• Clinical Research •

Using choroidal thickness to detect myopic macular degeneration

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Abstract

● **AIM:** To explore the usage of choroidal thickness measured by swept-source optical coherence tomography (SS-OCT) to detect myopic macular degeneration (MMD) in high myopic participants.

● **METHODS:** Participants with bilateral high myopia (≤−6 diopters) were recruited from a subset of the Guangzhou Zhongshan Ophthalmic Center-Brien Holden Vision Institute High Myopia Cohort Study. SS-OCT was performed to determine the choroidal thickness, and myopic maculopathy was graded by the International Meta-Analysis for Pathologic Myopia (META-PM) Classification. Presence of MMD was defined as META-PM category 2 or above.

● **RESULTS:** A total of 568 right eyes were included for analysis. Eyes with MMD (n=106, 18.7%) were found to have older age, longer axial lengths (AL), higher myopic spherical equivalents (SE), and reduced choroidal thickness in each Early Treatment Diabetic Retinopathy Study (ETDRS) grid sector (P<0.001). The area under the receiver operating characteristic (ROC) curves (AUC) for subfoveal choroidal thickness (0.907) was greater than that of the model, including age, AL, and SE at 0.6249, 0.8208, and 0.8205, respectively. The choroidal thickness of the inner and outer nasal sectors was the most accurate indicator of MMD (AUC of 0.928 and 0.923, respectively). An outer nasal sector choroidal thickness of less than 74 μm demonstrated the highest odds of predicting MMD (OR=33.8).

● **CONCLUSION:** Choroidal thickness detects the presence of MMD with high agreement, particularly of the inner and outer nasal sectors of the posterior pole, which appears to be a biometric parameter more precise than age, AL, or SE.

● **KEYWORDS:** high myopia; choroidal thickness; myopic macular degeneration; swept-source optical coherence tomography

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INTRODUCTION

Myopic maculopathy is a major cause of visual impairment in patients with high myopia[1-4]. According to a new grading system based on the long-term

observation of fundus lesions seen in high myopia using the International Meta-Analysis for Pathologic Myopia (META-PM) classification, myopic maculopathy lesions were divided into five categories: “no myopic retinal lesions” (Category 0), “tessellated fundus only” (Category 1), “diffuse chorioretinal atrophy (DCA)” (Category 2), “patchy chorioretinal atrophy” (Category 3), and “macular atrophy” (Category 4)[5]. Three additional features [lacquer cracks, choroidal neovascularization (CNV), and Fuchs spot] were deemed “plus” signs. Based on this new classification, the presence of myopic macular degeneration (MMD) is defined as myopic maculopathy of Category 2 or above or the presence of any “plus” signs.

DCA, which is regarded as the distinguishing feature of eyes with MMD, has traditionally been identified from color fundus photographs. The identification of this poorly demarcated yellow-white lesion is often affected by the exposure of the fundus photograph, which in turn is affected by quality of the fundus camera and pupil size. Furthermore, the assessment of DCA is highly dependent on the experience of the fundus graders and their familiarity with the pathology. Therefore, objective indicators are needed in order to accurately and consistently detect DCA.

The pathogenesis of DCA is thought to arise from axial elongation and posterior staphyloma formation causing mechanical stretching of the retina, choroid, and sclera, which ultimately thins each layer[6-9]. With the rapid development of optical coherence tomography (OCT) imaging technology in the last decade, it is now possible to perform more detailed assessments of the choroid. Choroidal thinning, which can be measured with non-invasive OCT, is a relatively specific characteristic of high myopia. Wong *et al*[10] demonstrated increased thinning of the choroid with increasing MMD severity by using swept-source OCT (SS-OCT), which may suggest that the progressive loss of choroid may be important in the pathogenesis of MMD. Moreover, Yokoi *et al*[11] noted that peripapillary DCA in children is associated with abrupt segmental thinning of the choroid in the temporal peripapillary region. The correlation between DCA and choroidal thinning may be used as a candidate biometric marker for the early detection of MMD.

