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Choriocapillaris Changes in Myopic Macular Degeneration

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Received: September 1, 2021
Accepted: January 28, 2022
Published: February 24, 2022

Keywords: choriocapillaris; myopic macular degeneration; optical coherence tomography angiography; retinal ischemia

Citation: Li J, Zhou H, Feinstein M, Wong J, Wang RK, Chan L, Dai Y, Porco T, Duncan JL, Schwartz DM. Choriocapillaris changes in myopic macular degeneration. Transl Vis Sci Technol. 2022;11(2):37, https://doi.org/10.1167/tvst.11.2.37

Purpose: Myopic macular degeneration (MMD) can cause irreversible vision loss. Thinner choroid is associated with increased MMD severity. This cross-sectional study analyzed choriocapillaris (CC) alterations in MMD.

Methods: Axial length (AL), best-corrected visual acuity (BCVA), fundus photography, and swept-source optical coherence tomography angiography (SS-OCTA) were assessed in controls and high myopes (spherical equivalent ≤ -6 diopters). Myopic patients with grade 2 MMD (macular diffuse chorioretinal atrophy [MDCA]), high axial myopia (AL $\geq$ 26.5 mm), and BCVA $\geq$ 20/40 were compared with controls without MMD. CC mean thickness was measured from 3 $\times$ 3-mm SS-OCTA scans by identifying CC peaks in A-scan intensity profiles. CC flow deficit percent (CC FD%) was quantified using a fuzzy C-mean local thresholding method on en face OCTA images. Multivariate regressions compared CC thickness and CC FD% between myopic patients and controls, correcting for age and other confounders.

Results: Sixteen eyes with MDCA (AL, 26.96–33.93 mm; ages, 40–78 years) were compared with 51 control eyes (AL, 21.65–25.84 mm; ages, 19–88 years). CC thickness in patients with MDCA was 66% lower than that in controls (5.23 $\pm$ 0.68 µm [mean $\pm$ SD] vs. 15.46 $\pm$ 1.82 µm; $P < 0.001$). CC FD% in patients with MDCA was 237% greater than in controls (26.5 $\pm$ 4.3 vs. 11.2 $\pm$ 4.6; $P < 0.001$).

Conclusions: Patients with MDCA with good visual acuity had thinner CC and increased CC FD%, or reduced CC flow, compared with controls. Patients with grade 2 MMD and good visual acuity demonstrated significant choriocapillaris alterations, suggesting that choriocapillaris perfusion defects contribute to the pathogenesis of MMD.

Translational Relevance: Given the potential vascular etiology for MMD, current research about revascularization of ischemic retina likely has implications for the treatment of MMD.

Introduction

The prevalence of myopia is increasing worldwide; it is estimated that, by 2050, there will be 5 billion myopes and 1 billion high myopes, defined as having a refractive error of spherical equivalent (SE) of ≤ -0.50 diopters (D) and ≤ -5.00 D, respectively.[1] In addition, not only is the worldwide prevalence of myopia increasing, but the prevalence of high myopia is also disproportionately increasing in East Asian young adults.[2–4] High myopia is associated with cataract, glaucoma, retinal detachment, and myopic macular degeneration (MMD).[1] The prevalence of pathologic myopia myopic changes that can lead to legal blindness increases when the SE crosses the threshold into high myopia, which has been variably defined in the literature as ≤ -5.00 to ≤ -6.00 D.[5,6] The international meta-analysis for pathologic myopia (META-PM) classification describes the increasing severity of MMD as grade 0 (no fundus changes), grade 1 (tessellated fundus), grade 2 (diffuse chorioretinal atrophy),

grade 3 (patchy chorioretinal atrophy), and grade 4 (macular atrophy). The latter stages are associated with severe, irreversible vision loss. Grades 0 and 1 are defined as absence of MMD, and grade 2 macular diffuse chorioretinal atrophy (MDCA) is defined as the first stage of MMD.[7]

Although the natural history of progressive MMD is well characterized, the etiology underlying this progression is unclear. Recent studies have shown an association between decreased choroidal thickness and progressively severe MMD.[8] However, it is unclear whether choroidal thinning is the primary antecedent event to MMD, or if MMD may be a primarily retinal or retinal pigment epithelium (RPE) degeneration with secondary effects on the choroid. In addition, although overall decreased choroidal thickness has been associated with progressively severe MMD, it is unclear if choriocapillaris (CC) thickness is affected, or if the thinning primarily affects the larger choroidal vessels of Sattler's and Haller's layers. Interestingly, in other disease processes affecting the outer retina, such as geographic atrophy in age-related macular degeneration, reduced CC perfusion is significantly correlated with photoreceptor loss, suggesting that reduced CC perfusion contributes to the development of macular atrophy.[9]

