological samples (blood, urine, and saliva) were collected from all participants. Participants identified their own race as either white, Chinese, Asian (in this cultural context, most were of Indian descent, but also included Pakistani and Bangladeshi subjects, as well as others), black, or mixed or other. People were asked whether they were current tobacco smokers; possible answers were no, occasional, or most or all days. Those who answered no to current smoking but who said they previously smoked occasionally or most or all days were considered former smokers. Health examination included BP and BMI. Eye data, including visual acuity, autorefraction, Goldmann-corrected IOP, and cornea-corrected IOP (Ocular Response Analyzer; Reichert, Depew, NY) were collected from 133 668 people. Retinal OCT measurements were acquired among the latter half of these; in total, 67 318 people underwent retinal OCT imaging. The North West Multi-center Research Ethics Committee approved the study (reference no., 06/MRE08/65), in accordance with the tenets of the Declaration of Helsinki. Detailed information about the study is available at the UK Biobank web site (www.ukbiobank.ac.uk).

Spectral-Domain Optical Coherence Tomography Imaging Protocol

Spectral-domain OCT imaging was performed using the Topcon 3D OCT 1000 Mk2 (Topcon, Inc, Oakland, NJ) after visual acuity, autorefraction, and IOP measurements were obtained. Image acquisition was performed under mesopic conditions, without pupillary dilation, using the 3-dimensional macular volume scan (512 horizontal A-scans/B-scan; 128 B-scans in a 6×6-mm raster pattern). The protocol specified that the right eye should be imaged first, but in 44 participants, the left eye was imaged first.

Analysis of Macular Thickness

All SD OCT images were stored as .fds image files on the UK Biobank supercomputers in Oxford, United Kingdom, with no prior analysis of macular thickness. Version 1.6.1.1 of the Topcon Advanced Boundary Segmentation (TABS) algorithm was used to segment the inner and outer retinal surfaces automatically.[17] Quality control measures included the image quality score, the internal limiting membrane (ILM) indicator, a validity count, and motion indicators. The image quality score gives a measure of signal strength for the scan, whereas the ILM indicator is a measure of the minimum localized edge strength around the ILM boundary across the entire volume. The ILM indicator is useful for identifying blinks, scans that contain regions of severe signal attenuation, segmentation errors, or a combination thereof. The validity count indicator is used to identify scans with a significant degree of clipping in the OCT scan's z-axis dimension. The motion indicators use both the nerve fiber layer (NFL) and full retinal thicknesses, from which Pearson correlations and absolute differences between the thickness data from each set of consecutive B-scans are calculated. The lowest correlation and the highest absolute difference in a scan serve as the resulting indicator scores. This last group of indicators identifies blinks, eye-motion artifacts, and segmentation failures. It should be noted that the various indicators, including the image quality score, tend to be highly correlated with one another.

Defining the Retinal Pigment Epithelium–Bruch's Membrane Complex on Spectral-Domain Optical Coherence Tomography

The TABS segmentation algorithm was used to delineate the RPE–BM complex. This slab of tissue on the OCT is represented by a thick hyperreflective band that lies on the outer aspect of the retina. The algorithm places a boundary on the inner and outer surfaces of this band, and the distance between these 2 boundary lines represents the thickness of RPE–BM complex.[18] Specifically, the inner boundary for the RPE–BM band corresponds to the TABS photoreceptor outer segment–RPE boundary, and the outer boundary is delineated by the BM–choroid boundary. Figure 1 shows an SD OCT line scan from the UK Biobank dataset with and without RPE segmentation lines.

Inclusion and Exclusion Criteria

The RPE–BM complex thickness values from the eyes of all patients who underwent SD OCT as part of the UK Biobank were used as a starting point for analysis. Patients were excluded from the analysis if they withdrew consent, had poor SD OCT signal strength and missing thickness values from any Early Treatment Diabetic Retinopathy Study subfield, image quality score less than 45, poor centration certainty, or poor segmentation certainty using TABS software (poorest 20% of images excluded based on each of the segmentation indicators). This led to the identification of the subset of patients with good-quality, well-centered images and central, stable fixation during the OCT scan. Patients with high refractive error of more than 6 D or less than −6 D, visual acuity worse than 20/30, self-reported glaucoma, IOP of 22 mmHg or

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