To date, the exact choroidal thickness cutoff value for assessing the presence or absence of MMD in highly myopic eyes remains unknown, and the utility of this particular objective measure is still yet to be explored. The purpose of this study was to explore the diagnostic value of choroidal thickness measured by SS-OCT in detecting MMD in high myopia.

SUBJECTS AND METHODS

Ethical Approval The participants were recruited from a subset of the Guangzhou Zhongshan Ophthalmic Center-Brien Holden Vision Institute High Myopia Cohort Study. Ethics approval for this study was obtained from the Research Ethics Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University, China (2012KYNL002). All procedures in this study were conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects involved after explanation of the purpose and possible risks of the study.

The details of the study have been previously described in the literature[12]. During a period from November 2011 to October 2012, participants with bilateral high myopia, defined as spherical equivalent (SE) worse than -6.00 D, who visited the optometry clinic of Zhongshan Ophthalmic Center, Sun Yat-sen University, were invited to participate in this study. A total of 890 participants undertook a baseline examination and were scheduled to return every 24mo for follow-up examinations for a total period of 10y. Participants who had attended the examination in 2013–2014 were enrolled in this study, and this cross-sectional data were included for analysis. The exclusion criteria were as follows: any history of intraocular or refractive surgeries; any history of severe eye disorders, including diabetic retinopathy, age-related macular degeneration, or uveitis; any severe systemic conditions; and poor quality OCT images or OCT images that were too thin for accurate measurement.

Data and Image Acquisition At the 24-month follow-up visit, each participant underwent a series of ophthalmic examinations, including visual acuity assessment, ocular biometry, intraocular pressure measurement, visual fields, cycloplegic refraction, slit lamp examination, fundus photography, autofluorescence, and SS-OCT. The study protocol has previously been described elsewhere[12].

SS-OCT Analysis and Measurement of Choroidal Thickness Posterior segment SS-OCT was carried out on all participants using a Topcon Atlantis DRI OCT-1 system (Topcon, Tokyo, Japan). A 1050 nm wavelength light source with a scanning speed of 100 000 A-scans per second was used, and a 12-line radial scan pattern was performed in the dilated eyes of all participants. Each image produced was an average of 32 overlapped consecutive scans focused on the fovea, covering an area of 12 mm × 12 mm. All measurements were conducted from 10 *a.m.* to 3 *p.m.* to reduce the impact of diurnal variation. Built-in software was used to identify the borders of each retinal layer and construct topographic maps.

Choroidal thickness was defined as the distance between Bruch’s membrane and the choroid–sclera interface. The Early Treatment Diabetic Retinopathy Study (ETDRS) grid was used for the choroidal thickness map, and the mean regional thickness was calculated for each of the nine sectors of the grid. The diameters for the central foveal circle, parafoveal