Recent advances in optical coherence tomography angiography (OCTA) allow further elucidation of the relationship between MMD and CC alterations. Compared with spectral domain OCTA, swept-source OCTA (SS-OCTA) allows better CC visualization due to the longer wavelength used and is less susceptible to gradual decay in sensitivity as a function of depth because it does not rely on a spectrometer.[10,11] This makes SS-OCTA advantageous for imaging highly myopic eyes with a long axial length (AL). Prior OCTA studies have shown a decrease in CC perfusion in eyes with MMD compared with highly myopic eyes, but these studies either were qualitative or did not perform an analysis based on the severity of MMD using the international classification.[12,13] A recent study by Zheng et al.[14] demonstrated that decreased retinal perfusion density was associated with worse MMD grade and showed larger CC flow deficits in peripapillary diffuse chorioretinal atrophy (PDCA) compared with tessellated fundus. However, the authors did not report the CC thickness and flow deficits quantitatively in eyes with MDCA.

The present study used novel quantitative algorithms to overcome the technical limitations of prior studies, enabling us to ask whether CC thickness and flow are abnormal in eyes with the earliest stage of pathologic myopia, in which visual acuity is well preserved.[15] We sought to quantitatively analyze changes in CC thickness and CC flow deficit percent (CC FD%) in patients with the earliest stage of myopic macular degeneration (MDCA), as compared with normal controls, in order to elucidate CC metrics in the first stage of disease.[7] These patients have good central acuity and preserved OCT outer retinal landmarks (external limiting membrane, ellipsoid zone, interdigitation zone, and RPE/Bruch's membrane). We hypothesized that a reduction in CC thickness and/or increased CC FD% in grade 2 MMD patients may presage development of frank chorioretinal atrophy that is characteristic of more severe MMD with visual loss.

Methods

We conducted a cross-sectional study at the University of California, San Francisco (UCSF). The study was approved by the Institutional Review Board of UCSF, and informed written consent was obtained from all subjects. The study adhered to the tenets of the Declaration of Helsinki and was compliant with the Health Insurance Portability and Accountability Act.

We recruited controls and high myopes (defined as SE ≤ -6.00 D in either eye in our study, with astigmatism no higher than -2.00 D) from optometry, comprehensive, and retina clinics at UCSF. Patients who fulfilled the inclusion criteria of having MDCA, high axial myopia (AL $\geq$ 26.5 mm), and BCVA 20/40 or better without significant ocular comorbidity were defined as the myopic patients. Subjects with a wide range of age and axial lengths, with MMD of 0 and no significant ocular comorbidities, were recruited as controls to improve precision in controlling for age and AL in multivariate regression. Age and best-corrected visual acuity (BCVA) were taken from the medical chart. Recruitment was performed from September 2019 to March 2020.

Patient Imaging

Axial length was measured with a ZEISS IOLMaster (Carl Zeiss Meditec, Jena, Germany), and fundus photographs were taken with a Topcon SL-7E slit lamp (Topcon Corporation, Tokyo, Japan) at least 20 minutes after pupillary dilation with 1% tropicamide and 2.5% phenylephrine. Based on the META-PM classification system, fundus photos were categorized into the appropriate MMD grade by two trained independent ophthalmologists, with a third ophthalmologist available for adjudication if the initial grades assigned did not match. Grade 2 MMD was defined as yellowish color in the posterior pole without discrete regions of RPE atrophy. All subjects were imaged by