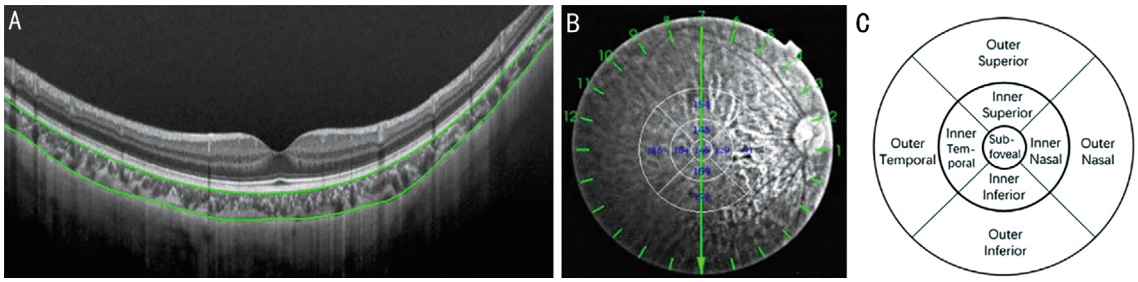

Figure 1 Swept-source optical coherence tomography scans showing the boundary of the choroid in a highly myopic eye and demonstrating how the Early Treatment Diabetic Retinopathy Study (ETDRS) grid was applied for the choroidal thickness map A: The boundary of choroidal thickness, from the outer surface of Bruch's membrane to the inner surface of the sclera, was automatically detected in the radical scan. B: Fundus image showing 12 scan lines running through the fovea. The ETDRS grid was applied, and the mean choroidal thickness was obtained in each sector. C: Diagram of the ETDRS grid. The central, middle, and outer circles, which represent, respectively, 1000, 3000, and 6000 μm in diameter, divided the posterior pole into nine sectors: subfoveal, outer nasal, outer temporal, outer superior, outer inferior, inner nasal, inner temporal, inner superior, and inner inferior sectors.

circle, and perifoveal circle measure 1000, 3000, and 6000 μm respectively, and each circle was further divided into superior, inferior, temporal, and nasal quadrants (Figure 1).

Two trained ophthalmologists (Liu R and Li ZX), who were blinded to the participants' characteristics, independently evaluated the segmentation and delineation of choroidal thickness. In cases where the built-in software failed to accurately identify the borders, these were manually adjusted. The choroidal thickness measurements provided by both graders were then averaged.

Fundus Color Photograph Grading Two 45-degree color fundus photographs, centered at the optic nerve and macula, were obtained for each eye through fully dilated pupils (Canon CR2, Tokyo, Japan). Fundus photographs were graded according to the International META-PM Classification (by Liu R and Li ZX)[5], which classifies myopic maculopathy into five categories: "no myopic retinal lesions" (C0), "tessellated fundus only" (C1), "DCA" (C2), "patchy chorioretinal atrophy" (C3), and "macular atrophy" (C4). Plus lesions, including lacquer cracks, myopic CNV, and Fuchs spots, were also identified.

Statistical Analysis Statistical analyses were performed using Stata software version 14.0 (Stata Corp., College Station, TX, USA). Continuous variables such as age, axial length (AL), SE, and the choroidal thickness of each ETDRS grid sector were compared between eyes with and without MMD using the independent *t*-test. The area (AUC) under the receiver operating characteristic (ROC) curve was determined for each of the biometric parameters in order to identify the ideal parameter to detect MMD in highly myopic eyes. For each parameter, the best cutoff was determined by the Youden index, and dichotomization was performed based on those cutoffs. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each variable with the Chi-square test.

RESULTS

Of the 657 enrolled participants, 89 were excluded: 77 without SS-OCT images or radical scans, two with blurry images, and eight with a choroid that was too thin to accurately distinguish its boundary. A further one eye with Fuchs spot and one eye with macular atrophy (C4; representing the scar stage and atrophy stage of CNV, respectively) were also excluded, leaving a total of 568 patients (86.5%) in this study. Only data from the right eyes were presented because of the high correlation between the two eyes of the same individual. The proportions of C0, C1, C2, and C3 myopic maculopathy were 59.7% (339 eyes), 21.7% (123 eyes), 17.3% (98 eyes), and 1.4% (8 eyes), respectively. Lacquer cracks were observed in 20 (2.38%) eyes, and always in coexistence with DCA (C2).

Eyes graded as C0 and C1 were classified into the non-MMD group, while C2 and above were classified into the MMD group. Table 1 shows a comparison of patient demographics and choroidal thickness data in eyes with and without MMD. Patients with MMD were older than those without MMD (P<0.001). No significant difference was found with gender between the groups (P=0.382). MMD eyes had longer ALs (P<0.001) and more severe spherical equivalent refractive error (P<0.001) than non-MMD eyes. For each ETDRS grid sector, the mean choroidal thickness of non-MMD eyes was significantly thicker than MMD eyes (P<0.001). These results were similar after adjusting for age and gender.

The ROC curves for age, SE, AL, and subfoveal choroidal thickness (SFCT) are shown in Figure 2. The accuracy of SFCT (AUC of 0.907) in distinguishing highly myopic eyes with MMD from those without MMD was better than age, AL, and SE (AUCs of 0.6249, 0.8208, and 0.8205, respectively). Table 2 summarizes the AUC for each parameter to detect MMD, as well as the OR, sensitivity, and specificity of the best cutoff points as determined by the Youden index. The

Table 1 Comparison of demographics, axial length, spherical equivalent, and choroidal thickness in eyes with and without MMD

Parameters	Non-MMD (*n*=462)	MMD (*n*=106)	*P*	*P*-value adjusted for age and gender
Age	21.5±10.1	29.3±16.3	<0.001	—
Gender (M/F)	218/244	55/51	0.382	—
Axial length (mm)	27.3±1.2	30.6±9.7	<0.001	<0.001
Spherical equivalent (D)	−9.7±2.4	−13.0±3.6	<0.001	<0.001
SFCT (μm)	172.0±63.6	73.1±47.4	<0.001	<0.001
Nasal CT (μm)				
Outer nasal	112.2±43.8	48.4±24.1	<0.001	<0.001
Inner nasal	150.1±56.0	61.2±34.4	<0.001	<0.001
Superior CT (μm)				
Outer superior	197.4±61.8	94.2±47.5	<0.001	<0.001
Inner superior	186.9±63.9	85.2±49.8	<0.001	<0.001
Inferior CT (μm)				
Outer inferior	166.1±56.4	78.3±37.1	<0.001	<0.001
Inner inferior	171.2±61.7	78.7±43.0	<0.001	<0.001
Temporal CT (μm)				
Outer temporal	200.8±58.7	108.2±58.6	<0.001	<0.001
Inner temporal	190.8±62.9	90.3±55.3	<0.001	<0.001

SFCT: Subfoveal choroidal thickness; CT: Choroidal thickness; MMD: Myopic macular degeneration; D: Diopter.

Table 2 Clinical parameters to detect myopic macular degeneration in high myopia

Parameters	AUC	*P*	Best cutoff	MMD risk		Sensitivity	Specificity
				For	OR (95%CI)		
Age (y)	0.627	<0.001	24	>24	3.0 (1.9–4.6)	53.0%	74.1%
Axial length (mm)	0.821	<0.001	28.34	>28.34	11.7 (7.2–19.0)	70.8%	84.4%
Spherical equivalent (D)	0.821	<0.001	−12.00	<−12.00	10.4 (6.4–16.6)	67.6%	84.1%
SFCT (μm)	0.908	<0.001	105	<105	25.8 (14.9–44.8)	82.1%	85.7%
Nasal CT (μm)							
Outer nasal	0.923	<0.001	74	<74	33.8 (17.7–64.3)	89.6%	80.7%
Inner nasal	0.928	<0.001	85	<85	27.7 (16.0–47.8)	81.3%	86.4%
Superior CT (μm)							
Outer superior	0.911	<0.001	120	<120	28.2 (16.4–48.4)	80.2%	88.7%
Inner superior	0.908	<0.001	120	<120	31.4 (19.0–62.2)	84.2%	85.6%
Inferior CT (μm)							
Outer inferior	0.909	<0.001	120	<120	24.4 (13.3–44.7)	87.7%	78.6%
Inner inferior	0.903	<0.001	118	<118	23.6 (13.2–42.1)	85.9%	80.5%
Temporal CT (μm)							
Outer temporal	0.867	<0.001	155	<155	13.7 (8.3–22.9)	78.3%	79.9%
Inner temporal	0.891	<0.001	127	<127	19.1 (11.4–32.2)	78.3%	84.4%

Measures include AUC, best cutoff, and OR for age, gender, spherical equivalence, and CT in each ETDRS grid measured by swept-source optical coherence tomography. AUC: Area under the curve; ETDRS: Early Treatment Diabetic Retinopathy Study; OR: Odds ratio; SFCT: Subfoveal choroidal thickness; CT: Choroidal thickness; D: Diopter; MMD: Myopic macular degeneration.

most accurate biometric parameter with the highest AUC was choroidal thickness in the nasal sectors (AUC of 0.923 for the outer nasal sector and 0.928 for the inner nasal sector). The choroidal thickness cutoff points that provided the greatest odds of differentiating MMD from non-MMD eyes were an outer nasal sector measuring less than 74 μm (OR=33.8), inner superior sector measuring less than 120 μm (OR=31.4), outer superior sector measuring less than 120 μm (OR=28.2), inner nasal sector measuring less than 85 μm (OR=27.7), and an SFCT measuring less than 105 μm (OR=25.8).