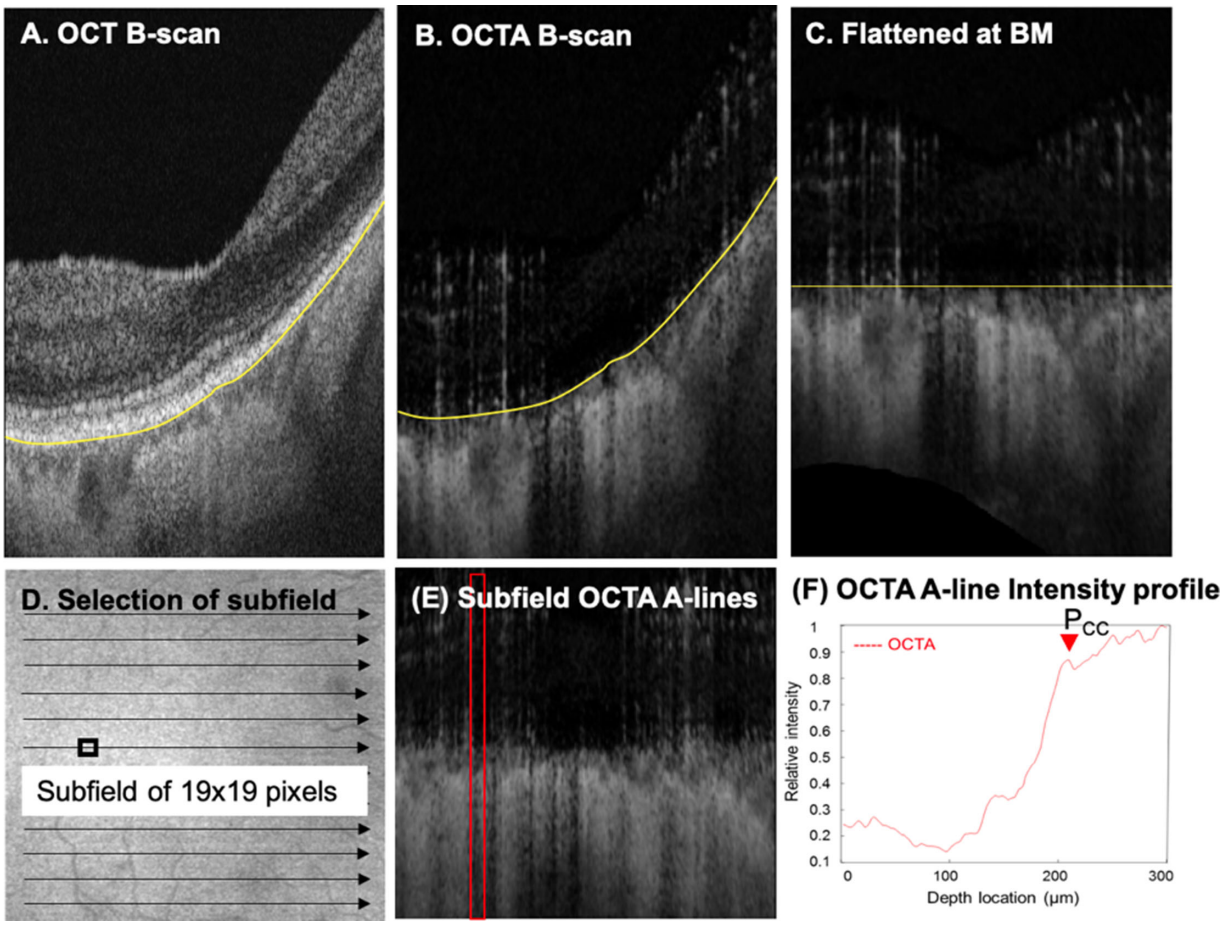

Figure 1. Methodology for generating OCTA A-scan intensity profiles from OCT B-scans. (**A**) BM segmentation (*yellow line*) on a representative OCT B-scan. (**B**) BM segmentation (*yellow line*) superimposed on the corresponding OCTA B-scan. (**C**) The OCTA B-scan was flattened at Bruch's membrane (BM; *yellow line*). (**D**) En face view of the moving window of a selected subfield of 19 × 19 pixels on an OCTA en face image. (**E**) Side view of the moving window of a selected subfield of 19 × 19 pixels on an OCTA B-scan. (**F**) A representative OCTA A-scan intensity profile generated by averaging the OCTA signals along depth within the selected subfield. Peak of CC (*arrow*) was identified as the first peak beneath BM.

SS-OCTA (PLEX Elite 9000; Carl Zeiss Meditec) using a standardized scanning protocol with scans extending 3 × 3 mm centered on the fovea. OCTA images were excluded if they contained significant motion or shadowing artifacts, had a signal strength less than 7 as defined by the manufacturer, or had other macular pathologies that were not attributed to MMD.

Analysis of Choriocapillaris Thickness

Choriocapillaris thickness was measured by an automatic method recently developed by Zhou et al.[16] Briefly, SS-OCTA scans were flattened at Bruch's membrane (semi-automatically segmented from corresponding OCT B-scans, with manual correction when necessary after automated segmentation).[17] An SS-OCTA A-scan intensity profile at each en face location was then generated by plotting the averaged SS-OCTA signal intensity along the depth direction in a subfield of 19 × 19 pixels. The CC peak was identified as the first peak after the location of Bruch's membrane, and CC thickness was measured as the full width at half maximum of the CC peak (Fig. 1). This method has been shown to have excellent repeatability and has been used in other diseased eyes with thin choroids.[18,19] Figure 2 shows representative OCTA A-scan intensity profiles in both an MDCA patient and control, with CC thickness measured as the full width at half maximum of the first peak after Bruch's membrane.