DISCUSSION

Although previous studies in the literature have demonstrated that the choroidal thickness of highly myopic eyes with MMD is thinner than those without MMD[13-14], a validated cutoff value has not been determined. In this study, highly myopic eyes with MMD were older and had a longer AL and more severe

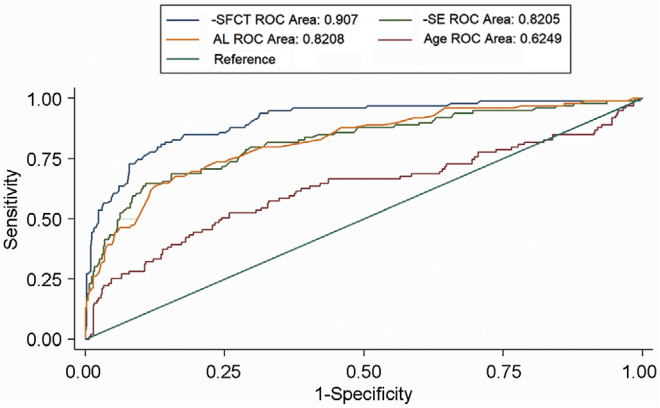

Figure 2 Receiver operating characteristic (ROC) curves of four biometrics for the detection of myopic macular degeneration The area under the curve (AUC) from the highest to lowest; subfoveal macular choroidal thickness (SFCT, 0.907), axial length (AL, 0.8208), spherical equivalent (SE, 0.8205), and age (0.6249).

refractive error. By using SS-OCT, we identified imaging parameters that could be used to differentiate eyes with MMD from those without. The choroidal thickness was considered to be the most accurate indicator of myopic degenerative changes and was superior to other biometrics such as age, AL, and SE. The choroidal thickness cutoff values for the subfoveal, inner nasal, and outer nasal sectors for screening eyes for the presence of MMD were 105, 85, and 74 μm, respectively.

The AUC for age to detect MMD in highly myopic eyes was relatively low, measuring only 0.627. The incidence of chorioretinal atrophy has traditionally been thought to increase with age[4]. However, there has been an increase in the detection of DCA in children due to an increase in the prevalence of high myopia in younger generations over the past decades[15]. In 2005, Kobayashi *et al*[16] reported on 46 children aged 1 to 8 years old with high myopia and found that 16.3% of eyes had mild DCA around the optic disc. Similarly, our unpublished data studying children with high myopia aged 7 to 12 (n=110) indicated that up to 20.9% had DCA located in the parapapillary zone. Therefore, older age may not be the best predictor for MMD since children clearly remain susceptible to chorioretinal atrophy, particularly in the setting of high myopia driven by genetic factors.

Elongation of the globe with or without posterior staphyloma formation is considered to be the most important factor in the development of degenerative changes in highly myopic eyes[17]. This study demonstrated that eyes with an AL of 28.34 mm or longer were 11.7 times more likely to develop MMD compared to eyes with an AL shorter than 28.34 mm. The AUC for AL and SE to detect MMD were well matched (both 0.821) since these parameters were generally highly correlated for each individual participant. Due to the fact that only patients with an SE worse than −6.00 D were included in this study (not taking into account refractive or axial high myopia), the sensitivity of SE (67.6%) was slightly lower than AL (70.8%), although they appeared to share a similar specificity (88.4% and 88.1%, respectively). However, pathologic chorioretinal changes, such as DCA, lacquer cracks, and Fuchs spot, can still occur in myopic eyes with an AL shorter than 26.5 mm, indicating that an SE and AL cutoff may not adequately predict the pathological fundus features of high myopia[18].

Several studies have demonstrated that high myopia is characterized by axial elongation, which causes biomechanical stretching and thinning of the choroid, and that choroidal thickness is strongly correlated with age, AL, and refractive error[4]. Consistent with our findings, Wong *et al*[10] measured 62 highly myopic eyes with SS-OCT and observed that eyes with MMD had a significantly thinner choroidal thickness than those without MMD. Fang *et al*[8] included 884 high myopes and found that the SFCT was thinning with increasing MMD severity. Moreover, previous studies have also found that the presence of lacquer cracks and CNV are significantly associated with thinning of the SFCT[19]. Similarly, in our study, the AUC of SFCT for detecting C2 or worse maculopathy was greater than age, AL, and SE, implying that choroidal thickness may be a reliable indicator of the severity of degeneration in these highly myopic eyes.

Besides mechanical stretching, vascular and ischemic components have also been proposed to play an important role in the pathogenesis of lacquer cracks and chorioretinal atrophy[20]. Loss of choroidal large vessels and the associated fibrotic changes may lead to obstruction of choroidal flow, changing the level of vascular endothelial growth factor (VEGF) from retinal pigment epithelium (RPE)[21-23], which in turn influences choroidal thickness and ultimately results in choroidal atrophy[13]. Compared to AL and SE, choroidal thickness may be a more comprehensive reflection of the pathologic changes in high myopia.

Compared to the findings of our previous study and the related study conducted by Li *et al*[24] and He *et al*[25], our current study further enhances the understanding of the varied subfield distribution of choroidal thickness in MMD and its importance in the classification of MMD. Our data indicate that the choroidal thickness of the outer and inner nasal sectors was more accurate than the SFCT in the detection of MMD. One explanation is that DCA generally first appears around the optic disc and then extends to the macular region, until the atrophy finally encompasses the entire area within the staphyloma. Yokoi *et al*[11] recently reported on 41 eyes of 21 highly myopic children (age ≤15y) and concluded that peripapillary DCA was characterized by an abrupt thinning of the choroid in the temporal parapapillary region and subfoveal

choroid. The suggested choroidal thickness cutoff value to distinguish children with and without parapapillary DCA was <60 μm at 2500 μm nasal to the foveola, which is similar to the present study cutoff value of <74 μm in the outer nasal sector. The cutoff for choroidal thickness established in our study offers significant promise for clinical application. Its precision and ease of measurement, coupled with the potential for early detection of MMD, make it an invaluable tool in diverse clinical settings. This is especially relevant considering the increasing prevalence of high myopia and the need for timely intervention. However, this conclusion warrants further validation in a future study with a larger sample size and caution must be applied when making direct comparisons of the cutoff value in the present study with other previous reports because of the different SD-OCT machines used, as well as the variation in age and refractive status of the participants.

There are several limitations of this study. First, the choroidal thickness cutoff values might not be applicable to non-Asian populations, which generally have a lower prevalence of high myopia and its associated complications. Second, 77 patients (11.7%) were excluded due to a lack of SS-OCT scans, which may have influenced the cutoff values of choroidal thickness. However, we expect the influence of this exclusion would be small because this patient selection would be random. Third, since this study was conducted retrospectively, any predictions on the longitudinal development of MMD should be cautiously interpreted. A prospective validation study is required to confirm the cutoff values. Finally, this study did not explore the relationship between choroidal thickness and the severity and extent of MMD, which would require a larger sample size.

In conclusion, we found choroidal thickness to be a more precise biometric parameter in the detection of MMD when compared to age, AL, and SE. In particular, the choroidal thickness of the inner and outer nasal segments was more accurate than the SFCT. We suspect this is because DCA generally starts from the temporal peripapillary region and eventually progresses toward the macular region. The findings of this study suggest that progressive thinning of the choroid may represent a useful objective marker for the early detection of MMD in high myopia.

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