Analysis of Choriocapillaris Flow Deficits

OCT en face images were scrutinized pixel by pixel through depth to qualitatively evaluate the thickness of CC slab. A choroidal vasculature map was produced using minimum projection of choroid slab in the

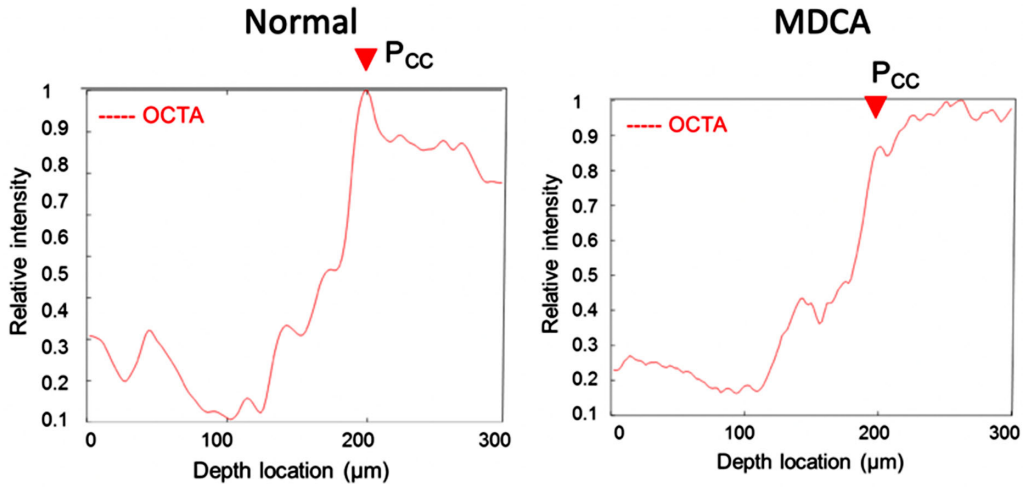

Figure 2. Representative OCTA A-scan intensity profiles with CC peak denoted in a normal control and MDCA patient. P_{CC}, choriocapillaris peak.

structural cube, which indicates the location of large choroidal vessels beneath the CC.[18] CC enface images were generated by the sum projection of OCTA slab located 2-μm below Bruch's membrane with a thickness of 8 μm. Quantification of CC FD% was then performed as previously published.[20] In brief, the en face CC OCTA image was first compensated with structural CC signals to minimize potential shadowing effects caused by possible heterogeneous properties of the RPE complex,[21] and then retinal projection artifacts were removed by a validated algorithm.[22] CC FDs were segmented using the fuzzy C-means method previously published.[16] CC FD% was finally calculated as the area percentage of CC FDs in the AL-corrected 3 × 3-mm region.[23] A 3 × 3-mm axial length-corrected region was used in part to minimize the influence of tilt artifact; no further correction was made, as any remaining tilt artifact would overestimate CC thickness, making any differences observed more significant. Figure 3 shows a representative CC FD% calculation in both an MDCA patient and a control, with flow deficits denoted in red pixels. Regions of retinal vessel projections were excluded in measurements (labeled in yellow).

Statistical Analysis

Descriptive statistics were calculated for characteristics of the myopic patients and controls. The primary outcome was the difference in CC thickness between myopic patients and controls, and the secondary outcome was the difference in CC FD% between myopic patients and controls. Univariate and multivariate regression models were analyzed for each of these outcomes, including confounders demonstrated to be significant in prior literature.[14] Specifically, age has been associated with decreased choroidal and CC thickness[14]; thus, the regression models included a linear correction for age. Gender and axial length were also considered as potential confounders in stepwise regression. A linear mixed model with random effect for person was used to account for paired eyes. Analysis was completed with R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) with statistical significance set at $P < 0.05$.

Results

Sixteen eyes of 11 patients met the inclusion criteria. Fifty-one eyes from 47 controls were included. Table 1 describes the demographics of the two groups. Mean BCVA (in logMAR) was 0.08 in MDCA patients and was 0.00 in controls. There were proportionally more females in the MDCA group than in the control group. The MDCA patients ranged in age from 40 to 78 years (mean ± SD, 65.7 ± 12.8 years) with AL from 26.96 to 33.93 mm (29.67 ± 2.04 mm). The controls ranged in age from 19 to 88 years (55.6 ± 23.3 years) with AL from 21.65 to 25.84 mm (23.87 ± 1.04 mm).

In stepwise multivariate linear regression, both decreased CC thickness (Table 2) and increased CC flow deficit percentage (Table 3) were significantly associated with MDCA. CC FD% was significantly associated with increased age, with the association between CC thickness and age trending toward significance. Potential confounding variables of gender and

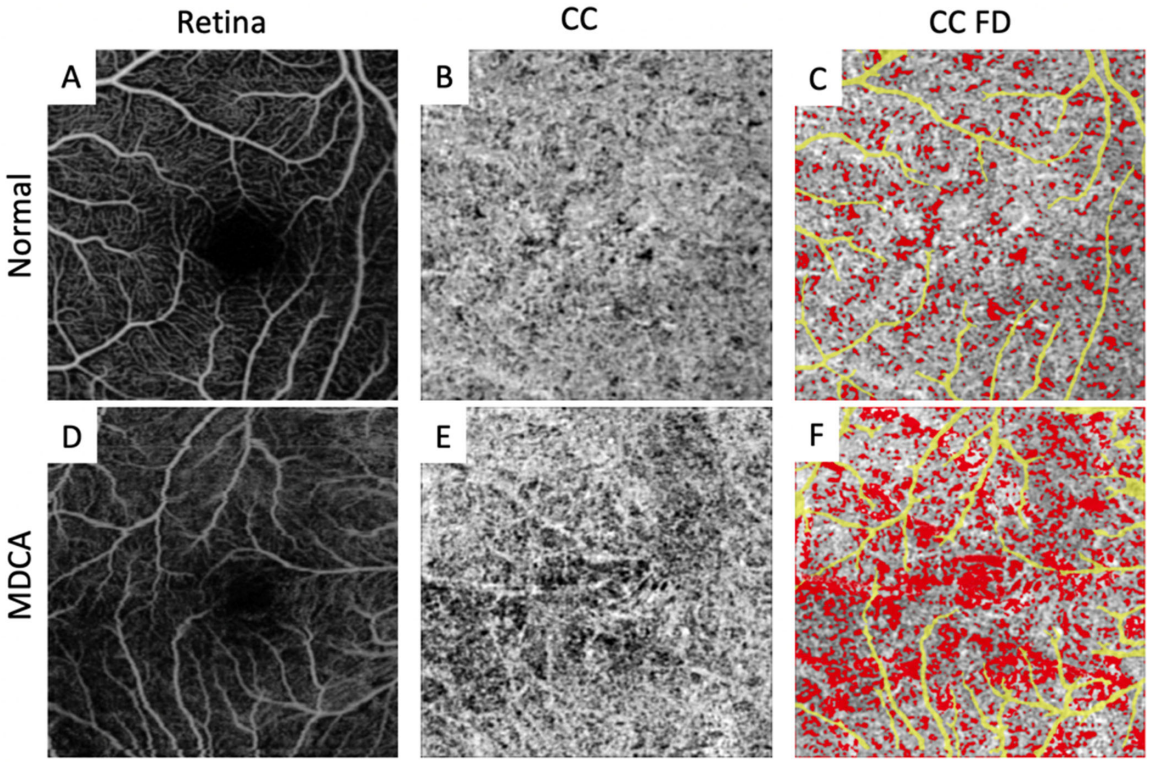

Figure 3. Representative CC flow deficit calculation in a normal control and MDCA patient. (A, D) En face OCTA image of retina. (B, E) En face OCTA image of CC. (C, F) En face OCTA image of CC overlaid with CC FD (*red*) and retinal vessels (*yellow*) in a normal eye and a MDCA eye, respectively.

Table 1. Characteristics of Eyes With Macular Diffuse Chorioretinal Atrophy Versus Controls

Characteristic	Macular Diffuse Chorioretinal Atrophy	Controls
Eyes, *n* (%)	16 (24)	51 (76)
Subjects, *n* (%)	11 (19)	47 (81)
BCVA (logMAR), mean ± SD	0.08 ± 0.11	0.00 ± 0.03
Age at examination (yr)		
Mean ± SD	65.7 ± 12.8	55.6 ± 23.3
Median (min, max)	70.0 (40.0, 78.0)	52.0 (19.0, 88.0)
Female gender, *n* (%)	10 (91)	26 (51)
Axial length (mm)		
Mean ± SD	29.67 ± 2.04	23.87 ± 1.04
Median (min, max)	29.63 (26.96, 33.93)	23.63 (21.65, 25.84)

axial length were not statistically significant. CC thickness in patients with MDCA measured 5.23 ± 0.68 µm versus 15.46 ± 1.82 µm in controls, whereas CC FD% in MCDA patients was 26.5 ± 4.3 compared with 11.2 ± 4.6 in controls (Table 4). The differences, demonstrating a 66% reduction in CC thickness and a 237% increase in CC FD% in MCDA, were both statistically significant ($P < 0.001$). The findings were unchanged when a polynomial correction for age was used.

Discussion

We found that CC thickness was significantly lower and CC FD% was significantly greater in patients with MDCA versus controls. Zheng et al.[14] recently showed no significant difference in total CC flow deficits between patients with tessellated fundus and PDCA, both earlier stages of MMD than MDCA; however, they were unable to segment the CC for quantitative

Table 2. Univariate and Multivariate Regression Modeling of Association of Risk Factors With Choriocapillaris Thickness

	Regression Beta Coefficient (95% CI)	
Risk Factor	Univariate	Multivariate
Age	−0.053 (−0.059 to −0.047); $P = 0.03$	−0.018 (−0.037 to 0.0003); $P = 0.06$
Gender		
Female	Reference	Reference
Male	2.62 (2.35 to 2.89); $P = 0.02$	−0.28 (−1.17 to 0.60); $P = 0.53$
AL	−1.32 (−1.35 to −1.29); $P < 0.001$	0.16 (−0.18 to 0.51); $P = 0.37$
Patient type		
Control	Reference	Reference
MDCA	−10.18 (−10.31 to −10.05); $P < 0.001$	−10.95 (−13.33 to −8.58); $P < 0.001$

Table 3. Univariate and Multivariate Regression Modeling of Association of Risk Factors with Choriocapillaris Flow Deficit Percent

	Regression Beta Coefficient (95% CI)	
Risk Factor	Univariate	Multivariate
Age	0.0017 (0.0016 to 0.0018); $P < 0.001$	0.0014 (0.0009 to 0.0018); $P < 0.001$
Gender		
Female	Reference	—
Male	−0.04 (−0.08 to 0.01); $P = 0.08$	—
AL	0.021 (0.020 to 0.022); $P < 0.001$	0.006 (−0.002 to 0.014); $P = 0.12$
Patient type		
Control	Reference	Reference
MDCA	0.16 (0.15 to 0.16); $P < 0.001$	0.11 (0.05 to 0.16); $P < 0.001$

Table 4. Choriocapillaris Parameters in Eyes With Macular Diffuse Chorioretinal Atrophy Versus Controls

Parameter	Macular Diffuse Chorioretinal Atrophy	Controls
Choriocapillaris thickness (µm)		
Mean ± SD	5.23 ± 0.68	15.46 ± 1.82
Median (min, max)	4.92 (4.41, 6.58)	14.81 (13.17, 20.06)
Choriocapillaris flow deficit (%)		
Mean ± SD	26.5 ± 4.3	11.2 ± 4.6
Median (min, max)	25.7 (20.0, 36.0)	10.7 (3.8, 21.3)

analysis in eyes with pathology worse than PDCA. Although prior studies had difficulty distinguishing the limits of the CC from other structures with similar reflectivity, such as RPE and Bruch's membrane, the current study employed the use of depth-resolved reflectivity profiles based on OCTA flow signals to delineate CC thickness. To the authors' knowledge, our work is the first to report quantitative analysis of CC thickness and CC FD% in MDCA by taking advantage of depth-resolved reflectivity and flow profiles, which made it possible to segment the CC layer from structural SS-OCT images in patients with very thin choroids.

Our results build on prior findings that patients with progressively higher grades of MMD have a thinner choroid.[8] In the study by Fang et al.,[8] patients with MDCA had an 82% thinner choroid compared to normals. In our study, patients with MDCA had a 66% thinner CC when compared to normal controls, demonstrating that overall choroidal thinning previously described in MMD does not spare the CC. In addition, our findings support the

qualitative results by Wong et al.[12] who used a grading schematic to show that qualitatively increased CC flow deficits were associated with increasing grade of MMD.

These quantifiable alterations in the CC are present in MDCA, a stage of MMD where BCVA is still well maintained and macular OCT demonstrates preservation of the RPE and photoreceptors. The presence of decreased CC thickness and increased CC FD% in these patients suggests that alterations in the CC occur during development of the chorioretinal atrophy in MDCA, the first stage of MMD. This supports the hypothesis that altered CC perfusion may play a role in the pathogenesis of MMD.[12–14]

The CC is unusual among capillary beds in that it has the highest blood flow per gram of tissue of any capillary bed in the body.[24] Its normal diameter of 15 to 20 µm is much greater than that of capillaries in other tissue beds which measure 5 to 9 µm.[25] And, although the high blood flow through the CC is associated with minimal drop in capillary partial pressure of oxygen (PO_2), oxygen extraction across the photoreceptors is profound.[26] Therefore, the current findings of CC alterations in MMD could have a profound impact on the pathophysiology of oxygen delivery to the outer retina.

Normal high flow of the CC appears to be altered in two important ways in MDCA. First, as noted, there is a 237% increase in CC flow deficit compared with controls without MMD. Second, given a 66% decrease in CC thickness, CC diameter is reduced from approximately 15 µm in patients without MMD to 5 µm in those with MDCA. In contrast to normal capillaries where red blood cells move in single file, the normal CC of 15 to 20 µm potentially allows for more rapid laminar flow, where flow is nearly static at the wall of the capillary and fastest near its center.[27] This rapid flow is critical because oxygen extraction by the photoreceptor inner segments is profound. Indeed, pioneering work by Linsenmeier and colleagues[26] measuring PO_2 in macaques and cats has shown that PO_2 nearly drops to zero at the level of the metabolically active inner segments. It is only because of unusually high CC blood flow that oxygen delivery is able to keep up with the high photoreceptor demand. However, in the case of MDCA where CC diameter is reduced to 5 µm, this converts more rapid laminar flow to single-file flow with potential dramatic slowing of CC blood flow. Resistance to laminar blood flow is inversely proportional to the fourth power of the radius (Poiseuille's equation), which would increase resistance with decreased CC radius; however, this relationship does not extend to single file flow.[25] In retinal capillaries of normal mice, single-file blood flow is several orders of magnitude less than flow through larger diameter arterioles with laminar flow.[27] Were capillary flow to slow dramatically by a reduction in the diameter of the CC in patients with MMD, whether through increased resistance in laminar flow or conversion to single-file blood flow, the normal state of excess CC oxygen delivery for high-demand photoreceptors might be compromised. Aggravating this, the significant increase in CC flow deficits observed in MDCA would further reduce the availability of oxygen to the outer retina. Resultant hypoxia could promote choroidal neovascularization, as well as macular atrophy, cardinal signs of advanced MMD.

Strengths of our study include the use of advanced imaging modalities (namely, SS-OCTA) and the use of recently developed automated methodologies to quantify alterations in CC thickness and flow deficits. However, there are important limitations. Our sample size is relatively small, although statistical analysis showed a robust difference in outcomes in our MDCA patients versus controls. In addition, we were able to replicate the association between increased age with increased CC FD% consistent with previous studies.[14] Second, we included only myopic patients with MDCA in this study and therefore cannot characterize the changes in the CC across the full spectrum of MMD. Previous studies quantified CC parameters in grades 0 and 1 MMD patients, whereas the focus of the present study was on quantifying changes in grade 2 MDCA, which have not been reported previously. Third, this is a cross-sectional study, and a longitudinal study could provide more information regarding the relationship of CC parameter changes to the progression of MMD and possibly elucidate risk factors to predict such progression. Fourth, although the mean and median ages of the controls are younger than the MDCA patients, we recruited a wide range of ages in the controls to improve precision in controlling for age in multivariate regression and to analyze the effect of age on CC parameters as a separate variable. For similar reasons, and because the authors' aim was to characterize CC parameters in the first stage of MMD as compared with normal controls and not those with MMD or at risk of developing it in the future, a range of ALs in normal controls was included. As noted, we were able to replicate the association between increased age with increased CC FD%, and the lack of association between CC parameters with AL.[28] Finally, in measuring CC FD%, SS-OCTA may not be able to distinguish the difference between very slow flow and true flow deficits, given that this modality can only detect the presence of flow above a certain sensitivity threshold.

In conclusion, patients with MCDA and good visual acuity had a 66% reduction in CC thickness and a 237% increase in CC FD% compared with controls. Although these patients have essentially normal BCVA and outer retinal layers on OCT scans, they demonstrate significant CC alterations that are consistent with reduced perfusion to the outer retina. Given the unique physiology of the CC, these results point to a potential vascular etiology for MMD, which may direct future advances in therapy.

Acknowledgments

The authors thank Igor Mitrovic, MD, Professor of Physiology at the University of California, San Francisco, for his expertise and assistance during preparation of this manuscript regarding the pathophysiology of the choriocapillaris and oxygen delivery to the outer retina.

Supported by the L.L. Hillblom Foundation and Hedco Foundation; by a UCSF Core Grant for Vision Research (NIH/NEI P30 EY002162); and by an unrestricted grant from Research to Prevent Blindness, Foundation Fighting Blindness, and the Claire Giannini Fund.

Disclosure: **J. Li**, None; **H. Zhou**, None; **M. Feinstein**, None; **J. Wong**, None; **R.K. Wang**, Carl Zeiss Meditec (C, F, I), Moptim Inc. (I); **L. Chan**, None; **Y. Dai**, None; **T. Porco**, None; **J.L. Duncan**, AGTC (C), DTx Therapeutics (C), Editas (C), Eyevensys (C), Gyroscope (C), Helios (C), Nacuity (C), Spark Therapeutics (C), SparingVision (C), ProQR Therapeutics (C), PYC Therapeutics (C), Verdere Bio (C), Acucela (F), Allergan/Abbvie (F), Second Sight Medical Products (F), Biogen/Nightstarx Therapeutics (F), Neurotech USA (F), RxSight (I); **D.M. Schwartz**, RxSight, Inc. (I, O, P, R); NVasc Inc. (I, O, P, R)

References

1. Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123(5):1036–1042.
2. Wang T-J, Chian T-H, Wang T-H, Lin LL-K, Shih Y-F. Changes of the ocular refraction among freshman in National Taiwan University between 1988 and 2005. *Eye (Lond)*. 2009;23(5):1168–1169.
3. Lin LLK, Shih YF, Hsiao CK, Chen CJ. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. *Ann Acad Med Singapore*. 2004;33(1):27–33.
4. Chen M, Wu A, Zhang L, et al. The increasing prevalence of myopia and high myopia among high school students in Fenghua city, eastern China: a 15-year population-based survey. *BMC Ophthalmol.* 2018;18(1):159.
5. Liu HH, Xu L, Wang YX, Wang S, You QS, Jonas JB. Prevalence and progression of myopic retinopathy in Chinese adults: the Beijing Eye Study. *Ophthalmology*. 2010;117(9):1763–1768.
6. Wong YL, Sabanayagam C, Ding Y, et al. Prevalence, risk factors, and impact of myopic macular degeneration on visual impairment and functioning among adults in Singapore. *Invest Ophthalmol Vis Sci.* 2018;59(11):4603–4613.
7. Ohno-Matsui K, Kawasaki R, Jonas JB, et al. International photographic classification and grading system for myopic maculopathy. *Am J Ophthalmol*. 2015;159(5):877–883.e7.
8. Fang Y, Du R, Nagaoka N, et al. OCT-based diagnostic criteria for different stages of myopic maculopathy. *Ophthalmology*. 2019;126(7):1018–1032.
9. Qin J, Rinell N, Zhang Q, et al. OCT angiography and cone photoreceptor imaging in geographic atrophy. *Invest Ophthalmol Vis Sci.* 2018;59(15):5985–5992.
10. Povazay B, Hermann B, Unterhuber A, et al. Three-dimensional optical coherence tomography at 1050 nm versus 800 nm in retinal pathologies: enhanced performance and choroidal penetration in cataract patients. *J Biomed Opt*. 2007;12(4):041211.
11. Lane M, Moult EM, Novais EA, et al. Visualizing the choriocapillaris under drusen: comparing 1050-nm swept-source versus 840-nm spectral-domain optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016;57(9):585–590.
12. Wong CW, Teo YCK, Tsai STA, et al. Characterization of the choroidal vasculature in myopic maculopathy with optical coherence tomographic angiography. *Retina* 2019;39(9):1742–1750.
13. Mo J, Duan A, Chan S, Wang X, Wei W. Vascular flow density in pathological myopia: an optical coherence tomography angiography study. *BMJ Open.* 2017;7:e013571.
14. Zheng F, Chua J, Ke M, et al. Quantitative OCT angiography of the retinal microvasculature and choriocapillaris in highly myopic eyes with myopic macular degeneration [published online ahead of

print January 4, 2021]. *Br J Ophthalmol.* https://doi.org/10.1136/bjophthalmol-2020-317632.

15. Ohno-Matsui K, Lai TYY, Lai CC, Cheung CMG. Updates of pathologic myopia. *Prog Retin Eye Res.* 2016;52:156–187.
16. Zhou H, Dai Y, Gregori G, et al. Automated morphometric measurement of the retinal pigment epithelium complex and choriocapillaris using swept source OCT. *Biomed Opt Express.* 2020;11(4):1834–1850.
17. Yin X, Chao J, Wang RKK. User-guided segmentation for volumetric retinal optical coherence tomography images. *J Biomed Opt*. 2014;19(8):086020.
18. Zhou H, Chu Z, Zhang Q, et al. Attenuation correction assisted automatic segmentation for assessing choroidal thickness and vasculature with swept-source OCT. *Biomed Opt Express.* 2018;9(12):6067–6080.
19. Shi Y, Zhang Q, Zhou H, et al. Correlations between choriocapillaris and choroidal measurements and the growth of geographic atrophy using swept source OCT imaging. *Am J Ophthalmol.* 2021;224:321–331.
20. Chu Z, Zhou H, Cheng Y, Zhang Q, Wang RK. Improving visualization and quantitative assessment of choriocapillaris with swept source OCTA through registration and averaging applicable to clinical systems. *Sci Rep.* 2018;8(1):16826.
21. Zhang Q, Zheng F, Motulsky EH, et al. A novel strategy for quantifying choriocapillaris flow voids using swept-source OCT angiography. *Invest Ophthalmol Vis Sci.* 2018;59(1):203–211.
22. Zhang Q, Zhang A, Lee CS, et al. Projection artifact removal improves visualization and quantitation of macular neovascularization imaged by optical coherence tomography angiography. *Ophthalmol Retina.* 2017;1(2):124–136.
23. Dai Y, Xin C, Zhang Q, et al. Impact of ocular magnification on retinal and choriocapillaris blood flow quantification in myopia with swept-source optical coherence tomography angiography. *Quant Imaging Med Surg*. 2021;11(3):948–956.
24. Bill A, Sperber GO. Control of retinal and choroidal blood flow. *Eye (Lond)*. 1990;4:319–325.
25. Barrett K, Barman S, Brooks H, Yan J. *Ganong's Review of Medical Physiology*. 26th ed. New York: McGraw-Hill Education; 2019.
26. Zhang H, Linsenmeier R. Retinal oxygen: from animals to humans. *Prog Retin Eye Res*. 2017;58:115–151.
27. Joseph A, Guevara-Torres A, Schallek J. Imaging single-cell blood flow in the smallest to largest vessels in the living retina. *eLife*. 2019;8:e45077.
28. Panda-Jones S, Holbach L, Jonas J. Choriocapillaris thickness and density in axially elongated eyes. *Acta Ophthalmol.* 2021;99(1):104–110.